Asymmetric Synthesis of Arylglycines

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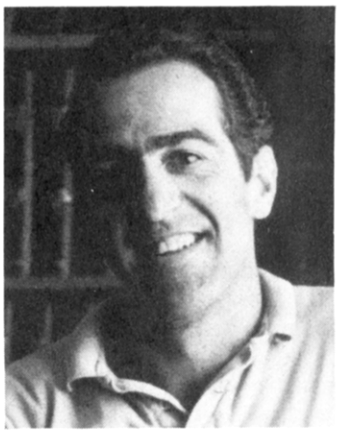
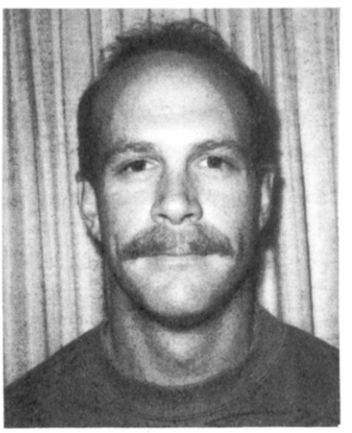


Robert M. Williams was born in New York in 1953. He obtained a B.A. degree in Chemistry from Syracuse University in 1975 and completed his doctoral studies in organic chemistry in 1979 at the Massachusetts Institute of Technology. After a 1-year postdoctoral fellowship at Harvard University in the laboratories of the late Professor R. B. Woodward, he joined the faculty at Colorado State University in 1980. He was promoted to the rank of Associate Professor in 1985 and Full Professor in 1988. Professor Williams is the recipient of an Alfred P. Sloan Foundation Fellowship, an Eli Lilly Young Investigator Award, an NIH Research Career Development Award, and a Merck Academic Development Award. His research interests are in the areas of bioorganic chemistry, natural products synthesis, asymmetric synthesis, mechanism of action of various antitumor and antimicrobial agents, secondary metabolism of fungi, and molecular biology.



James A. Hendrix was born in 1961 in Columbus, OH. He received a B.A. degree from the University of Northern Colorado in 1984 and a Ph.D. in chemistry from Colorado State University in 1991 under the direction of Professor R. M. Williams. He currently holds a post-doctoral position with Professor Anthony G. M. Barrett at Colorado State University. His research interests include the organic synthesis of biologically significant compounds.

A. Background

α-Amino acids have been the focus of great interest in all areas of both the physical and life sciences for over 150 years. It is well known that α-amino acids are vital to life itself as the "building blocks" of peptides, proteins, and many other natural products. Beyond this fundamental role, amino acids are used extensively as food additives, agrochemicals, and pharmaceuticals. Amino acids have also been used in organic synthesis as synthetic targets, as a source of chiral raw materials, and as constituents for reagents and/or catalysts in asymmetric synthesis. The importance of amino acids has prompted the development of a multitude of methods for their racemic and asymmetric synthesis.[1]

An interesting and important nonproteinogenic class of amino acids are the arylglycines. The isolation of arylglycines from natural sources is rare but has increased in frequency over the past 25 years. For example, *m*-hydroxy- and 3′,5′-dihydroxyphenylglycine were isolated from latex.[2] One of the best-studied and most interesting sources of arylglycines are the glycopeptide antibiotics. In 1956, the first glycopeptide antibiotic, vancomycin (1), was discovered.[3] Vancomycin's structure (1), not completely known until the early 1980s, consists of a heptapeptide in which three of the amino acid residues are arylglycines. Vancomycin (1) is isolated from *Amycolatposis orientalis* (previously designated as *Streptomyces orientalis*) and is active against Gram-positive bacteria. It is used clinically in the treatment of severe staphylococcal infections such as endocarditis and wound septicaemia.[4] Vancomycin (1) is also used to treat pseudomembranous colitis, a potentially lethal infection usually associated with antibiotic treatment after major gastrointestinal surgery.[5] Teicoplanin, another glycopeptide antibiotic, was recently approved for use in Italy

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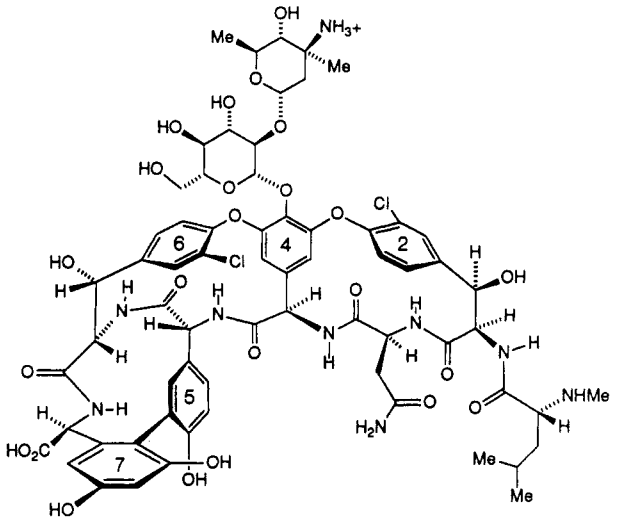


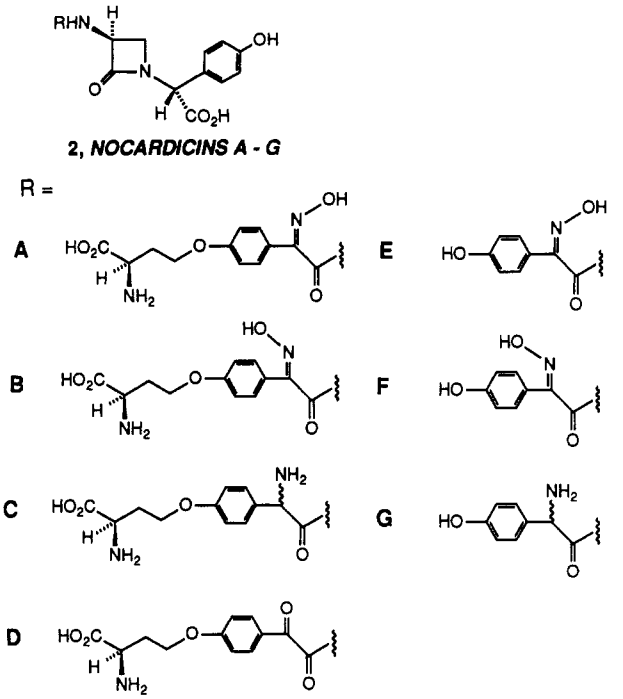
1, VANCOMYCIN

and France and is under clinical trials in other European countries and the United States.[4d] Since the discovery of vancomycin, many other glycopeptide antibiotics have been isolated and characterized. Members of the vancomycin group include ristocetin,[6] teicoplanin,[7] avoparcin,[8] ristomycin,[9] and actaplanin.[10] The isolation and characterization of new glycopeptide antibiotics continues to be very active areas of research as a review of the current literature will attest.[11]

Glycopeptide antibiotics are inhibitors of bacterial cell-wall biosynthesis.[12] It is now known that vancomycin blocks cell-wall biosynthesis by complexing strongly to the cell-wall peptidoglycan precursor at a specific D-Ala-D-Ala site near the C-terminus.[13] Furthermore, the binding site on vancomycin has been determined by the use of NMR experiments indicating that the amino acid residues, 5, 6, and 4 form the binding pocket for the D-Ala-D-Ala cell-wall subunit. Computer and molecular modeling support the idea that hydrogen bonding from these amino acid residues holds the D-Ala-D-Ala cell-wall subunit in place.[14] This proposal is also supported by the X-ray structure for the vancomycin analog, CDP-1.[14] Further work with ristocetin A also indicates that a conformational change is associated with binding.[15] It is believed that all members of the vancomycin group inhibit cell-wall biosynthesis in an analogous manner.[4]

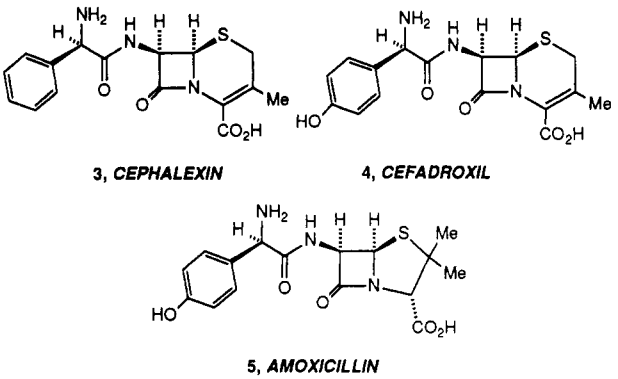
Another natural source of arylglycines is the family of monocyclic β-lactam antibiotics known as the nocardicins (2).[16] Nocardicin A, the best-known and most active member of this group of β-lactam antibiotics, was isolated from *Nocardia uniformis* ssp. *tsuyamanensis*. The nocardicins contain two *p*-hydroxyphenylglycine derivatives in their unusual structure (Figure 1). It is hypothesized that two molecules of *p*-hydroxyphenylglycine serve as the starting material for nocardicin (2) biosynthetically.[16]

Aside from the interesting naturally occurring arylglycines, there are also a number of unique synthetic arylglycines. Synthetic D-arylglycines are used as a side-chain moiety of semisynthetic penicillins and cephalosporins. The arylglycine side chain aids in the oral absorption of these β-lactam antibiotics. For example, the synthetic antibiotic cephalexin (3) contains phenylglycine as a side-chain constituent,[17] and *p*-hydroxyphenylglycine is used as a side-chain moiety in the antibiotics cefadroxil (4) and amoxicillin (5)[18] (Figure 2).



2, NOCARDICINS A - G

Figure 1



3, CEPHALEXIN 4, CEFADROXIL

5, AMOXICILLIN

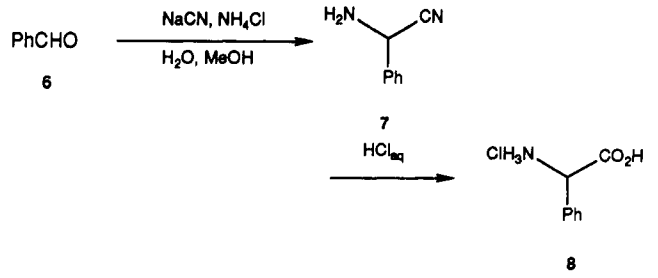
Figure 2

B. Synthesis of Racemic Arylglycines

The arylglycines are an example of a class of α-amino acids that are difficult to synthesize in optically pure form due to the ease at which the α-methine proton can undergo base-catalyzed racemization. As a result, many arylglycines are synthesized in racemic form, and the enantiomers are then carefully separated by resolution. The synthesis of racemic arylglycines dates back over 100 years. To gain some historical perspective it may be instructive to look at the synthesis of the simplest arylglycine, phenylglycine. In 1878 Stockenius[19] reported a synthesis of phenylglycine by heating α-bromophenylacetic acid with excess ammonium hydroxide to 100–110 °C. In 1885, Elbers[20] prepared phenylglycine by the reduction of benzoylformic acid phenylhydrazone with sodium amalgam in dilute sodium hydroxide. Starting in 1880, several groups utilized the Strecker synthesis to produce α-aminophenylacetonitrile (7) which was hydrolyzed to phenylglycine (8) in hydrochloric acid[21] (Scheme 1).

Over the years, the Strecker synthesis has been the most widely used method for the synthesis of arylgly-

Scheme 1



Scheme 2

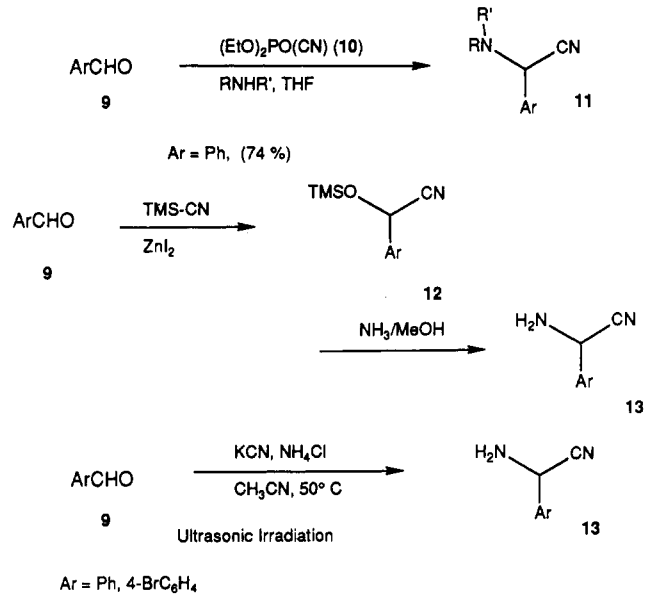


Table 1

Ar	R	R′	% yield (13)
2-ClC_6H_4	H	H	96
3-ClC_6H_4	H	H	97
4-ClC_6H_4	H	H	98
2,6-$Cl_2C_6H_3$	H	H	98
2-$MeOC_6H_4$	H	H	99
4-MeC_6H_4	H	H	96
4-$MeSC_6H_4$	H	H	97
4-NCC_6H_4	H	H	15
4-$MeO_2CC_6H_4$	H	H	77
2-furyl	H	H	94
2-thienyl	H	H	92
2-ClC_6H_4	$C_6H_5CH_2$	H	94
2-ClC_6H_4	CH_3	CH_3	96
2-ClC_6H_4	$(CH_2)_2$-O-$(CH_2)_2$		93
2-ClC_6H_4	$(CH_2)_4$		91
3-$NO_2C_6H_4$	$(CH_2)_4$		95
3-HOC_6H_4	$(CH_2)_4$		87

cines. In recent years there have been modifications of the classical Strecker synthesis. The advent of organic-soluble cyanide sources has provided new-found versatility to the Strecker reaction. Diethyl phosphorocyanidate (**10**)[22] and trimethylsilyl cyanide[23] have both been used in the synthesis of a variety of α-amino arylnitriles. Another interesting modification has been the application of ultrasound to the Strecker synthesis[24] (Scheme 2, Table 1). The Strecker synthesis has also been utilized in the asymmetric synthesis of arylglycines, the details of which will be discussed below.

Aside from the Strecker synthesis, there are numerous modern examples of racemic arylglycine syntheses. It is not the goal of this article to provide a comprehensive review of racemic arylglycine syntheses, but only to give the flavor of some of this chemistry. Nitriles **14** and isonitriles **18** have been converted to arylglycines under quite harsh conditions[25] (Scheme 3, Tables 2 and 3). Electrophilic aromatic substitution of a variety of glycinate equivalents is a popular method in the synthesis of arylglycines. α-Hydroxyglycine equivalents **21** and **24** have been used in amidoalkylation reactions to produce arylglycine derivatives[26] (Schemes 4–6). The standard amidoalkylation conditions were modified for acid-sensitive aromatic groups such as furyl groups.[26b]

Scheme 3

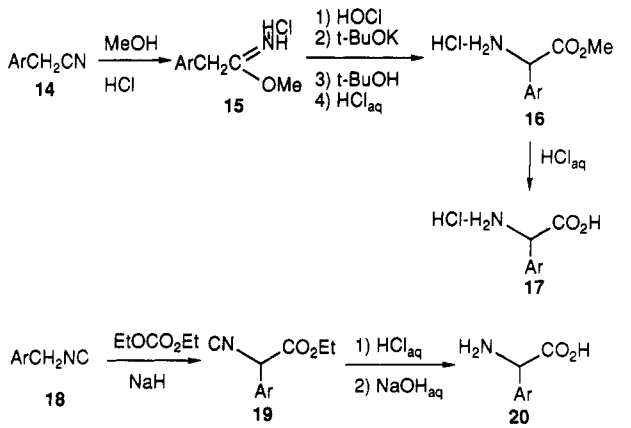


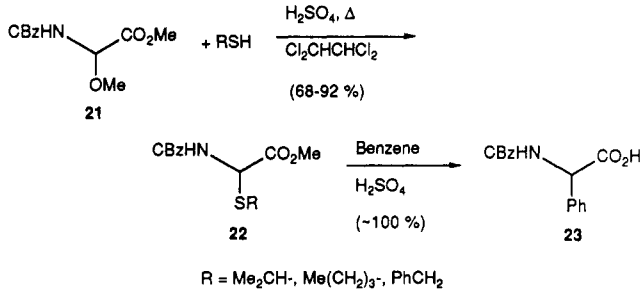
Table 2

Ar	% yield (15)	% yield (16)	% yield (17)
Ph	71–100	69–75	54–74
1-naphthyl	79–89	44–54	43–53
4-$MeOC_6H_4$	64–77	32	31
4-MeC_6H_4	74		67
4-ClC_6H_4	80		55
4-$NO_2C_6H_4$	25		0

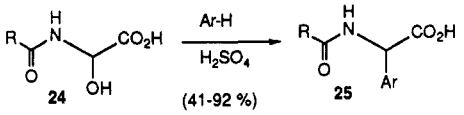
Table 3

Ar	% yield (19)	% yield (20)
Ph	63	57
2-furyl	61	55
4-$MeOC_6H_4$	60	54
4-MeC_6H_4	59	51
4-ClC_6H_4	62	56

Scheme 4

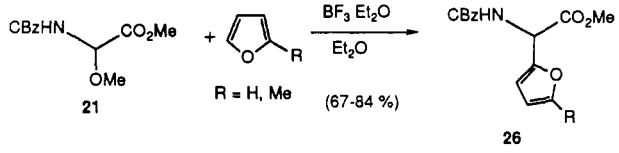


Scheme 5

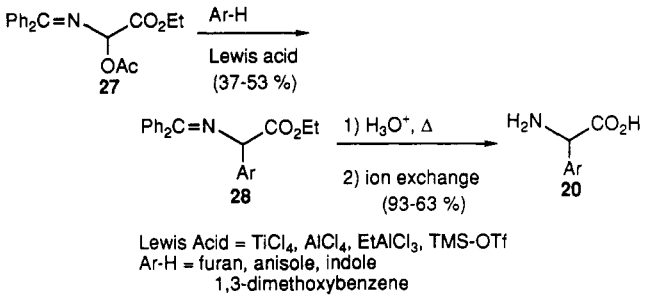


R = Ph, $PhCH_2$, MeO, $PhCH_2O$
Ar = Ph, p-MeC_6H_4-, p-ClC_6H_4-, p-$AcNHC_6H_4$-, p-$MeOC_6H_4$-, p-HOC_6H_4-, 1-naphthyl, $C_{14}H_9$-, thienyl, o-nitropenol, p-nitrophenol, flurobenzene, guaiacol, 2-naphthol

Scheme 6



Scheme 7



Scheme 8

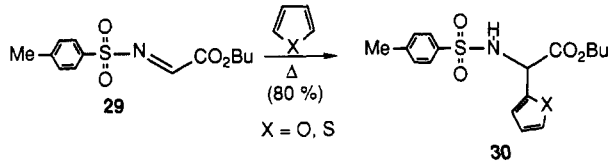


Table 4

Ar	% yield (28) via 31	% yield (28) via 31a	% yield (20)
Ph	57	70	55
1-naphthyl	64	63	37
2-thienyl	47	71	40

Regiochemical control is sometimes difficult to attain with substituted aromatics in these reactions. In an analogous reaction, O'Donnell and Bennett[27] have utilized an electrophilic Schiff's base ester **27** in reactions with active aromatics under Friedel–Crafts conditions. The resulting arylated amino ester **28** can easily be hydrolyzed to the desired free amino acid **20** (Scheme 7). In yet another electrophilic substitution reaction, furan and thiophene were reacted with an active iminoacetate **29**, yielding the desired arylglycine derivative **30**[28] (Scheme 8).

The use of organometallic reagents as a source of aromatic nucleophiles in reactions with electrophilic glycine equivalents is also a popular method in the synthesis of arylglycines. O'Donnell's[29] electrophilic Schiff's base **27** has also been used with organoboranes, **31**, and cuprates to make arylglycines (Scheme 9, Table 4). Cuprates as well as Grignard reagents were reacted with iminoacetates **34** yielding arylglycines[30] (Schemes 10 and 11). Many of the same basic bond-forming reactions used in the synthesis of racemic arylglycines have also been modified for use in asymmetric synthesis.

C. Resolution of Arylglycines

The most common method of obtaining optically active arylglycines is via the separation of synthetically prepared racemic mixtures. Four general methods can be employed: (1) fractional crystallization of diastereomeric salts; (2) chromatographic resolution on columns with chiral carriers; (3) the enzymatic resolution of racemic arylglycine derivatives; and (4) the relatively new technique of retroracemization. Chemical resolution represents a classical technique that has long been applied to a variety of amino acids including arylglycines. For example, the fractional crystallization with camphorsulfonic acid of D-phenylglycine has long been known.[1b] The optical resolution of a variety of amino acids and amino acid derivatives has also been achieved using chiral column chromatography.[31] While this technique can be quite effective in the separation of arylglycine racemates, it is often difficult to use this method on a preparative scale.

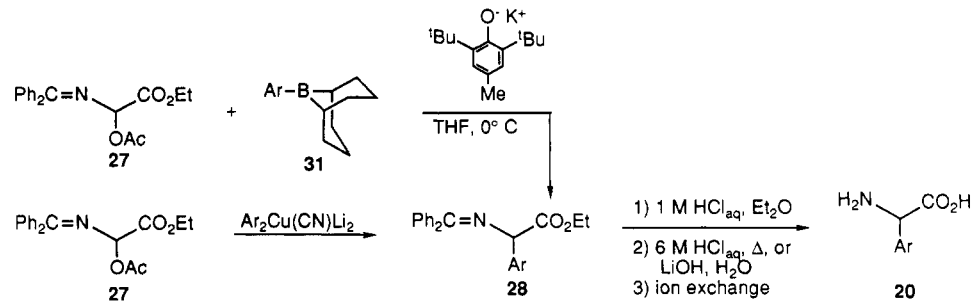
1. Enzymatic Methods

A more recent and promising development for the resolution of amino acids is the use of enzymes. The enzymes used for this purpose are purified, immobilized enzymes, cell-free enzymes, or whole-cell systems. The use of this technology has become quite popular in industry since the desired amino acids can be prepared on both large and intermediate scales.[32] Esterases, amidases, and hydantoinases are three types of enzymes that have proven effective in the production of optically active arylglycines.

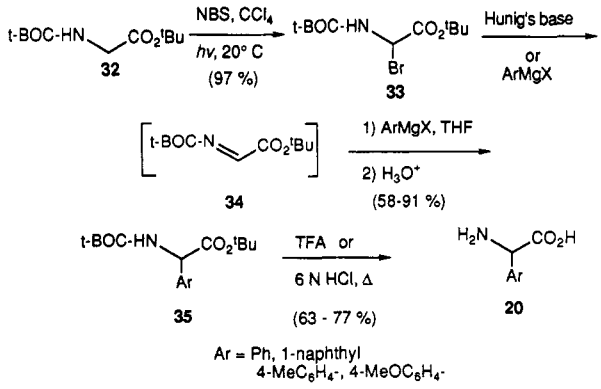
a. Esterases

Esterases have been used in the industrial preparation of D-arylglycines which are important side-chain constituents of semisynthetic penicillins and cephalosporins. Specifically, the immobilized proteolytic enzyme *subtilisin* has been used in the resolution of arylglycines such as D-*p*-hydroxyphenylglycine. D-*p*-Hydroxyphenylglycine is a very important arylglycine as it is used as a side-chain constituent of the β-lactam antibiotic, amoxicillin (**5**).[33] This amino acid can be obtained by the enantiospecific hydrolysis of *d,l-N*-acylarylglycine methyl esters with subtilisin (Scheme 12). The L acid can be readily separated from the unreacted D ester, giving each antipode in high optical purity.

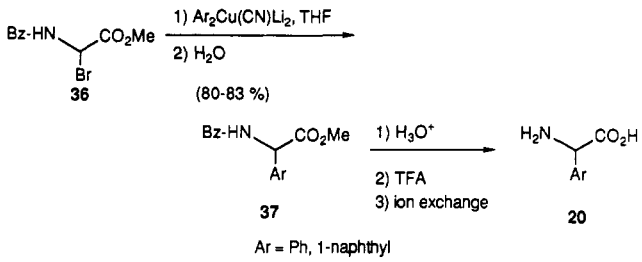
Scheme 9



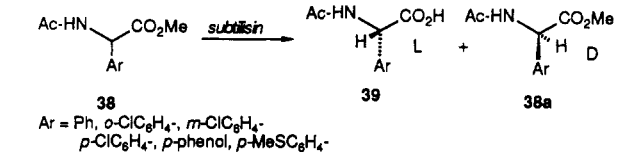
Scheme 10



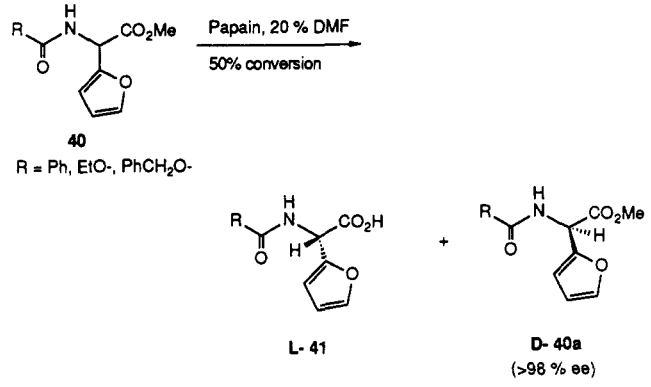
Scheme 11



Scheme 12



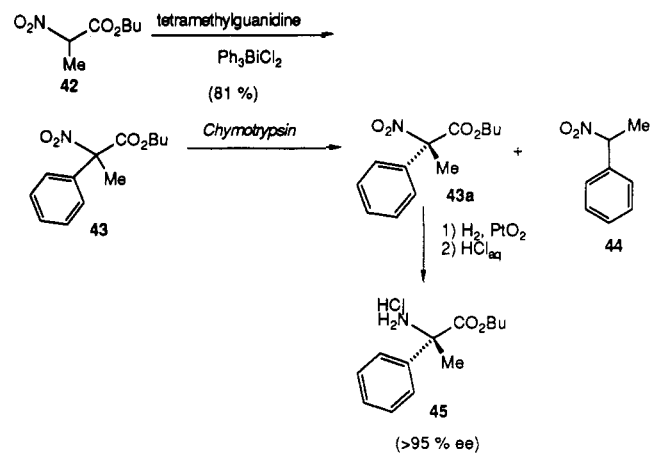
Scheme 13



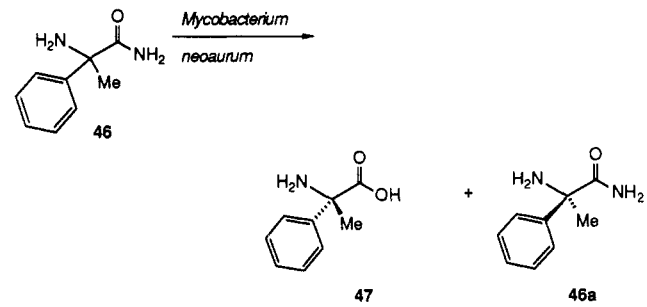
Papain has been reported to act as an effective esterase in the resolution of D,L-furylglycine. The D methyl esters **40a** were obtained in greater than 98% ee but in only 31–44% yield[34] (Scheme 13). The authors report that the *N*-benzoyl, *N*-ethoxycarbonyl, and *N*-benzyloxycarbonyl substrates (**40**) all give equally satisfactory results.

A creative application of enzymatic resolution involving the use of α-chymotrypsin to resolve α-nitro-α-methyl carboxylic acid ester **43** was recently reported by Lalonde, Bergbreiter, and Wong.[35] As shown in Scheme 14, the 2-nitropropionates **42** are alkylated to afford the racemic substrates **43**. Treatment of these substances with α-chymotrypsin effects hydrolysis of the D ester to the corresponding free acid. Under the reaction conditions (0.25 M, pH 7, phosphate buffer in 2:1 buffer/DMSO), the resulting D acid spontaneously decarboxylated leaving a mixture of **43a** and **44**; these

Scheme 14



Scheme 15

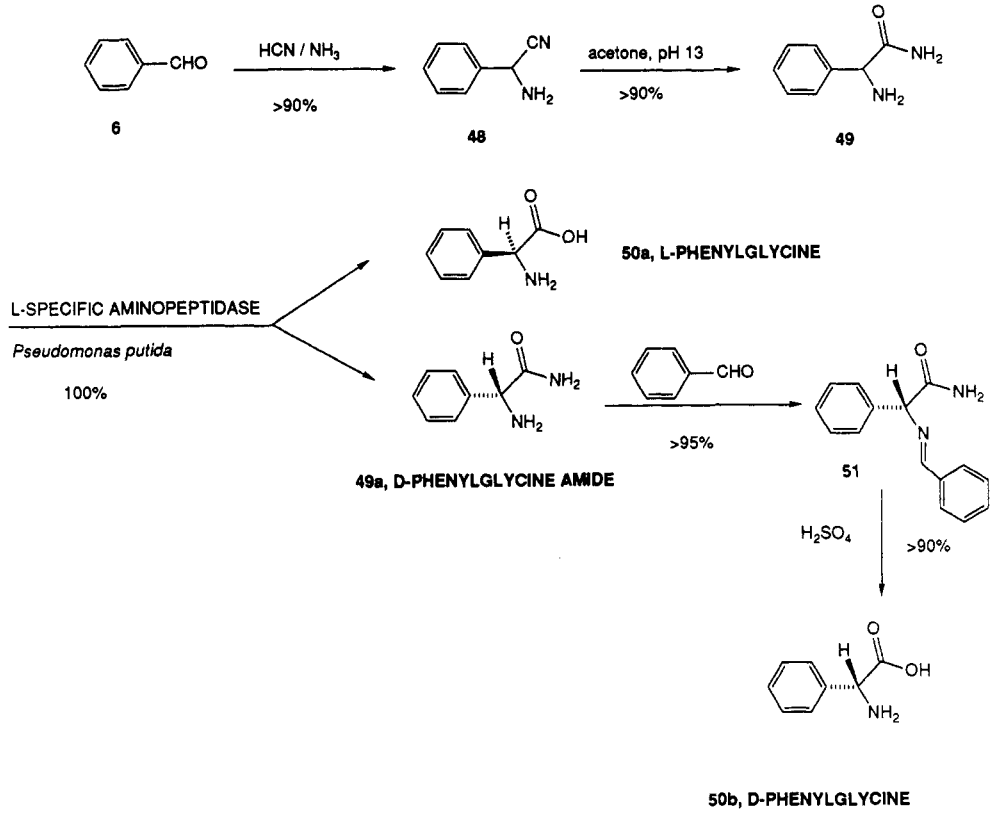


substances were then separated by radial chromatography. The authors note that lipases and esterases were found to be ineffective. The optically active nitro ester **43a** can then be reduced to the corresponding α-methyl-α-amino acid ester **45** using Adam's catalyst. The authors note that substrates containing unsaturated R′ groups give the best results; this observation is consistent with the well-known substrate specificity of chymotrypsin. This procedure provides a potentially very powerful and economical method to synthesize the important α-methyl-α-amino acids; α-methyl-α-amino acid derivatives are commonly poor substrates for hydrolytic enzymes compared to their unsubstituted counterparts. The enantiomeric excess of the product amino acid **45** was >95% ee. This approach is limited to α-methylated amino acids since the mono-α-substituted substrates have a very acidic α-proton that readily undergoes exchange resulting in racemic products. Experimental details accompany this report.

b. Amidases

The ease of preparing racemic α-amino amides by the Strecker synthesis has made use of selective amidases in effecting a kinetic resolution of considerable importance. A Dutch group has extensively developed this approach in the synthesis of numerous optically active amino acids as illustrated below. Aromatic amino acid amides **46** can be hydrolyzed stereoselectively to produce the L-arylglycine **47** and the D-aryl amide **46a** using an amino peptidase from *Mycobacterium neoaurum* ATCC 25795.[36] As shown in Scheme 15, the α-substituted *d,l*-amino acid amide **46** was treated with whole cells of *M. neoaurum* in water at 37 °C. The two components produced, the L acid **47** and the D amide **46a**, are separated by differences in solubility in an organic solvent such as chloroform (the acid is insoluble

Scheme 16



in chloroform). These workers also report a fast and simple ^{1}H NMR method to determine the % ee on the product amino acids by acylation with (*S*)-2-chloropropionyl chloride. Resolvable doublets for the CH_3-CHCl residue can be accurately integrated to within ±2%. The microfilm edition of this paper in *The Journal of Organic Chemistry* contains complete experimental details.

Racemization-prone phenylglycine has been prepared via the efficient hydrolysis of *d,l*-phenylglycine amide (**49**) with an L specific aminopeptidase from *Pseudomonas putida*.[18] This process produces in quantitative yield, L-phenylglycine (**50a**) and D-phenylglycine amide (**49a**) (Scheme 16). The authors report that the crude enzyme preparation displays nearly 100% stereoselectivity in hydrolyzing the L amide to the L acid. The two components (**49a** and **50a**) are separated by Schiff's base formation with benzaldehyde; the Schiff's base of the amide **51** was fortuitously found to be completely insoluble in water and is simply filtered off. After acidic hydrolysis at 100 °C, the D-amino acid **50b** is obtained without racemization. It is noted that the amino acid amide must contain an α-H atom and have an unsubstituted amino group to be a substrate for the aminopeptidase of *P. putida*. Thus, both *N*-alkylamino acid derivatives and the interesting α-substituted amino acids cannot be prepared by this method. As mentioned above, D-phenylglycine (**50b**) is a side-chain precursor to ampicillin and enjoys a significant world-wide demand. The unwanted L isomer **50a** does not have such a large market demand and is therefore racemized, esterified to the methyl ester, subjected to aminolysis forming *d,l*-**49**, and is reused in the above resolution.

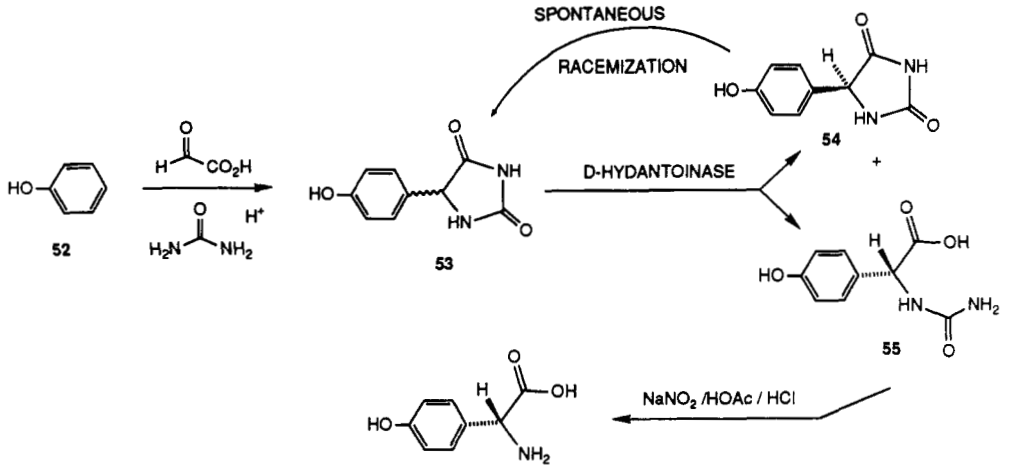
c. Hydantoinases

The β-lactam antibiotic amoxicillin (**5**) contains the amino acid D-*p*-hydroxyphenylglycine (**56**) as a side-chain residue. An interesting enzymatic synthesis of this amino acid has been developed[18] as shown in Scheme 17. Racemic (*p*-hydroxyphenyl)hydantoin (**53**) is prepared from phenol, glyoxylic acid, and urea under acidic conditions. This substrate is selectively hydrolyzed to D-*N*-carbamoyl-*p*-hydroxyphenylglycine (**55**) by a D-specific hydantoinase from *Bacillus brevis*. The unreacted L isomer **54** spontaneously racemizes under the conditions of the enzymatic reaction. Thus, a theoretical 100% turnover of the *d,l* substrate **53** can be achieved by this protocol. The carbamoyl product **55** can be chemically converted into D-*p*-hydroxyphenylglycine (**56**) with sodium nitrite in a mixture of hydrochloric and acetic acids. Alternatively, a two-enzyme, one-reactor procedure[37] with cells of *Agrobacterium radiobacter* directly converts **53** into **56**. This microbe produces both the D-hydantoinase and *N*-carbamoyl-D-amino acid hydrolase.

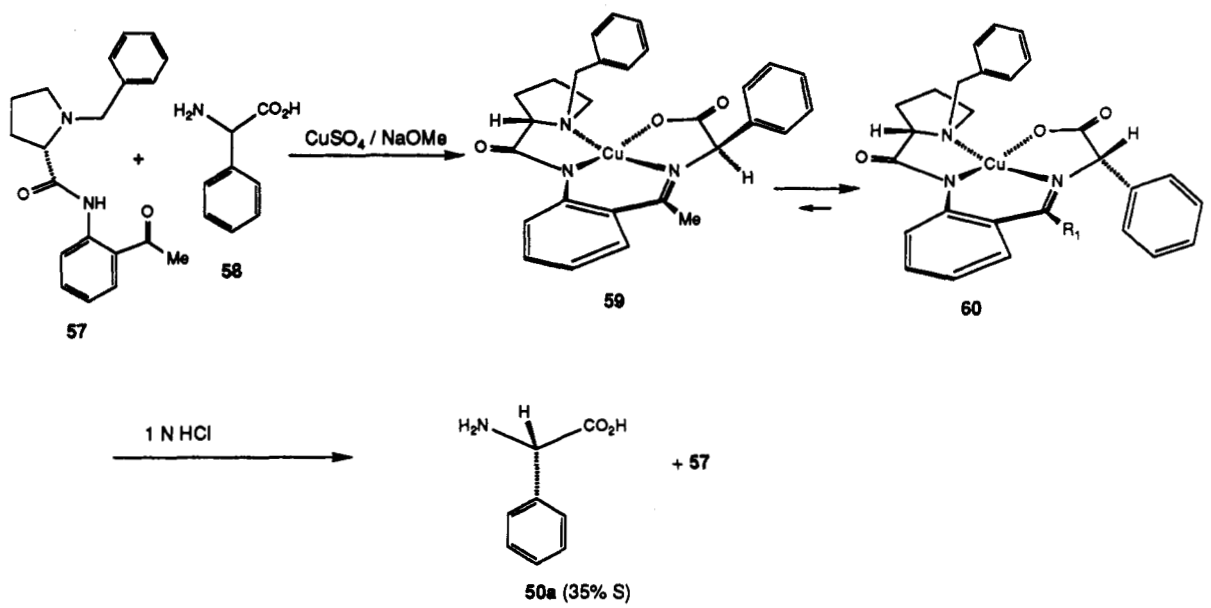
2. Retroracemization

Apart from enzymatic methods for the resolution of arylglycines, the chemical method of deracemization or retroracemization has also been employed. Belokon and associates[38] used a chiral copper Schiff's base complex (**59**/**60**) to perform a thermodynamic retroracemization and resolution on phenylglycine (**50**). The complex is formed by the condensation of racemic phenylglycine with (*S*)-2-[(*N*′-benzylprolyl)amino]acetophenone (BPAAPh, **57**) in the presence of Cu^{II}. The chiral Schiff's base complex undergoes thermodynamic equilibration under basic conditions to the more stable anti complex **60**. Acidic hydrolysis separates the chi-

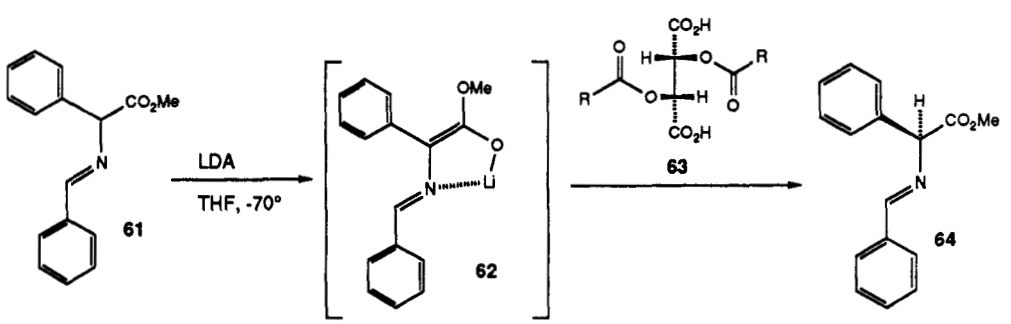
Scheme 17



Scheme 18



Scheme 19



ral auxiliary from the optically enriched phenylglycine, (35%, *S*, Scheme 18).

Duhamel and co-workers[39] have developed a strategy for the enantioselective kinetic protonation of the lithium enolate of a phenylglycine Schiff's base (**62**, Scheme 19, Table 5). The benzylidenephenylglycine derivative **61** was treated with LDA, yielding the desired enolate **62**. This enolate **62** was then protonated with a series of tartrates **63** furnishing the phenylglycine derivative **64** in moderate enantiomeric excess, (Scheme 19). The chemical yields are rather good, but the enantiomeric excess is generally modest; the best example is 62% ee for the phenylglycine case employing the 1-adamantyl tartrate. In a related study,[40,39b] the same group substituted a chiral amide base for LDA. The authors hypothesize that the lithium enolate (i.e., **62**) is coordinated to the amine employed as the base. The additional chiral induction of the optically active ligand (L*) improves the % ee up to a maximum of 70% ee in the phenyl glycine case.

In a related study, Duhamel and co-workers[41] have also examined the asymmetric carboxylation of the α-lithioamine **67** employing a chiral amide base (**66**, Scheme 20, Table 6). This disconnection for the

Scheme 20

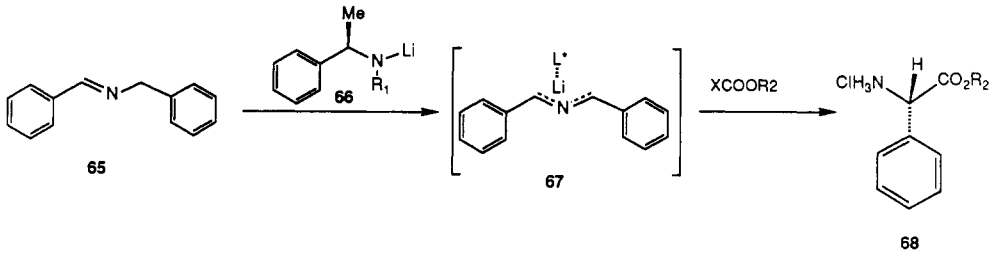


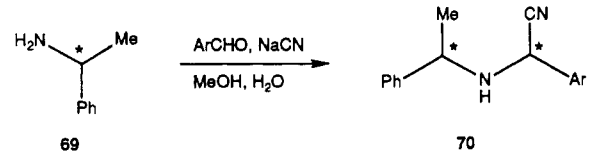
Table 5

R	*S*:*R* ratio (**64**)	% yield (**64**)
t-Bu	79:21	85
t-$BuCH_2$	59:41	84
t-$BuCH_2CH_2$	70:30	82
Ph	57:43	80
$PhCH_2$	55:45	81
$PhCH_2CH_2$	54:46	83
$(Me)_2CBr$	70:30	85
cyclohexyl	71:29	85
β-styryl	65:35	86
1-adamantyl	81:19	79

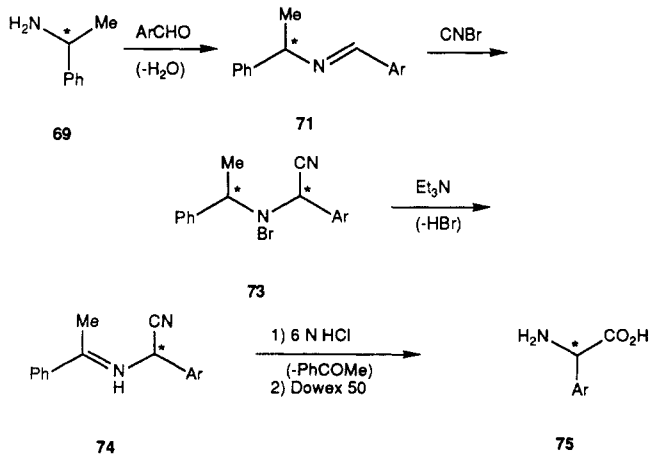
Table 6

R_1	R_2	X	yield (% **68**)	% ee
Et	Me	MeO	40	0
Et	Me	Cl	58	35 (*S*)
Pr	Me	Cl	60	32 (*S*)
Et	Et	Cl	56	41 (*S*)
Pr	Et	Cl	55	34 (*S*)
Et	Bu	Cl	40	40 (*S*)

Scheme 21



Scheme 22



synthesis of amino acids is a surprisingly rarely studied approach. Numerous new methods for the asymmetric carbanionic C–C functionalization α to nitrogen have recently become available and may portend a future area of investigation. Carboxylation of the anion **67** with various chloroformates or dimethyl carbonate furnishes the esters **68** after acidic removal of the benzylidene. The % ee's are low, ranging from 0–41% ee.

Table 7[a]

Ar	overall yield (% **75**)
Ph	47
$2\text{-}MeOC_6H_4$	39
$3,5\text{-}(MeO)_2C_6H_3$	35
$3,4,5\text{-}(MeO)_3C_6H_2$	21

[a] Approximately 50% optical purity for phenylglycine.

D. Asymmetric Synthesis of Arylglycines

As previously stated, arylglycines have been difficult to synthesize in optically active form due to the ease with which the α-methine proton can undergo base-catalyzed racemization. However, there have recently been several groups that have addressed the asymmetric synthesis of arylglycines in a variety of ways. One approach has been the asymmetric modification of the Strecker synthesis. Other strategies include the asymmetric alkylation of nucleophilic glycinates, the asymmetric alkylation of electrophilic glycinates, enantioselective carboxylation, the asymmetric electrophilic amination of enolates, and the asymmetric nucleophilic amination of α-substituted acids, as well as other unique methods that defy categorization.

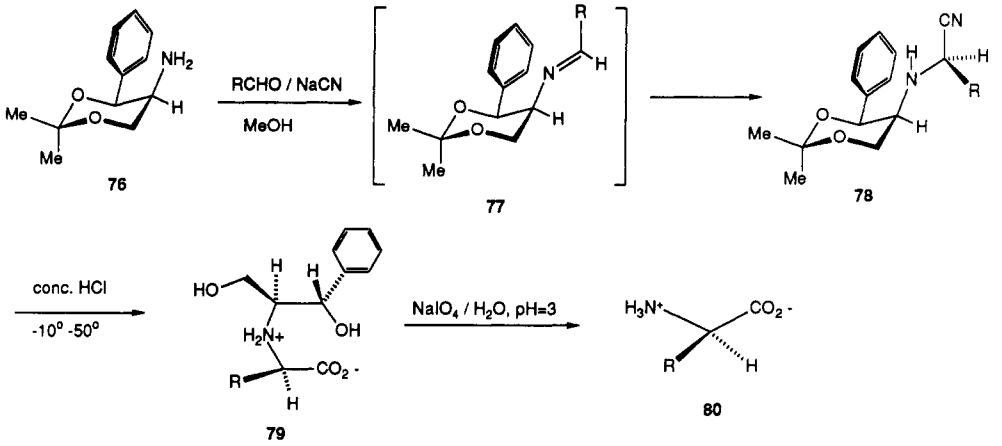
1. The Asymmetric Strecker Synthesis

The first asymmetric Strecker synthesis was reported in 1963 by Harada.[42] Since that time, the general strategy for the induction of asymmetry in the Strecker synthesis has been to generate a chiral Schiff's base from the condensation of an aldehyde and an optically active amine. The subsequent addition of a nitrile source forms an optically active α-amino nitrile that is then hydrolyzed to the amino acid. This methodology has been quite successful in the synthesis of many amino acids but has rarely been used in the synthesis of arylglycines.

One reason that the asymmetric Strecker synthesis has not been applied often to arylglycines is the difficulty in removing the chiral auxiliary. For example, Stout and co-workers[43] examined the asymmetric synthesis of α-amino nitriles **70** using (*R*)- and (*S*)-α-methylbenzylamine (**69**) and a collection of benzaldehydes. The authors found that the α-amino nitriles **70** were formed with poor diastereoselection and concluded that the reaction proceeded under thermodynamic rather than kinetic control. Another problem with this method was that the α-amino nitriles **70** could not be converted into the desired arylglycines. The reductive procedure usually employed to remove the *N*-α-methylbenzyl moiety could not be used since this method would also result in the cleavage of the second benzylic residue present (Scheme 21).

More recently, however, Panse and associates[44] were able to selectively remove the *N*-α-methylbenzyl moiety

Scheme 23



76 77 78 79 80

Table 8

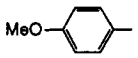
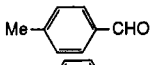
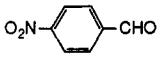
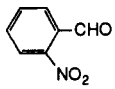
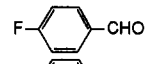
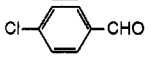
R	yield (% 78)	yield (% 79)	yield (% 80)
	65	82	68
	60	73	49
	24	65	64
	35	76	60

Table 9

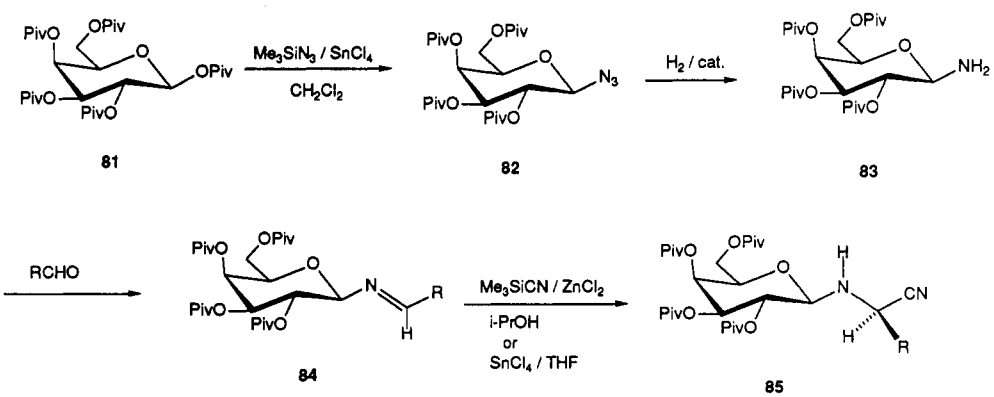
RCHO	solvent	catalyst (mol %)	diastereomeric ratio (*R*:*S*)	yield (% pure (*R*)-85)
	*i*-PrOH	$ZnCl_2$ (100)	6.5:1	78
	THF	$SnCl_4$ (130)	12:1	87
	*i*-PrOH	$ZnCl_2$ (5)	7:1	80
	THF	$SnCl_4$ (130)	1:0	91
	*i*-PrOH	$ZnCl_2$ (5)	6.5:1	75
	THF	$SnCl_4$ (130)	10:1	84
	THF	$SnCl_4$ (130)	11:1	84

which gave rise to optically active arylglycines (Scheme 22, Table 7). The protocol called for the addition of cyanogen bromide to the chiral Schiff's base **71** yielding the *N*-bromo-α-amino nitrile **73**. Dehydrobromination occurred with the addition of triethylamine followed by acid hydrolysis that furnished the desired arylglycine **75**.

Weinges and co-workers[45] have extensively studied the use of an alternative chiral amine for the asymmetric Strecker synthesis. The most significant feature of this work was the development of an oxidative method for the cleavage of the chiral auxiliary that allowed access to arylglycines. As shown in Scheme 23 (Table 8), condensation of aromatic aldehydes with **76** in the presence of sodium cyanide affords the adducts **78** which are obtained diastereomerically pure by crystallization. The nitrile and acetonide moieties are hydrolyzed to the corresponding oxazinone which is opened with water to the hydroxy acids **79**. Treatment of these substances with sodium periodate in water at pH = 3 results in the selective cleavage at the amino alcohol positions giving the enantiomerically pure aryl glycine derivatives **80**.

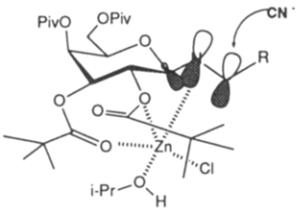
Very recently, Kunz and associates[46-48] have examined the asymmetric Strecker synthesis utilizing β-1-amino tetra-*O*-pivaloylgalactose (**83**, Scheme 24, Table 9) as the chiral matrix. The protocol is similar to those above, specifically involving imine formation to **84** and diastereoselective addition of cyanide to the imine forming the α-amino nitriles **85**. These workers have found that anomerization of the carbohydrate moiety (from β to α) can be minimized by using trimethylsilyl cyanide and a Lewis acid such as zinc chloride or tin tetrachloride, giving high yields of the adducts **85** under mild conditions. The authors propose that the imines possess the *E* geometry and adopt a conformation (**86**) that is stabilized by overlap of the C=N p orbital with

Scheme 24



81 82 83 84 85

the σ^* orbital of the glucose C_1–O bond. This conformation is further supported by a strong NOE in the ^1H NMR spectrum between the imine methine and the H_1 methine at the anomeric center of the sugar. The bulky pivaloyl group at C-2 would then hinder attack from this side forcing addition from the side of the ring oxygen; this hypothesis is in accord with the observed diastereoselectivity.



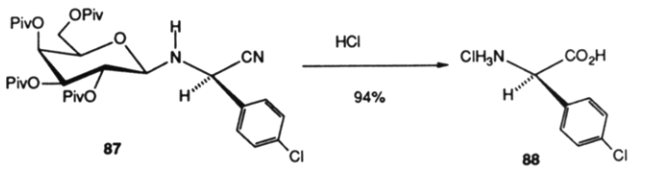
86

A single example of hydrolyzing the nitrile with concomitant hydrolytic removal of the carbohydrate was reported as shown in Scheme 25. Hydrolysis of the *p*-chlorophenyl adduct **87** with hydrochloric acid affords the enantiomerically pure phenylglycine derivative **88** in high yield. The carbohydrate moiety can be recovered as the corresponding hemiacetal in 70–90% yield by extraction with methylene chloride after hydrolysis. This method is nicely complementary to the systems detailed above since the chiral auxiliary is removed under hydrolytic rather than reductive or oxidative conditions.

These workers[47] have also found an interesting solvent effect that *reverses* the diastereofacial selectivity of addition to the Schiff's bases **84** as shown in Scheme 26 (Table 10). When the addition of trimethylsilyl cyanide to **84** is carried out in chloroform solution using zinc chloride as the Lewis acid, a preponderance of the *S* isomer results. All of the examples performed on the *same* substrates in either tetrahydrofuran or 2-propanol exhibited selectivity for the corresponding *R* isomers. The authors demonstrate by ^1H NMR that the conformation of the imine (see **86**) is the same in THF as it is in chloroform. Thus, the reasons for this marked reversal in stereochemical outcome are not presently clear but may be a manifestation of aggregation and salt complexation differences in the different solvents. From a practical standpoint, this simple change in reaction solvent allows for convenient access to either the D- or L-configured amino acids from the same chiral imine. Full experimental details for this elegant work have not yet appeared.

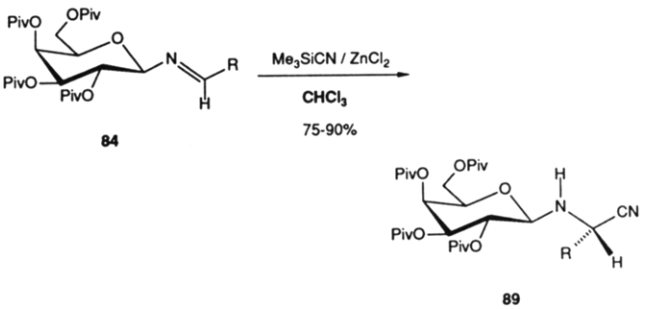
In a related study employing the same chiral matrix, Kunz and associates[48] have examined the asymmetric Ugi condensation as shown in Scheme 27 (Table 11). The galactose derivative **83** is condensed with an aldehyde, an isonitrile, formic acid, and zinc chloride to afford the Ugi products **90**. The chemical yields for the formation of **90** are high and the kinetic ratio of isomers produced is excellent. These substances (**90**) can be obtained diastereomerically pure by a simple recrystallization; the yields for the pure isomers are tabulated. Hydrolysis of the chiral auxiliary with methanolic HCl affords the amides **92** and the hemiacetal **91** which can be recovered and recycled. Hydrolysis of the amides with hot 6 N hydrochloric acid followed by ion-exchange chromatography furnishes the free amino acids **93**. It is very significant that two good examples

Scheme 25



87 88

Scheme 26



84 89

Table 10

R	$ZnCl_2$ (mol %)	diastereomeric ratio (**89**) (*R*:*S*)
Me-	100	1:4.5
F-	100	1:3
Cl-	5	1:4
	300	1:5
Cl	5	1:6
	100	1:5

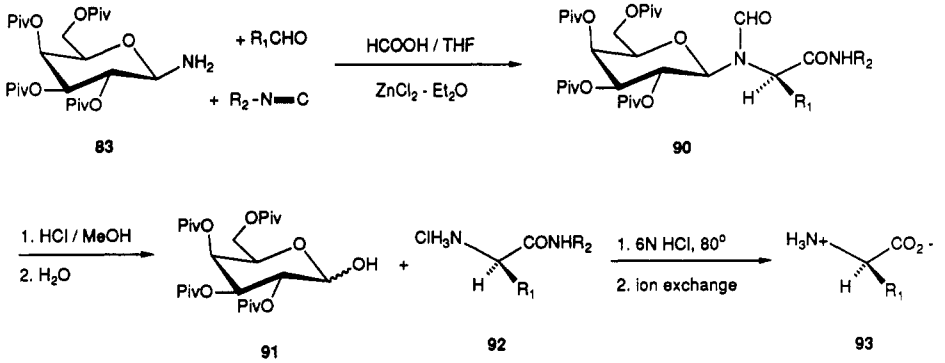
of the racemization-prone phenylglycine derivatives are reported. It can thus be inferred that numerous base-labile but acid-stable classes of amino acids should become accessible by this protocol. Full experimental details have been published for this work.

2. Alkylation of Nucleophilic Glycinates

The alkylation of nucleophilic glycinates is a method that has been widely used to prepare α-alkylated phenylglycine products. These dialkylated amino acids are not prone to racemization, as are standard arylglycines, and are thus stable to the basic conditions used for alkylation. An example of this approach reported by Schöllkopf[49] utilized optically active heterocycles **96** which are prepared from phenylglycine and several optically active α-hydroxy acids **95**. This product was then converted to a monolactim ether **97** that was then subjected to an enolate alkylation with activated electrophiles. The resulting oxazinones **98** were cleaved with mild aqueous acid yielding the desired α-alkylated phenylglycine derivatives **99** (Scheme 28, Table 12). In a related approach,[50] 2-furylglycine was used as the amino acid template. Following the same alkylation procedure as above, α-alkylated-2-furylglycine derivatives were produced (Scheme 29, Table 13).

In another nucleophilic alkylation approach, Seebach and associates[51] prepared an α-ethylphenylglycine derivative, **112**, using an optically active imidazolidinone (Scheme 30, **111**). The imidazolidinone was synthesized from phenylglycine ethyl or methyl ester **108** which, when treated with concentrated methyl

Scheme 27



Scheme 28

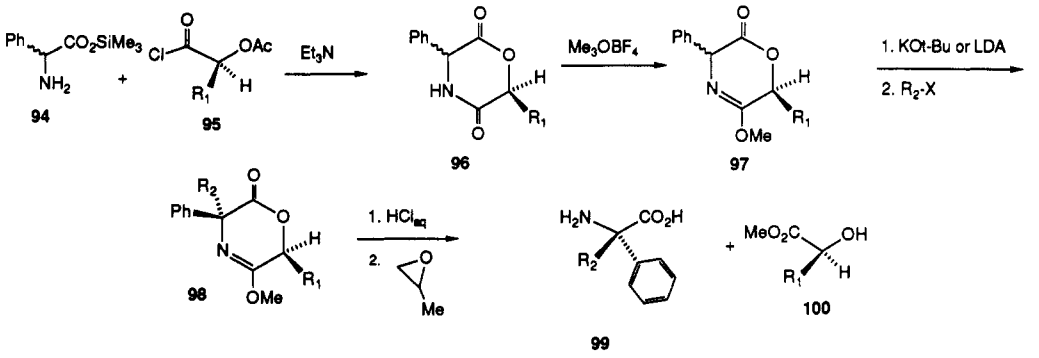


Table 11

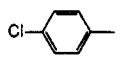
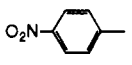
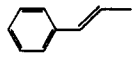
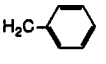
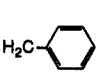
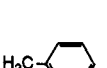
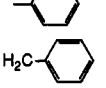
R_1	R_2	kinetic ratio (90) (2*R*:2*S*)	yield (% pure 2*R*-90)	yield (% 93)
	*t*-Bu	95:5	90	
	*t*-Bu	96:4	93	
	*t*-Bu	91:9	81	85
	*t*-Bu	97:3	92	90
	*t*-Bu	94:6	91	
	*t*-Bu	95:5	75	

Table 12

R_1	R_2	alkylation yield (98)	% de (98)	absolute config
		90	>95	*S*
		95	83	*S*
	Me	95	60	*S*
		90	>95	*S*
	Me	95	90	*S*
	Me	85	77	*S*
		91	>95	*S*
	Me	86	49	*S*

amine, formed the corresponding *N*-methyl amide. Treatment of the amide with pivaldehyde coupled with the azeotropic removal of water produced the pivaloyl imine **109**. This substance was then reacted with methanolic HCl followed by acylation with benzoyl chloride which resulted in a stereoselective ring closure to the *anti*-imidazolidinone **110** as the major product. The *syn*-imidazolidinone **111** can be formed from the same pivaloyl imine **109** when treated with benzoic anhydride at 130 °C. Enolate alkylation with ethyliodide of the *syn*-imidazolidinone **111** proceeded in 80% yield and >95% ds. The deprotection of this substrate to the amino acid was not reported. Other alkylated imidazolidinones were, however, deprotected to amino acids under quite harsh acidic conditions (6 N HCl, 175–185 °C, sealed tube).

In related work, Seebach and co-workers[52] arylated proline at the α-position via the enolate of a bicyclic animal **114** with retention of configuration (Scheme 31). To describe the observed stereochemical outcome, the authors have used the phrase "self reproduction of chirality". This term is used to describe how the proline stereogenic center controlled the relative stereochemistry in the formation of the animal stereogenic center and was, subsequently rendered planar upon the formation of the enolate **99**. The researchers believe that the conformation of the enolate **116** placed the animal methine in a pseudoaxial geometry which hindered the approach of the electrophile anti to the *tert*-butyl group. The diastereoselectivity of this process was excellent (>99%); however, cleavage of **115** to the free amino acid was not described. The authors point out that steric hindrance and stereoelectronic factors may be responsible for the reluctance of the carbonyl group in the α-alkylated heterocycles, such as

Scheme 29

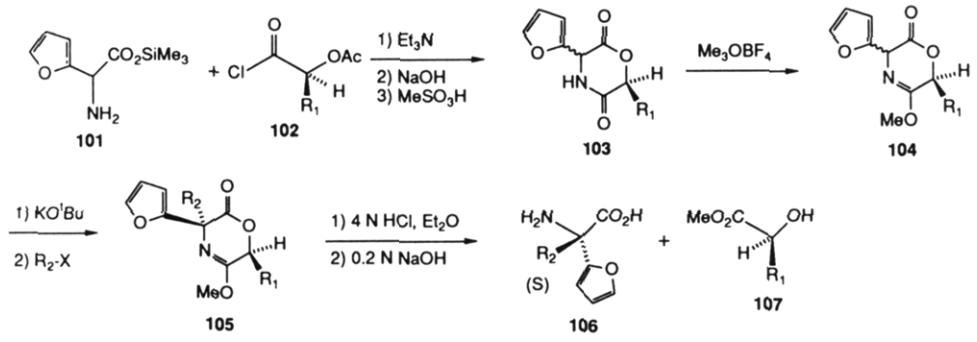
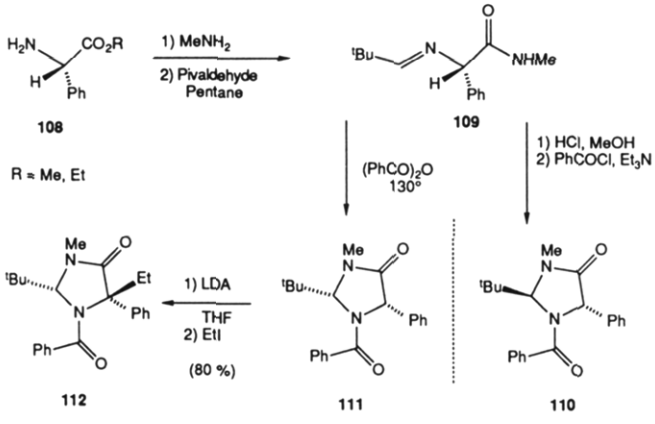


Table 13

R_1	R_2	yield (105)	config	% de (105)
i-Pr	H_2C–Ph	91	*S*	>95
i-Pr	H_2C–3-pyridyl	85	*S*	>95
i-Pr	H_2C–2-thienyl	92	*S*	>95
i-Pr	H_2C–2-naphthyl	91	*S*	>95
i-Pr	H_2C–CH=CH_2	93	*S*	70
i-Pr	CH_3	92	*S*	58
i-Pr	C_2H_5	83	*S*	61
i-Pr	$CH(CH_3)_2$	81	*S*	62
i-Pr	H_2C–cyclohexyl	75	*S*	62
t-Bu	H_2C–Ph	92	*S*	>95
t-Bu	H_2C–CH=CH_2	85	*S*	>95
t-Bu	CH_3	92	*S*	>95

Scheme 30

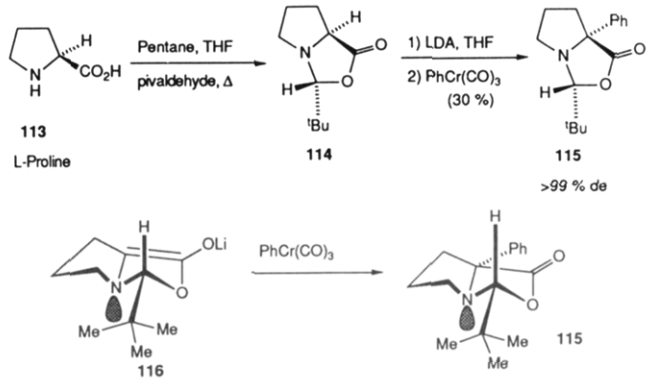


115, to form the tetrahedral intermediate under both acidic and alkaline hydrolysis conditions. Lithium amide and related lithiated amines have been shown in a few cases to effect ring opening of the bicyclic lactone hemiaminals leading to the corresponding α-alkylated amino acid amides.

3. Alkylation of Electrophilic Glycinates

The pioneering work of Kagan[26a] and Ben-Ishai[26b,c] describing racemic electrophilic glycine equivalents primarily for Friedel–Crafts type of C–C bond-forming reactions has been recently translated into several asymmetric versions.

Scheme 31



Schöllkopf and co-workers[53] found that chlorination of the enolate derived from the Val-Gly bis-lactim ether **117** with hexachloroethane provided the labile chloride **118** as a 94:6, cis/trans mixture (Scheme 32, Table 14). The authors found that **118** was labile to elimination of HCl forming the corresponding aromatic 2,5-dimethoxy-3-isopropylpiperazine (**122**); thus immediate condensation of **118** with various electron-rich aromatic compounds in the presence of tin(IV) chloride in methylene chloride gave the anti adducts **119** in good yields. Hydrolysis of these substances in dilute hydrochloric acid gave the arylglycines **120**/**121** in good yields and ~84 to >95% ee. The well-known propensity of arylglycines to racemize illustrates that the present methodology is a potentially powerful means to access these difficult amino acids in optically active form. The major drawback to the electrophilic bis-lactim ether **118** is the lability and unwelcome aromatization to **122** which accompanies the desired coupling products.

In another example, Obrecht and co-workers[54] employed the 8-phenylmenthyl ester **123** to synthesize *N*-*t*-BOC-phenylglycine (**127**). The 8-phenylmenthyl ester was brominated with NBS giving a 1:1 mixture of the bromide **124** that was used immediately without purification. The addition of the phenyl Grignard reagent promoted the elimination of HBr from the phenylmenthyl ester yielding a putative imine which, in turn, was attacked by the Grignard reagent from the less hindered face. The authors indicated that their attempts to remove the chiral auxiliary via hydrolysis or transesterification without racemization failed. Therefore, the authors developed a reductive method using LAH which did indeed cleave the chiral auxiliary but gave the amino alcohol **126**. This substance was successfully oxidized to the *N*-*t*-BOC-phenylglycine (**127**) with ruthenium (Scheme 33).

Harding and Davis[55] developed another optically active electrophilic glycinate by using a camphor sul-

Scheme 32

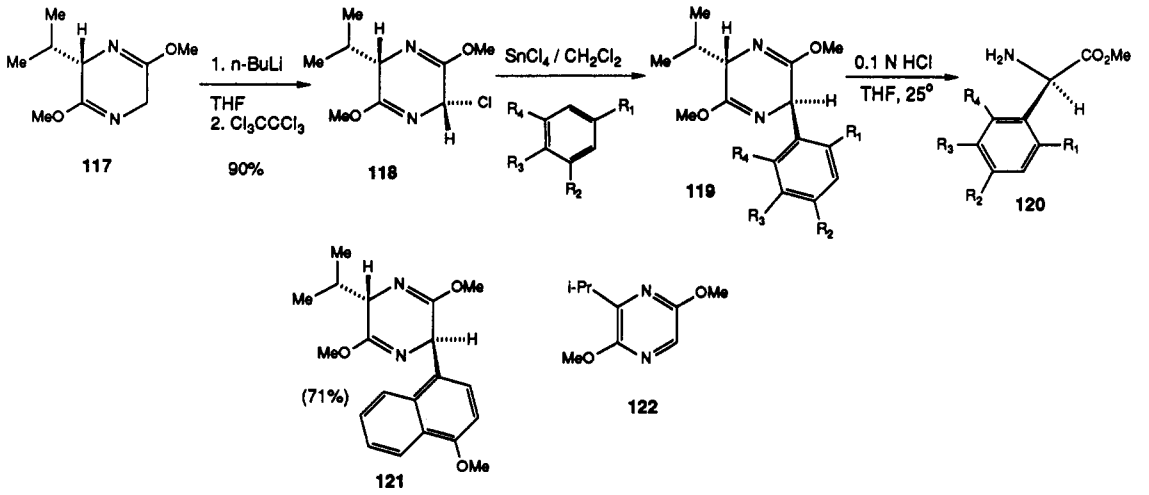


Table 14

R_1	R_2	R_3	R_4	yield (% 119)	yield (% 120)	% ee (120)
OEt	H	OEt	H	65	89	>95
OMe	OMe	H	OMe	67	60	>95
H	OMe	H	H	62 (11.5:1; *p*:*o*)	69	~84
OMe	H	H	H			

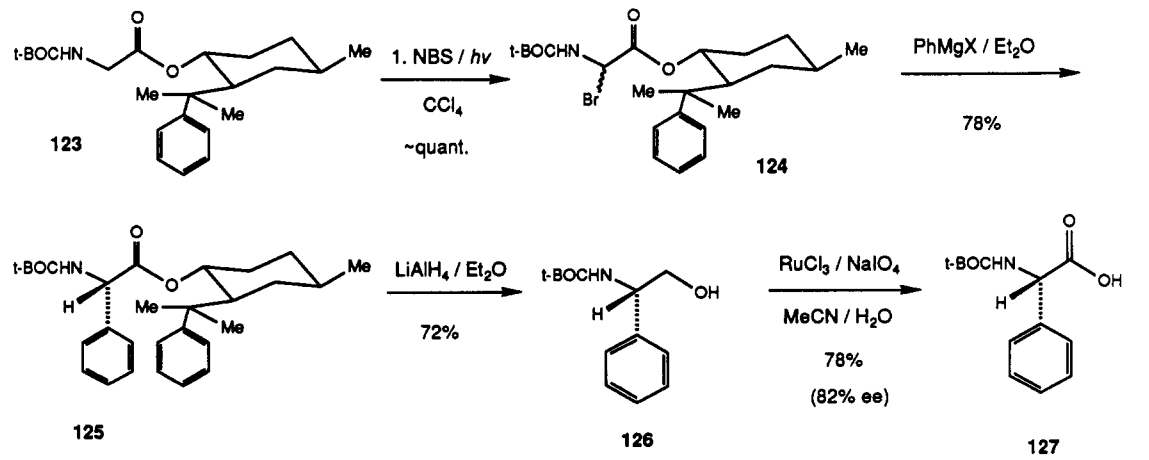
tam chiral auxiliary **128** originally developed by Oppolzer. The camphor sultam **128** was functionalized in three steps, in excellent yield, to the electrophilic glycinate **130** as a mixture of diastereomers. The electrophilic glycinate **130** was then reacted with anisole and boron trifluoride etherate in quantitative yield in a >96:4 mixture of diastereomers **131** (Scheme 34). As seen previously with other hindered esters, the authors found that hydrolytic cleavage of the chiral auxiliary without racemization was a problem.

Seebach and Schickli[56] have recently explored the Friedel–Crafts arylation of bromoglycinate **133** with resorcinol dimethyl ether as shown in Scheme 35. The syn-arylation product **134** was obtained in modest yield; conversion of **134** to the free N-methylated amino acid was not described.

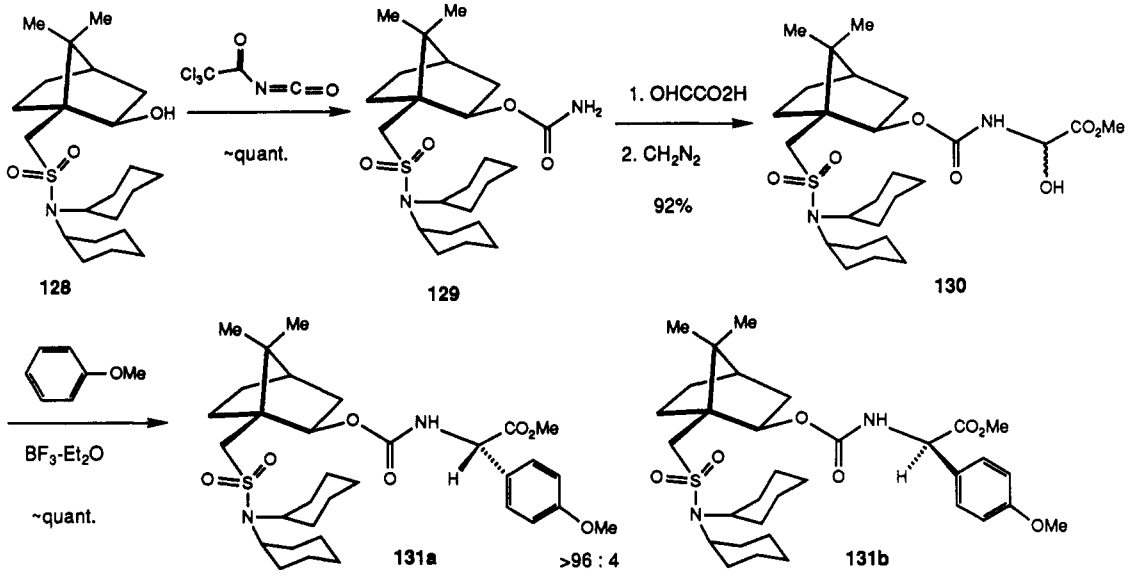
Williams and Hendrix[57] have exploited the glycinates **135** and **139** for the synthesis of a variety of arylglycines. As illustrated in Scheme 36 (Table 15), glycinate **135** is brominated with NBS in warm carbon tetrachloride to furnish the bromide **136**. Reaction of this material with either an arylcuprate or electron-rich aromatic under Friedel-Crafts conditions provides the anti-arylated substances **137**. Cleavage of the chiral auxiliary posed an interesting selectivity problem since **137** contains three potentially reducible benzylic bonds and the newly formed aryl C–N benzylic bond must survive this process. The authors found that the oxidative cleavage protocol devised by Weinges[45] (see Scheme 23) for a related oxazinone cleavage problem effected the selective removal of the (diphenylamino)-ethanol residue without disturbing the arylglycine moiety. The *t*-BOC group is first removed from **137** with trimethylsilyl iodide followed by hydrolytic ring opening of the lactone. Treatment of the resulting hydroxy acid with sodium periodate at pH 3 removes 2 equiv of benzaldehyde leaving the free amino acids **138**. Varying amounts of partial racemization accompany the final deprotection as diastereochemically homogeneous materials (**137**) are obtained from the couplings to **136**. These were reported to be quite substrate dependent and consistent for each substance on repeated processing.

It was also found that the *N*-CBz substrate **139** (Scheme 37) could be converted into 2-furylglycines (**142**/**143**) by a selective three-step method involving: (1) selective removal of the *N*-CBz group with 5% Pd–C/H_2 at atmospheric pressure; (2) ring opening of the lactone; and (3) periodate cleavage. It is noteworthy that the furan ring is not saturated in the first step, nor

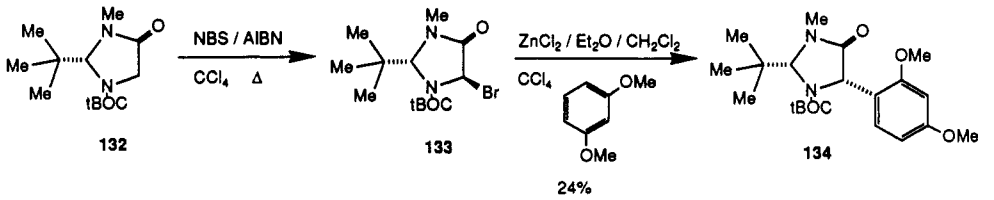
Scheme 33



Scheme 34



Scheme 35



Scheme 36

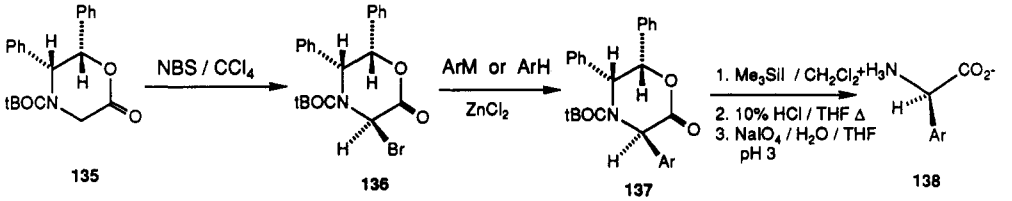


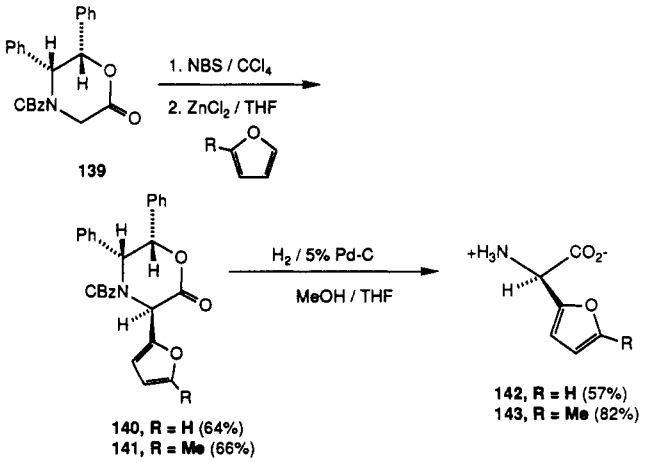
Table 15

	ArM/ArH	conditions	yield (% 137)	yield (% 138)[a]	% ee (138)
a	$(\bigcirc)_2CuLi$	Et_2O/THF, −78 °C 1 h	56	52	82
b	$(\text{naphthyl})_2CuLi$	Et_2O/THF, −78 °C 1.5 h	55	29	94
c	2,5-dimethoxyphenyl	$ZnCl_2$/THF, 25 °C 4.5 h	83[b]	62	91
d	2-furyl	$ZnCl_2$/THF, 25 °C 5.5 h 4A mol sieves	50	26	90
e	5-methyl-2-furyl	$ZnCl_2$/MeCN, 25 °C 4 h 4A mol sieves	39	73	93

[a] Yield for three steps. [b] Two-step yield for the lactone after TMSI removal of the *t*-BOC group.

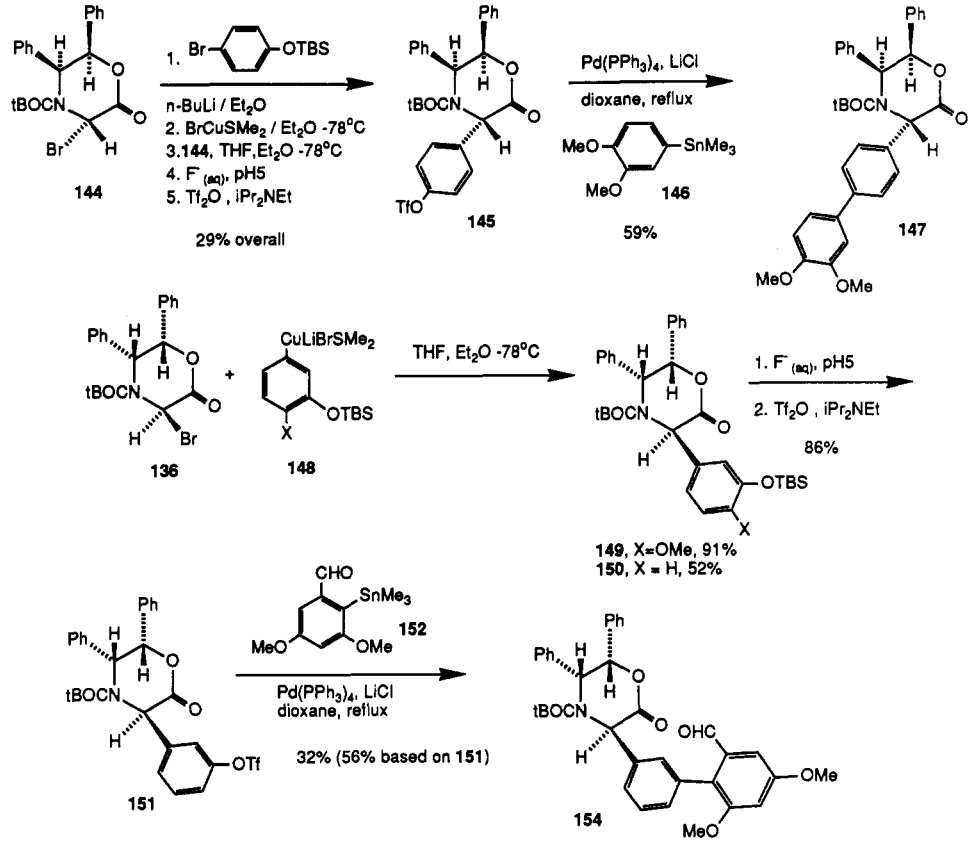
oxidized in the last step. In one remarkable instance, it was reported that the furan adducts **140** and **141** could be cleanly hydrogenated to the corresponding amino acids **142** and **143**, respectively in 57% (90% ee) and 82% (93% ee) yields, respectively. This reaction is noteworthy in that, the furan ring is not saturated nor is the "benzylic" C–N moiety of the amino acid

Scheme 37



cleaved under these conditions. Based on extensive experience hydrogenating these type of oxazinones to the amino acids, the authors note that the *N*-CBz group is cleaved first followed by the lactone C–O benzylic bond and, lastly, the C–N residue. They have been able to isolate these stepwise reduction products by carefully varying the pressure and loading of the catalyst. It would seem reasonable that the anti stereochemistry of **140**/**141** and the relative sluggishness of reducing the furan C–N benzylic residue relative to

Scheme 38



that of the benzyl C–N bond contribute to the observed selectivity in these two cases. At higher pressure on a Pd^0 catalyst, substrates **140** and **141** suffer clean conversion to the corresponding 2-tetrahydrofuranylglycine derivatives.[58] The direct hydrogenation of other α-aryl-*N*-CBz substrates corresponding to **140** were examined, but with only limited success. In most cases, small amounts (~10%) of the arylglycine can be obtained with 1 atm of H_2/Pd–C, but myriads of other products are produced. The furan substrates would seem to be an unsual (but reproducible) exception. The oxidative periodate protocol is consistently successful for all of the aryl substitutions that have been examined.

Scheme 38 illustrates some additional cuprate couplings that were part of an investigation[59] to access bisarylglycines such as that found in the glycopeptide antibiotics exemplified by vancomycin. Coupling of **144** with *p*[(*tert*-butyldimethylsilyl)oxy]phenyl cuprate proceeded in 52% isolated yield. Removal of the silyl group and conversion of the incipient phenol with triflic anhydride gave **145** in 29% overall yield from **144**. The cuprate couplings are compatible with silyl-protected phenolic groups, and the resultant α-arylated lactones can be further manipulated with no detectable loss of stereochemical integrity. Palladium-catalyzed cross-coupling[60,61] of **145** with **146** proceeded in 59% yield with no detectable loss of stereochemical integrity. Coupling of **136** with cuprate **148**, where X = H, proceeded in 52% yield (furnishing **150**); coupling of **136** with cuprate **148**, where X = OMe proceeded in excellent yield (91%) furnishing **149**. Substrate **149** (X = OMe) is currently being further investigated for biaryl couplings with a variety of highly functionalized arylstannanes to access actinoidic acid. In one instance, compound **150** was converted into the corresponding triflate **151** and subjected to Stille biaryl coupling[60,61] to furnish **154** in 32% yield. Under identical conditions, the corresponding triflate was prepared from **149**, but unfortunately did not yield any detectable cross-coupling product with **152** under a range of reaction conditions with either palladium(0) or palladium(II) catalysts. Compound **154** is a potential substrate from which deoxyactinoidic acid might be prepared providing that an asymmetric Strecker reaction can be conducted on the congested and electron-rich aldehyde of **154**. In this context, it should be noted that there are very few successful examples of asymmetric Strecker reactions with electron-rich aldehydes. No attempt has yet been made to convert **147** or **154** into the corresponding free amino acids.[59] The additional atropisomer complications inherent in the actinoidic acid/vancomycin problem underscore the challenges inherent in these very highly functionalized arylglycines.

4. Asymmetric Electrophilic Amination of Enolates

The asymmetric electrophilic amination of enolates is a relatively recent advance in amino acid synthesis due to the general lack of electrophilic nitrogen sources. Boche and Schrott[62] developed a chiral electrophilic aminating reagent **157** which they used to synthesize phenylglycine derivatives (Scheme 39, Table 16). Their reagent was prepared from (–)-ephedrine (**155**), phosphorous oxychloride, and *N*,*N*-dimethylhydroxylamine. The enantiospecific amination with several lithio carbanions **158** was achieved yielding the *N*,*N*-dimethylphenylglycine derivative (**159**). The yields of the aminations were moderate and the % ee's were low, indicating that the nitrogen atom of **157** was too far

Scheme 39

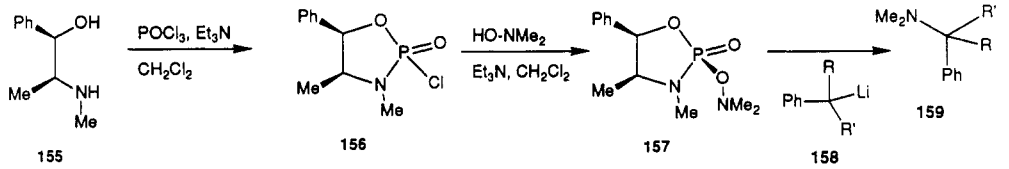


Table 16

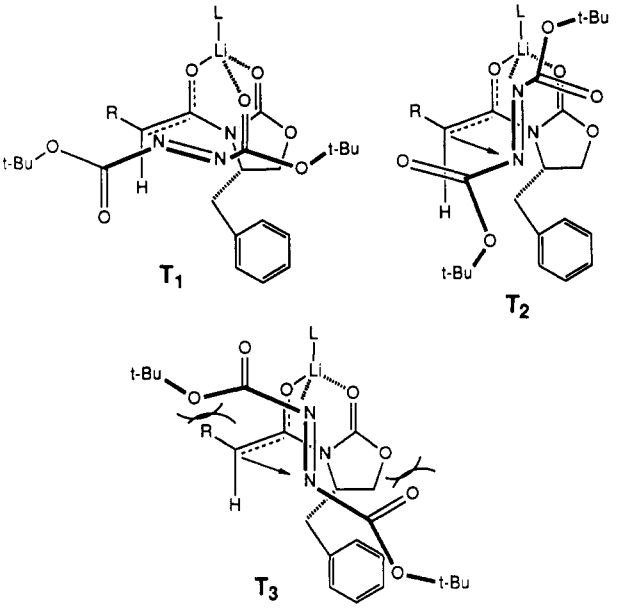
R	R′	yield (% 159)	% ee (159)
H	CO_2Et	50	23
Me	CO_2Et	56	21
H	CN	62	8

away from the P stereogenic center to exert significant diastereochemical control.

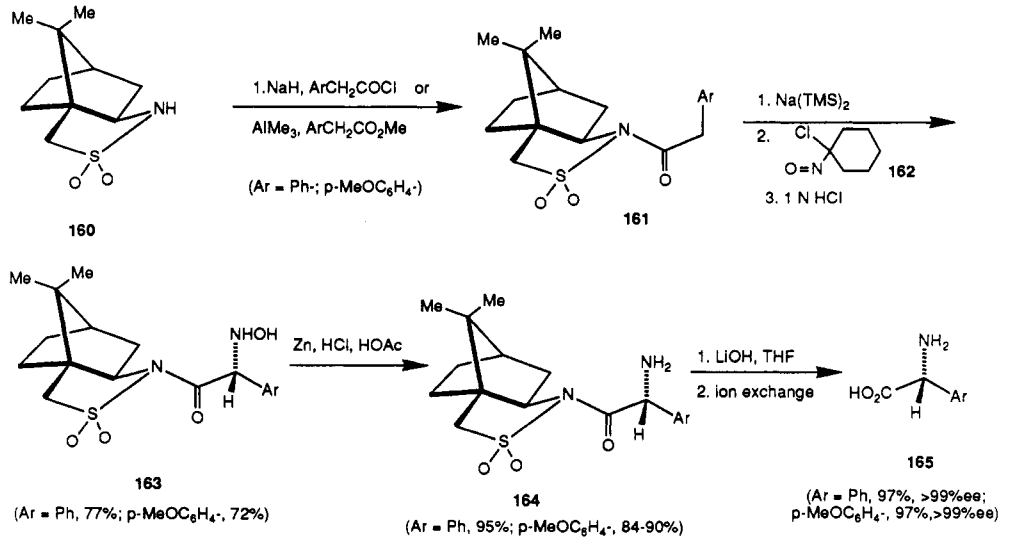
In a recent communication, Oppolzer and Tamura[63] reported the use of their sultam chiral auxiliary **160** in an electrophilic amination. The sultam was smoothly N-acylated and subsequently deprotonated with sodium hexamethyldisilazide. The chiral enolate was then aminated with 1-chloro-1-nitrosocyclohexane (**162**) yielding the desired hydroxylamine **163** after an aqueous acidic quench. The hydroxylamine was reduced to the amino sultam **164** with zinc dust. The sultam auxiliary was then cleaved and recovered after hydrolysis with aqueous LiOH which also afforded the desired arylglycines **165** in >99% ee (Scheme 40). Both *R* and *S* enantiomers of *p*-methoxyphenylglycine were selectively synthesized depending on which sultam antipode was chosen as the starting material.

Evans and associates[64] have extended the use of their chiral carboximide enolates to electrophilic aminations in the synthesis of amino acids. The chiral carboximide enolate of **166** was generated with LDA and aminated with di-*tert*-butyl azodicarboxylate (**167**) to give a 97:3 ratio of diastereomers. Hydrolysis of the hydrazide **168** with LiOH produced the hydrazido acid **169** with no perceptible racemization. However, attempts to transesterify the hydrazido acid **170** produced significant racemization. Therefore, an alternate deprotection was developed in which the hydrazido acid **170** was esterified with diazomethane followed by trifluoroacetic acid cleavage of the *t*-BOC group. The resulting solution was carried on directly and subjected to Raney nickel hydrogenation yielding an impure product that was acylated with (+)-MTPA chloride yielding **171** (Scheme 41).

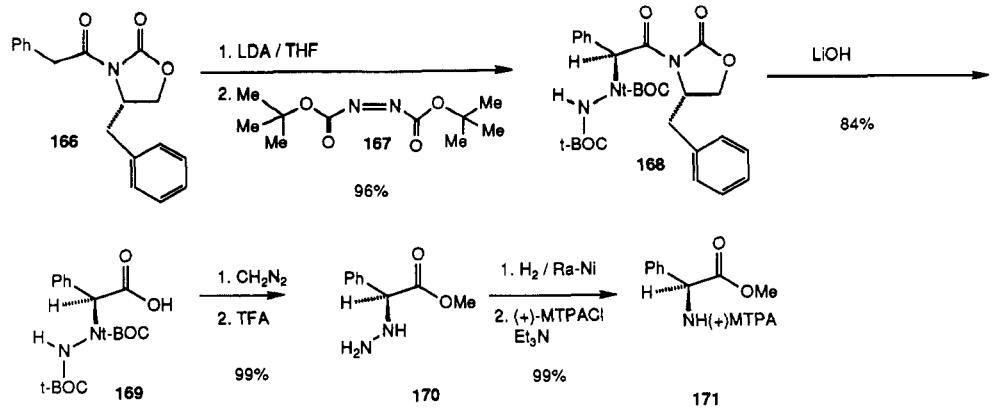
Diastereomeric analysis of the resulting Mosher's amide **171** by gas chromatography showed a 99:1 mixture of isomers. In an attempt to explain the stereochemical outcome of the amination reaction, the authors considered three possible chelated transition states, T_1, T_2, and T_3. In T_1, an 8-centered transition state is formed by chelation of lithium to the oxygen of the azodicarboxylate; in T_3, lithium chelates to one of the nitrogen atoms of the azodicarboxylate, forming a Zimmerman–Traxler-type 6-centered pericyclic transition state; however, the authors favor T_2 for stereoelectronic reasons.



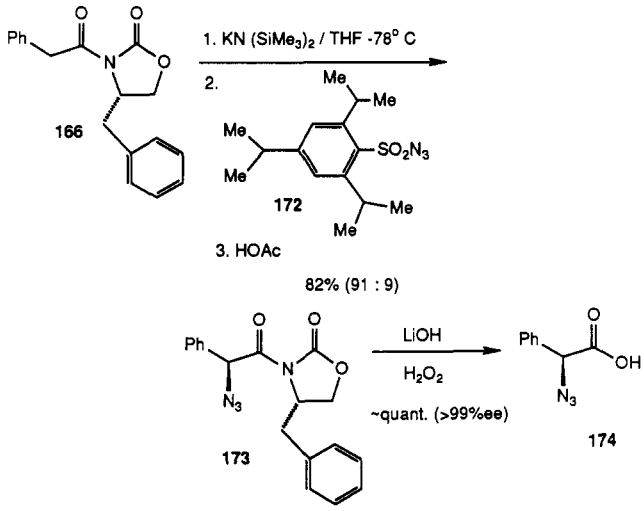
Scheme 40



Scheme 41



Scheme 42



In related work, Evans and Britton[65] generated the enolate of optically active carboximide **166** with potassium hexamethyldisilazide. A diastereoselective azidation was achieved with the use of 2,4,6-triisopropylsulfonyl azide ("trisyl azide", **172**) yielding the α-azidocarboximide (**173**) after a glacial acetic acid quench. The chiral auxiliary was removed via LiOH hydrolysis which afforded the desired α-azido acid **174** without racemization (Scheme 42). A more complete study of this transformation was recently published with full experimental details.[69]

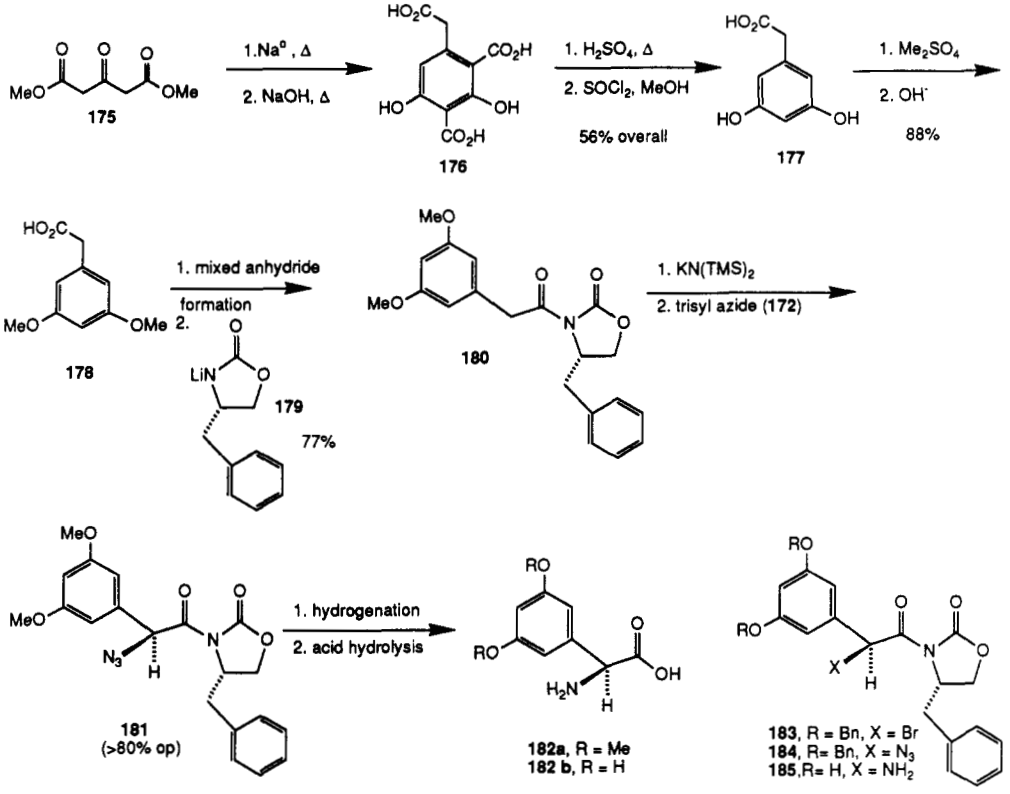
Williams and co-workers,[66] have employed the Evans' carboximide azidation protocol to prepare racemic 3,5-dihydroxyphenylglycine and optically active 3,5-dimethoxyphenylglycine derivatives as shown in Schemes 43 and 44. The key diastereoselective azidation of **180** proceeded in unspecified yield furnishing **181**; hydrogenation of the azide and hydrolysis of the chiral auxiliary furnished **182a** in >80% optical purity. Cleavage of the methyl ethers with a variety of reagents was reported to be unsuccessful. An analogous series of transformations was attempted with benzyl ethers in place of methyl ethers, but the attempted azidation with trisyl azide gave only the triazine adduct which could not be broken down to the azide. In another approach, the bisbenzyl ether derivative of **180** was converted into the boron enolate and brominated with NBS (**183**); azide displacement with tetramethylguanidinium azide gave a 2.8:1 ratio of diastereomeric azides **184** which were separated and hydrogenated to **185**. Attempted coupling of **185** to an N-protected tyrosine was reported to fail, presumably due to interference by the side chain phenols. Finally, a racemic synthesis of 3,5-dihydroxyphenylglycine was performed from the bis-*tert*-butyldimethylsilyl ether *tert*-butyl ester derived from **177**. Enolate deprotonation with LDA followed by trisyl azide azidation and reduction proceeded in 57% overall yield (**186**). Sequential treatment of **186** with pyridine–acetic acid and tetra-*n*-butylammonium fluoride afforded 3,5-dihydroxyphenylglycine (**182b**). Attempted resolution of this substance by co-crystallization with chiral acids proved unsuccessful. However, **186** could be coupled to tyrosine derivative **187** furnishing diastereomers **188** that could be separated by chromatography. The difficulties encountered in this study clearly demonstrate the severe challenges associated with the arylglycine moieties present in the vancomycin antibiotics.

Very recently, Evans and co-workers[67] have improved the procedure to azidate the carboxamide enolates as shown in Scheme 45 (Table 17). Use of potassium hexamethyldisilazide in THF at low temperature followed by addition of trisyl azide and quenching with acetic acid at low temperature, affords the corresponding triazenes **190**. These are generally not isolated and decompose to the azides **191** when warmed to room temperature. The authors note that the potassium acetate generated in the quench is responsible for the triazene decomposition. Table 16 shows a variety of specific substrates that have been subjected to this procedure. In one case (**189g**), it was found that the triazene was stable to the standard decomposition conditions and could be isolated in 65% yield by chromatography. Subjecting this substance (generated via the lithium enolate) to sodium iodide and sodium acetate provided the desired azide (**191g**) in 61% yield with 92:8, *R*/*S* diastereoselection. The procedure developed in this work has led to the synthesis of several very highly functionalized arylglycines related to the vancomycin class.

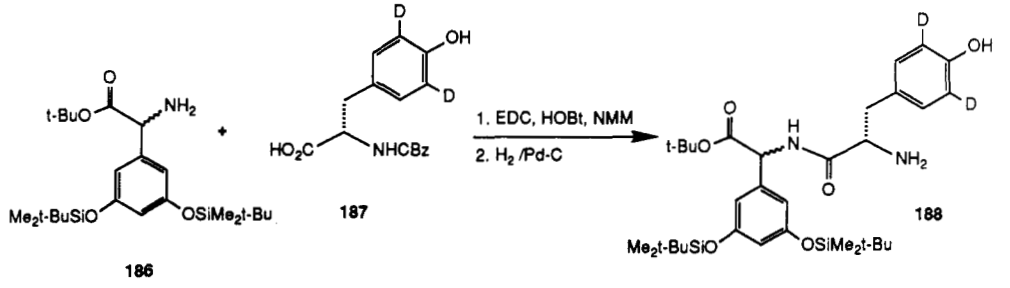
5. Asymmetric Nucleophilic Amination of α-Substituted Acids

Another approach to amino acids has been the displacement of a leaving group α- to a carboxylic acid by a nucleophilic amine equivalent. The Evans group[67-69] has utilized this strategy through the use of their optically active carboximide enolates (Scheme 46). The chiral carboximide **193** is converted to the di-*n*-butylboron enolate **194** in a reaction with the corre-

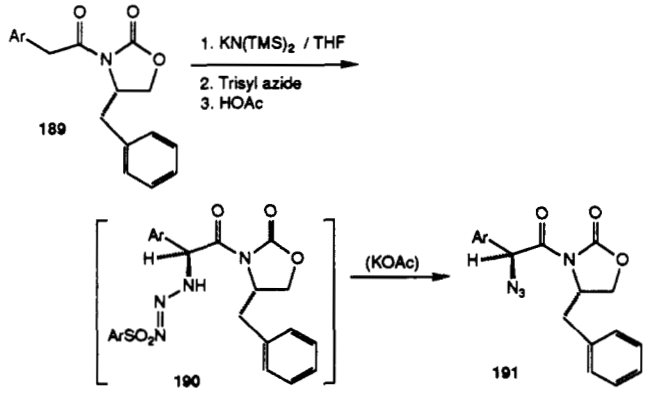
Scheme 43



Scheme 44



Scheme 45



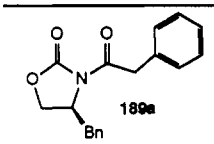
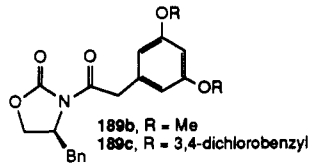
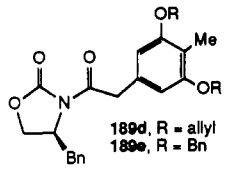
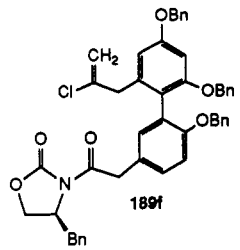
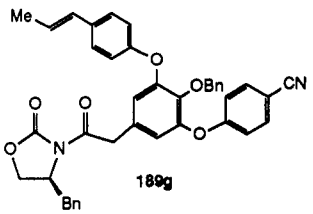
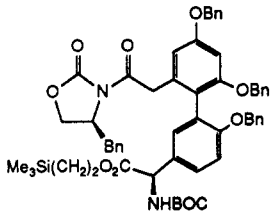
sponding triflate and an amine base. The boron enolate **194** is oxidized with NBS yielding the α-bromo carboximide **195** with moderate stereocontrol. Tetramethylguanidinium azide displaces the bromide cleanly giving the desired azide **196** in 67% yield and a 78:22 ratio of diastereoisomers. The azido carboximide was then deprotected in a variety of ways. Basic hydrolysis with lithium hydroxide gave the azido acid **198** without racemization. In contrast, transesterification to the benzyl ester with titanium(IV) benzyloxide showed evidence of epimerization (**199**, 82:18 ratio observed). The azido carboximide (**196**) was also reduced to the amine via hydrogenation and was subsequently acylated with (+)-MTPACl. The acylated phenylglycine derivative **200** was also saponified without racemization under the same conditions as above, yielding the acylated phenylglycine **201**. The transesterification of **200** using the same conditions as above, yielded the desired benzyl ester **199** also without loss of stereochemistry (Scheme 46).

In another nucleophilic amination, Ottenheijm and associates[70] produced *N*-(benzyloxy)phenylgycine methyl ester (**205**) via *O*-benzylhydroxylamine displacement of a triflate (**204**). The optically active α-hydroxy acid **203** was converted to the triflate **204** with triflic anhydride and lutidine. Substitution of the triflate **204** with *O*-benzylhydroxylamine yields the phenylglycine derivative (**205**) with inversion in 88% yield and 76% ee, (Scheme 47).

6. Miscellaneous Enantioselective Arylglycine Syntheses

In a very useful application of the Sharpless asymmetric epoxidation, Sharpless and co-workers[71] found that the 3-phenyl epoxy alcohol **206** could be regiospe-

Table 17

substrate	azidation conditions	triazene decomposition conditions	stereoselection (S:R)	yield (% 91)
 189a	1.1 equiv $KN(TMS)_2$/THF −78 °C; 1.2–1.3 equiv trisyl azide, −78 °C; then 5 equiv HOAc	25–30 °C, 30 min	91:9	(*S*) 82
 189b, R = Me 189c, R = 3,4-dichlorobenzyl	1.1 equiv $KN(TMS)_2$/THF −78 °C; 1.2–1.3 equiv trisyl azide, −78 °C; then 5 equiv HOAc	30 °C, 2 h 30 °C, 1 h	90:10 88.12	(*S*) 78 (*S*) 76
 189d, R = allyl 189e, R = Bn	1.1 equiv $KN(TMS)_2$/THF −78 °C; 1.2–1.3 equiv trisyl azide, −78 °C; then 5 equiv HOAc	25 °C, 3 h 25–30 °C, 18 h	90:10 88:12	(*S*) 75 (*S*) 81
 189f	1.1 equiv $KN(TMS)_2$/THF −78 °C; 1.2–1.3 equiv trisyl azide, −78 °C; then 5 equiv HOAc	25 °C, 2 h	<5:95	(*R*) 77
 189g	1.5 equiv $LiN(TMS)_2$/THF −78 °C; 2 equiv trisyl azide, −78 °C; then 10 equiv HOAc	NaI (5 equiv), NaOAc (3 equiv); acetone, 25 °C, 5 h	8:92	(*R*) 61
 189h, Atropisomer A 189h, Atropisomer B	2.5 equiv $KN(TMS)_2$/THF −78 °C; 3 equiv trisyl azide, −78 °C; then 5 equiv HOAc	KOAc (10 equiv), THF; 25 °C, 16 h	>95:5 93:7	(*S*) 60 (*S*) 60

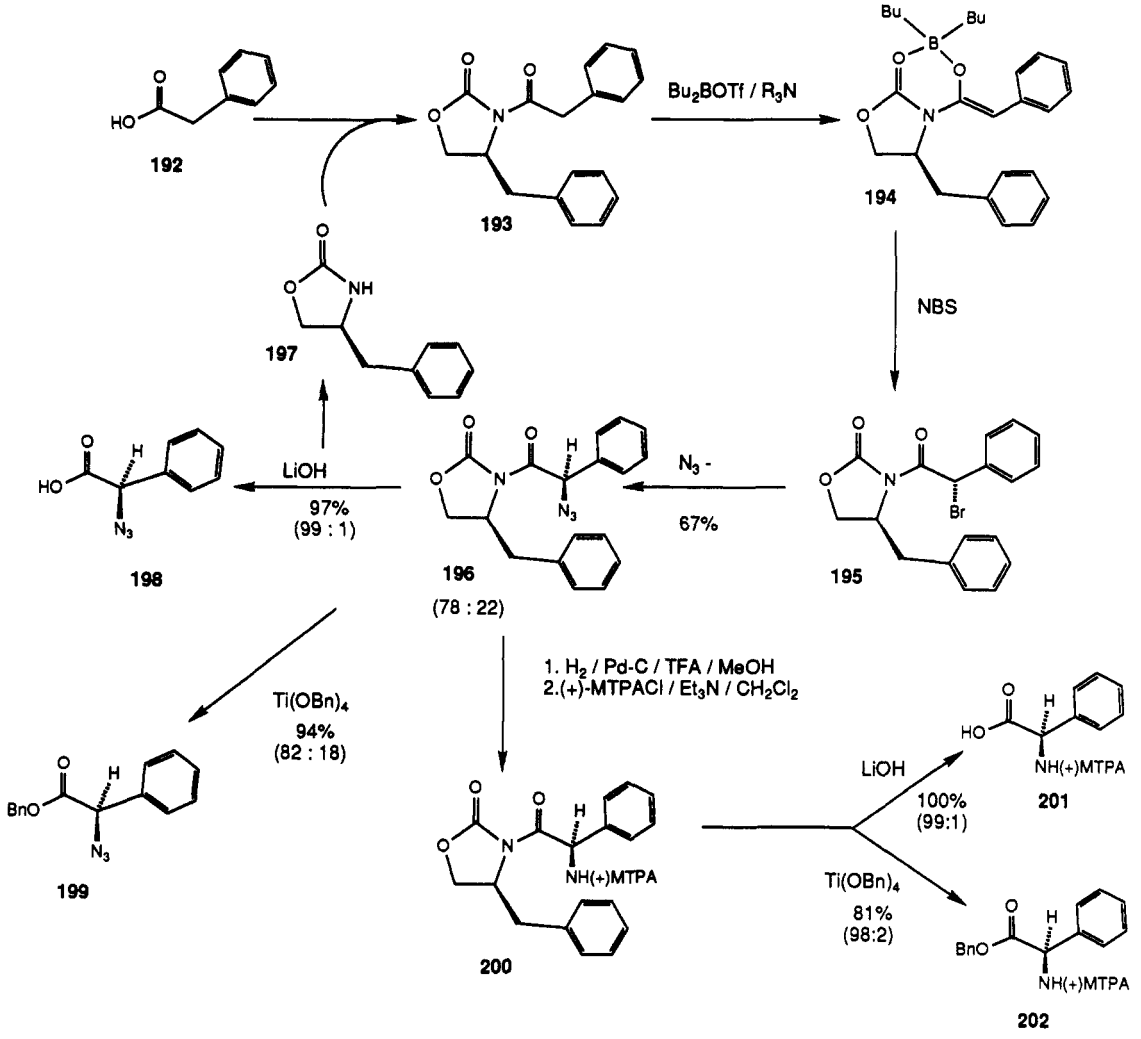
cifically opened by azide attack at the 3-position. The resulting azido diol **207** was converted to phenylglycine **209** by a ruthenium-catalyzed oxidative cleavage of the diol substituent yielding the azido acid **208**. The azide was reduced to the amine via hydrogenation with palladium on carbon which gave phenylglycine **209** in 86% ee. The slight racemization observed was attributed to the lability of the α-azido aldehyde, an intermediate in the ruthenium catalyzed oxidation (Scheme 48).

Pearson and co-workers[72a,b] have employed the addition of the Schöllkopf bis-lactim ether enolates to arene–manganese tricarbonyl complexes to prepare some oxygenated arylglycines related to the arylglycine–tyrosine biaryl subunits of the vancomycin/ristocetin antibiotics. As shown in Scheme 49, addition of lithiated bis-lactim ether **210** to the arene–manganese tricarbonyl complexes **211a–c** affords the anti-arylation adducts **212a–c** in good yield. NBS oxidation removes the manganese providing the anti-aryl products **213a–c** in moderate to good yields and 70–95% de. Cleavage of the bis-lactim ether with dilute hydrochloric acid provides the arylglycines **214a–c** in high yields.

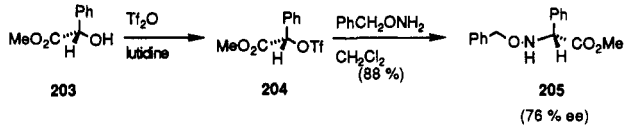
Extending this chemistry to the manganese-mediated aryl ether coupling (Scheme 50) provides the tyrosine complex **217**. Lithiated bis-lactim ether addition to this complex provides the undesired ortho and desired meta isomers **218** and **219** (1:10 ratio, 49% combined yield and 65% de for **219**), respectively. Hydrolysis of the bis-lactim ether as above provided the interesting biaryl ethers **220** but in somewhat low yield (28–30%).

These strategies were further examined for the preparation of an analog of ristomycinic acid as shown in Scheme 51. Coupling of complex **221** with *m*-hydroxyphenylglycine derivative **222** afforded the biaryl ether complex **223**. Demetalation of **223** with aceto-

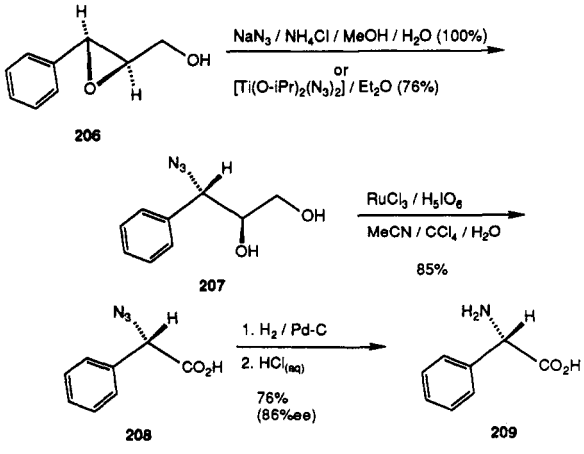
Scheme 46



Scheme 47



Scheme 48



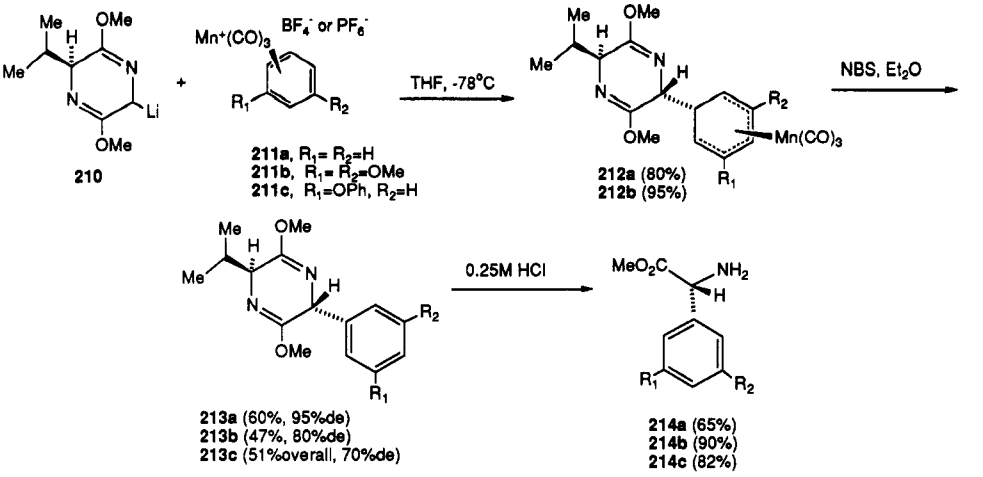
nitrile provided **224** which proved to be optically pure by chiral shift NMR. Coupling of **223** with the Schöllkopf nucleophile (**210**) furnished adduct **225** as a separable 3:1 diastereomeric mixture in 35% overall yield. Mild acid hydrolysis of the bis-lactim ether and removal of the BOC group with TFA provided the deoxy ristomycinic acid derivative **226** in 59% yield. NMR studies indicated that no racemization accompanied the bis-lactim ether hydrolysis at the trisubstituted arylglycine subunit.

Related racemic[72c] and asymmetric[72d] electrophilic arylations have recently appeared, indicating that this approach will continue to be developed as a viable method for preparing functionalized arylglycines.

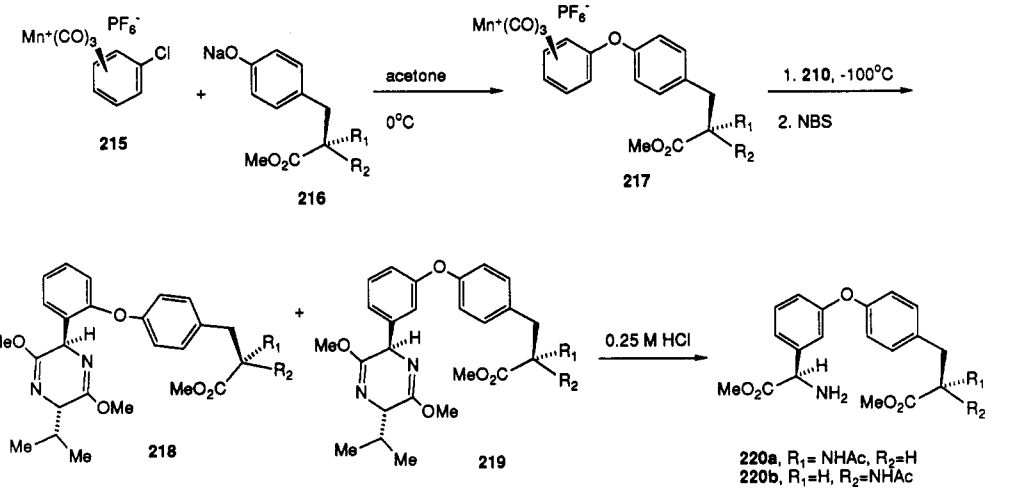
Hobbs and Still[73] have recently examined the radical coupling of diiodophenylglycine derivatives to access novel bis-thioether analogs of the central core unit of ristocetin (Scheme 52). Reaction of **227** with thiophenol at −33 °C under sunlamp irradiation gave a good yield of the bis-phenyl thioether **228**, but was totally racemized. When the BOC group is removed from **227** (yielding **229**), the reaction proceeds in high yield but, significantly, without racemization. Extending this reaction to the thiotyrosine (**231**) coupling, **232** was obtained in >95% yield. Compound **232** is an interesting analog of the central bis-aryl ether unit of the vancomycin group. The authors note that these substances differ from the natural oxygen analogs primarily by the longer C–S bonds (1.72 vs 1.36 Å) and the lower barrier to rotation (1 kcal/mol for thioanisole vs 5 kcal/mol for anisole).

Yamamura[74] and associates have developed a useful thallium(III) trinitrate (TNN) oxidative coupling re-

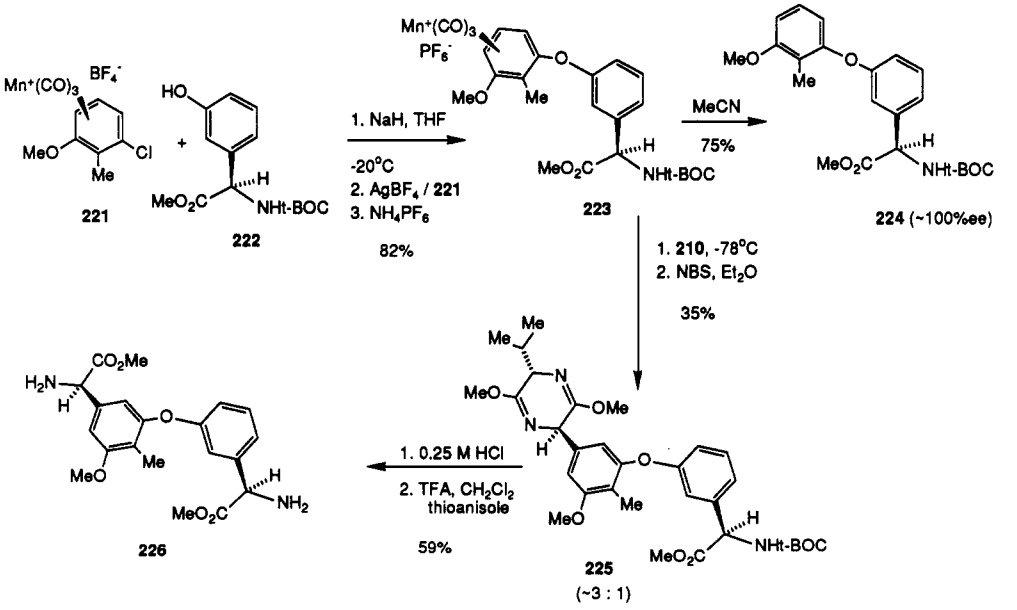
Scheme 49



Scheme 50

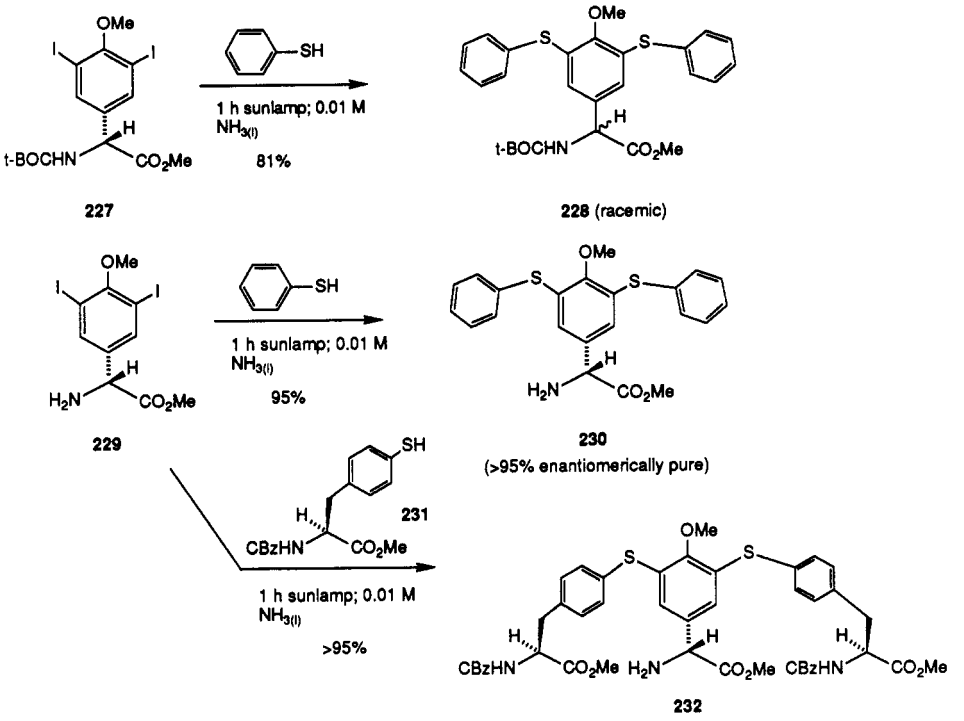


Scheme 51

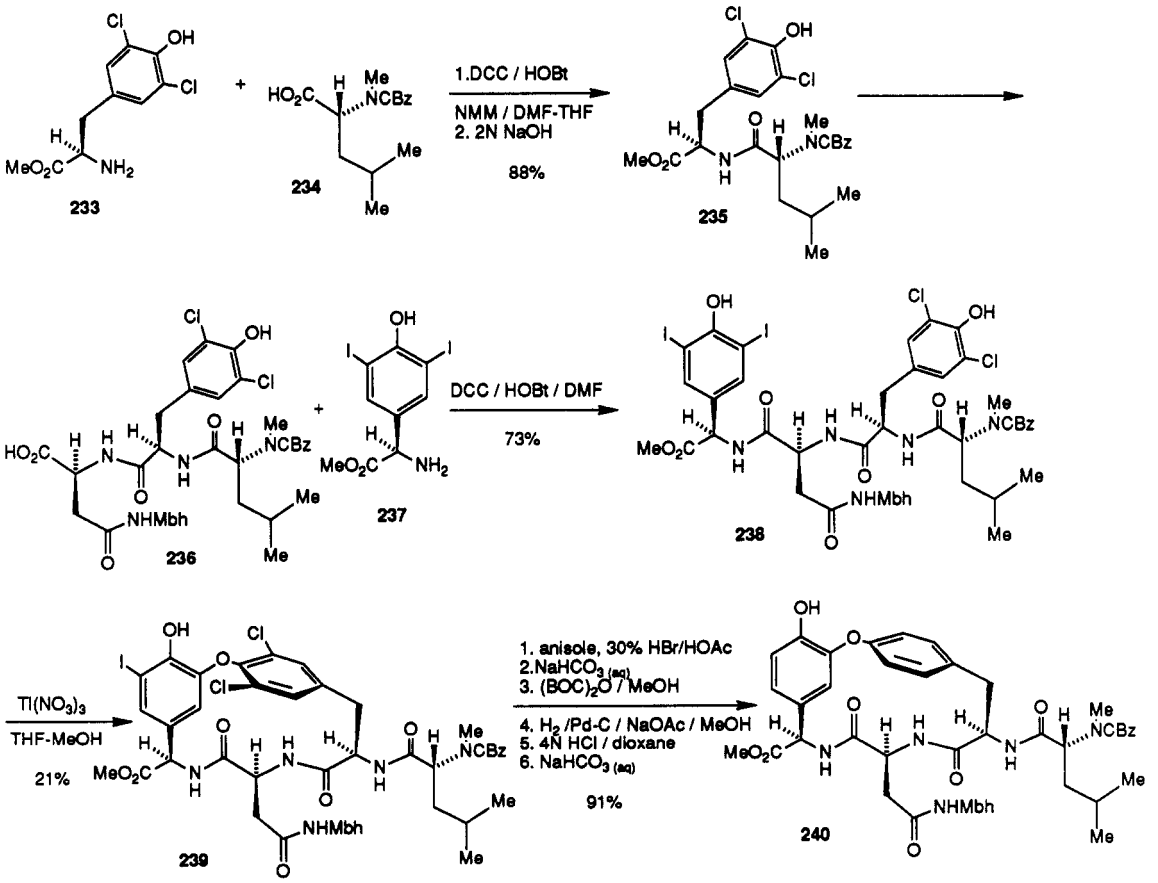


action to construct the bis-aryl ether subunits of the vancomycin family. As shown in Scheme 53, tetrapeptide **238** is built up utilizing DCC peptide couplings. The key thallium(III) trinitrate coupling provided the macrocyclic ether **239** in 21% yield (characterized as the corresponding free Asn amide). The authors note that, unlike their related synthesis[75] of K-13, epimerization of the arylglycine moiety does not take place. In the K-13 system, the TNN oxidation affords an incipient (and racemization-prone) dienone that is subsequently reduced with zinc to the biaryl. No explanation is offered for the differences between these

Scheme 52



Scheme 53

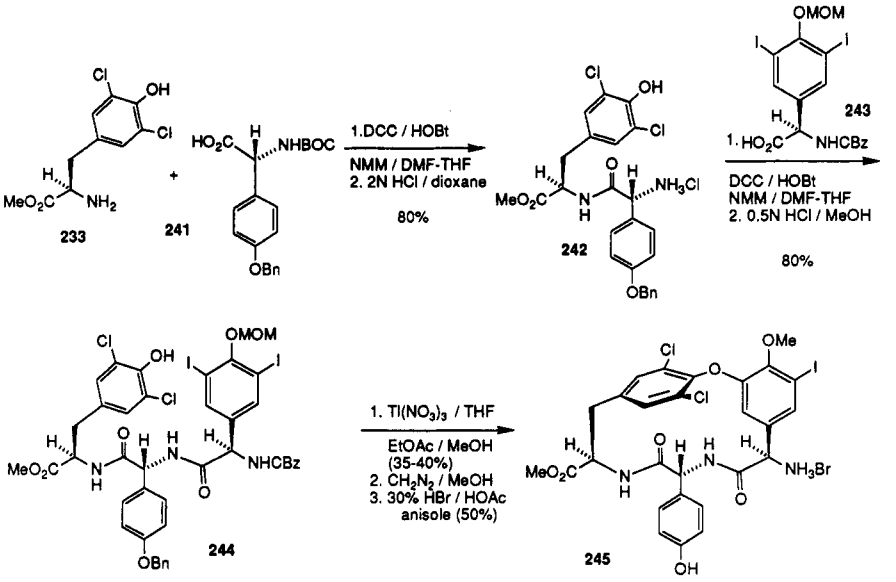


systems with respect dienone formation. Final reductive processing and protecting group manipulations furnishes the tetrapeptide **240** in high yield.

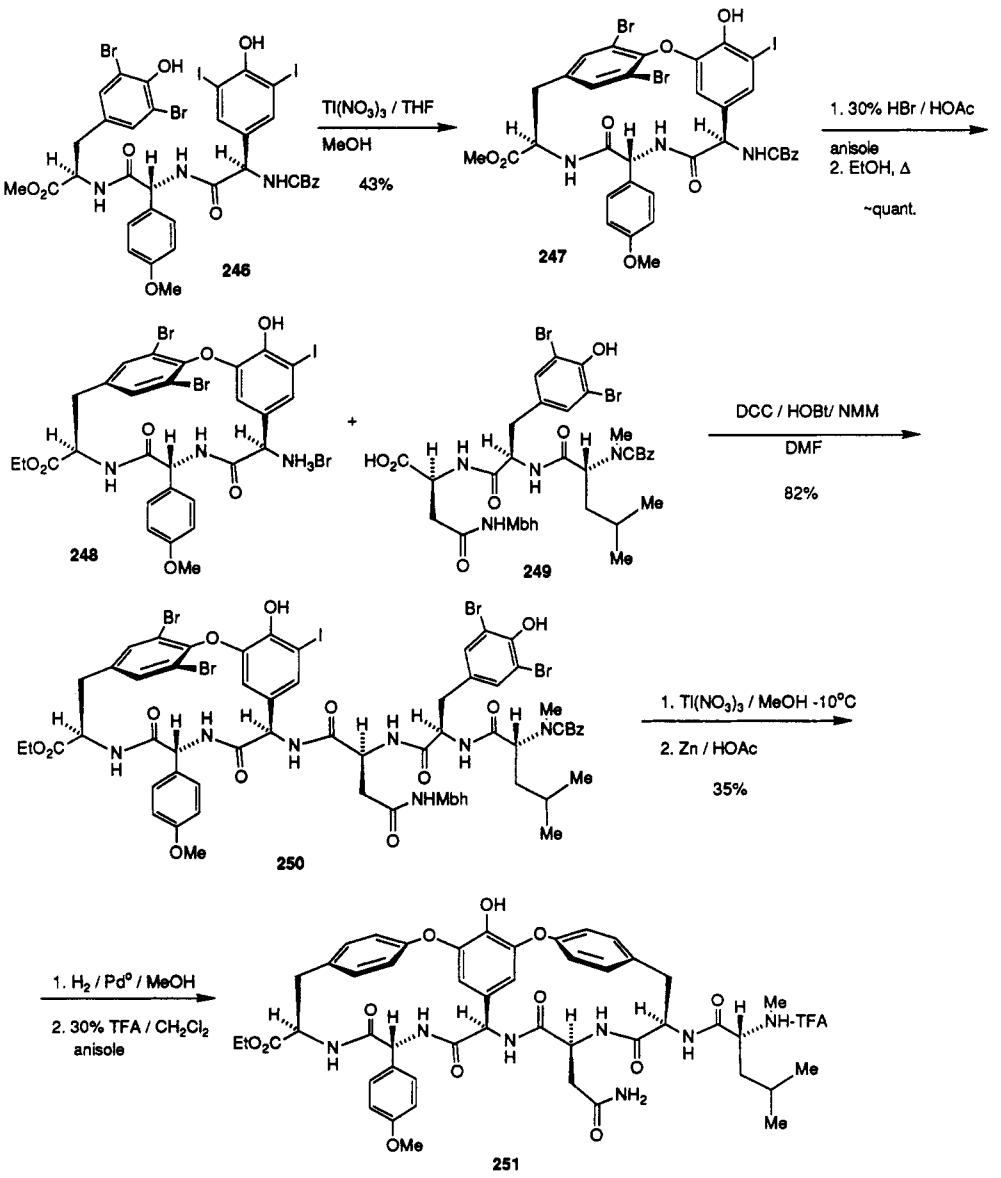
Using the same protocol, the macrocycle **245**, corresponding to the top left-hand portion of the vancomycin structure was synthesized as depicted in Scheme 54. As above, the TNN oxidation proceeded to give the desired macrocyclic bis-aryl ether framework in 35–40% yield without the appearance of the dienone which is presumably an intermediate in all of these couplings.

In an impressive combination of the above two subunits, Yamamura and associates[74] constructed a macrobicyclic aryl diether which closely resembles the entire top half of the vancomycin structure as shown

Scheme 54

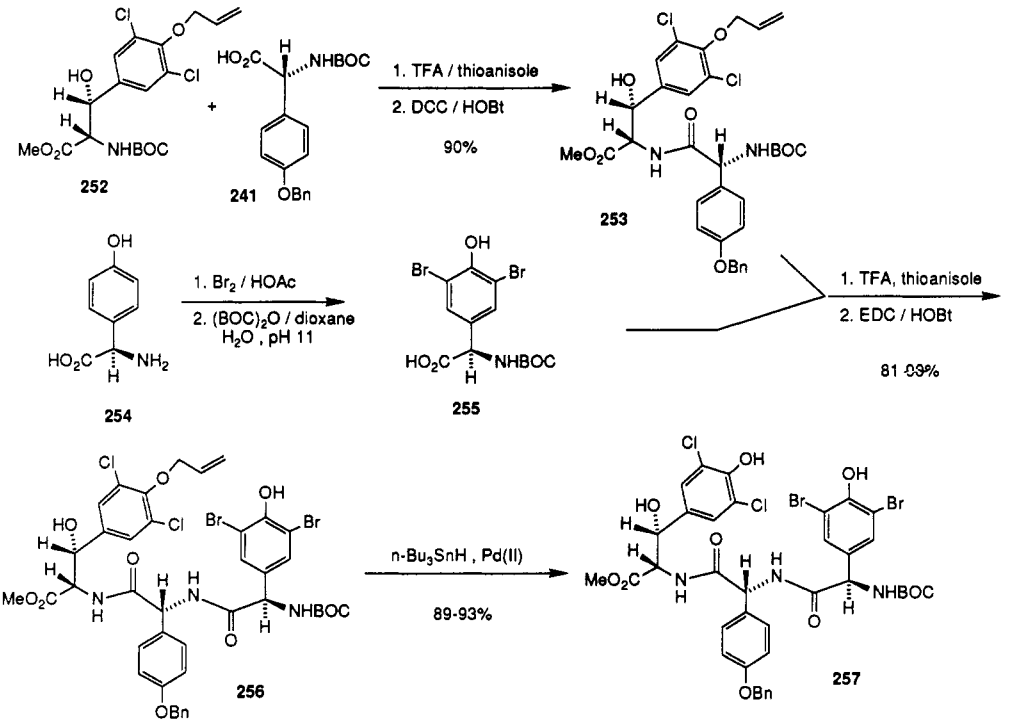


Scheme 55

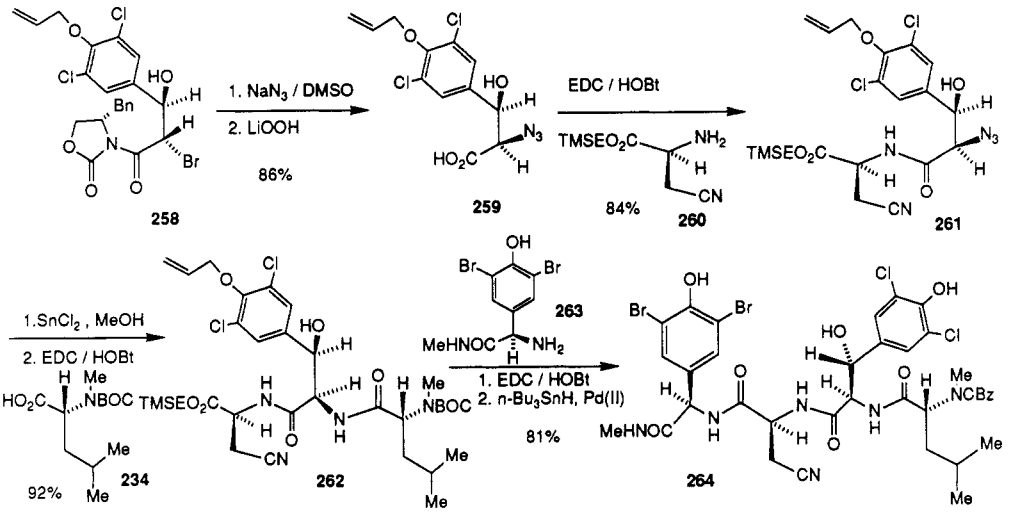


in Scheme 55. Oxidative cyclization of **246** (prepared in a similar fashion to that described in Scheme 54) with TNN afforded macrocycle **247** in 43% yield without a reductive workup. Coupling of the derived

Scheme 56



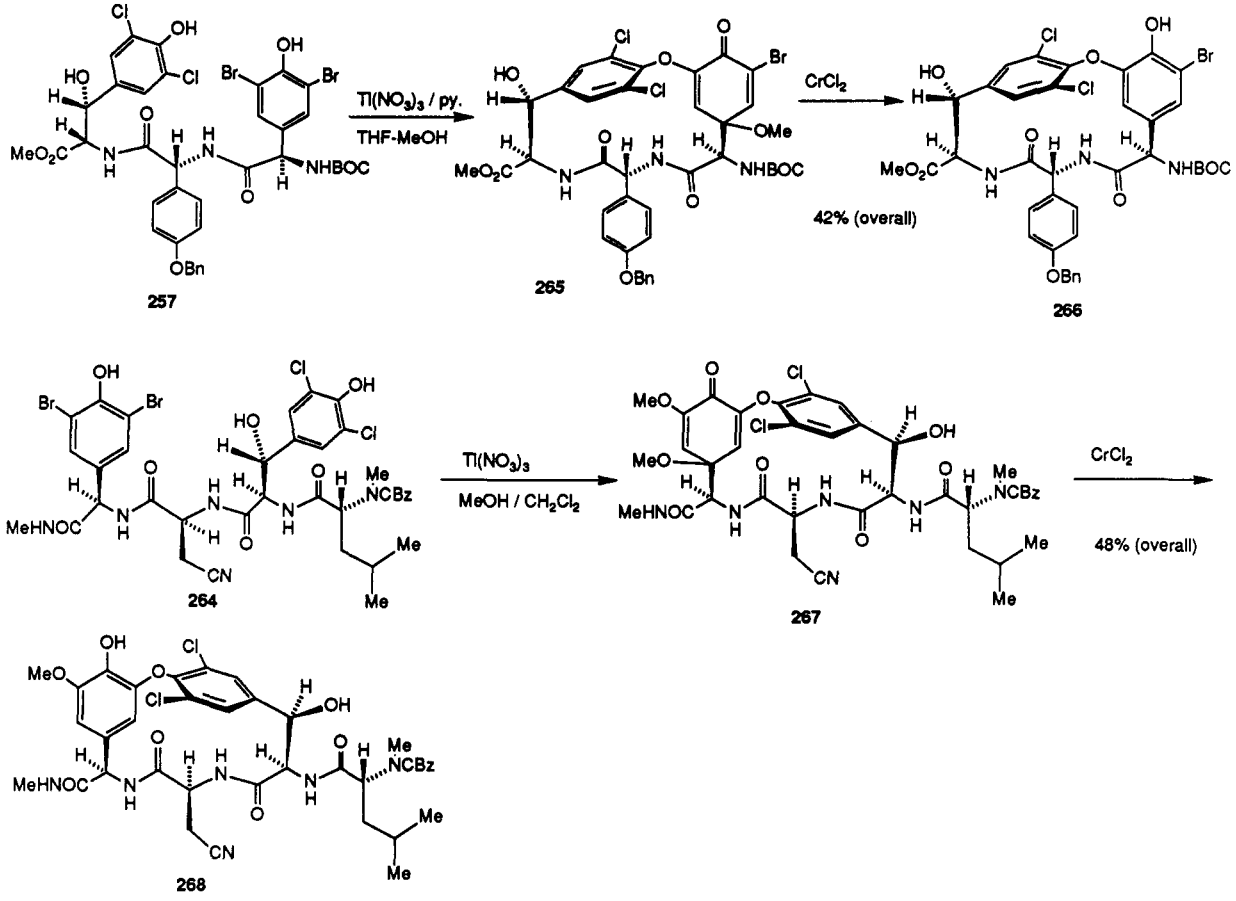
Scheme 57



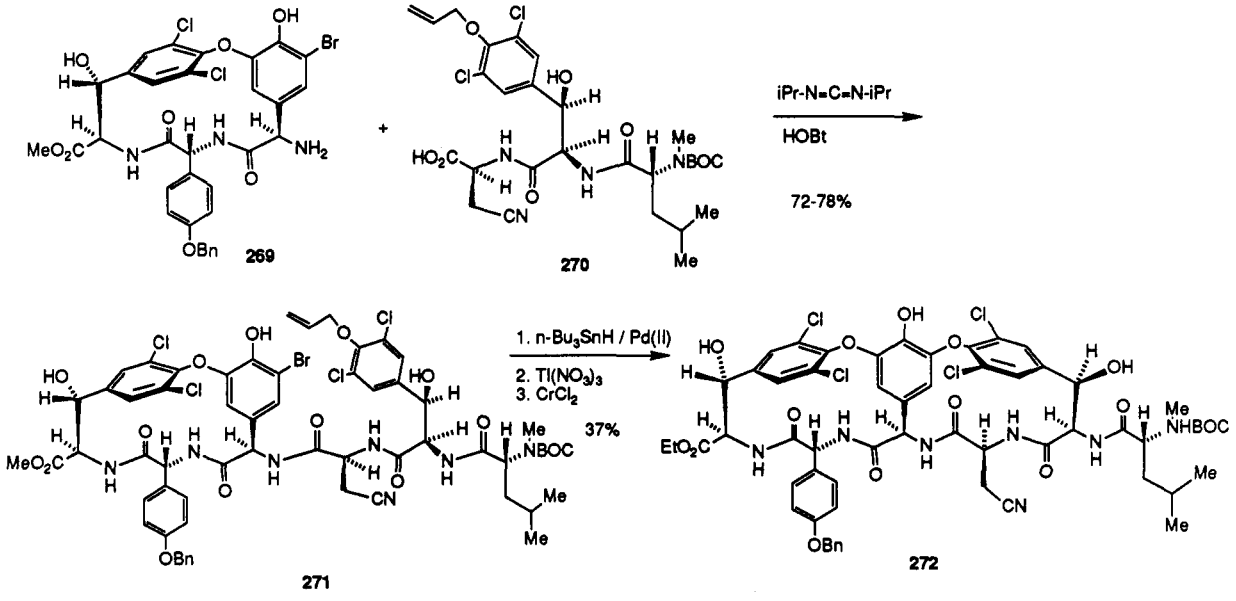
amine **248** with tripeptide **249** yielded the hexapeptide **250** in good yield. The TNN oxidative cyclization was performed in this instance with the zinc reductive workup (35% yield, two steps) to give, after removal of the Asn protecting group and dehalogenation, the macrobicyclic aryl diether **251**.

Evans and co-workers[76] have recently reported on a vancomycin model system employing the Yamamura TNN oxidative cyclization protocol. The Evans work, outlined in Schemes 56–59 closely parallels that of Yamamura (shown above) with the very significant difference that the β-hydroxytyrosine residues of the vancomycin structure are incorporated in a stereocontrolled fashion. This constitutes the most advanced approach to the vancomycin structure to date. The syntheses of the two key subunits (**257** and **264**) are outlined in Schemes 56 and 57, respectively. The β-hydroxytyrosine residues (**252** and **258**) are constructed using stereocontrolled boron enolate aldolizations of 2-bromoacetate by the elegant Evans chiral oxazolidinone protocol.[77] The peptide coupling of **252** and **241** proceeds with less than 4% racemization (Scheme 56). The phenolic allyl protecting group could be removed with tri-*n*-butyltin hydride in the presence of a Pd(II) catalyst without hydrodehalogenation. Bromination of *p*-hydroxyphenylglycine (**254**) and urethane protection afforded **255** which was condensed with **253** in high yield to furnish tripeptide **256**. The allyl protecting group was removed with tri-*n*-butyltin hydride in the presence of a Pd(II) catalyst to provide the 4/6 cyclization precursor **257**. The 2/4 cyclization precursor was assembled as shown in Scheme 57. α-Bromo carboximide **258** was treated with sodium azide in DMSO and the chiral auxiliary subsequently removed with basic lithium peroxide in high yield. Coupling of this substance (**259**) with the (trimethylsilyl)ethyl ester (TMSE) of β-cyanoalanine (**260**) provided dipeptide **261**. Reduction of the azide, and coupling to D-*N*-Boc-*N*-methylleucine gave tripeptide **262** in excellent yield. Finally, coupling **260** with **262** followed by removal of

Scheme 58



Scheme 59

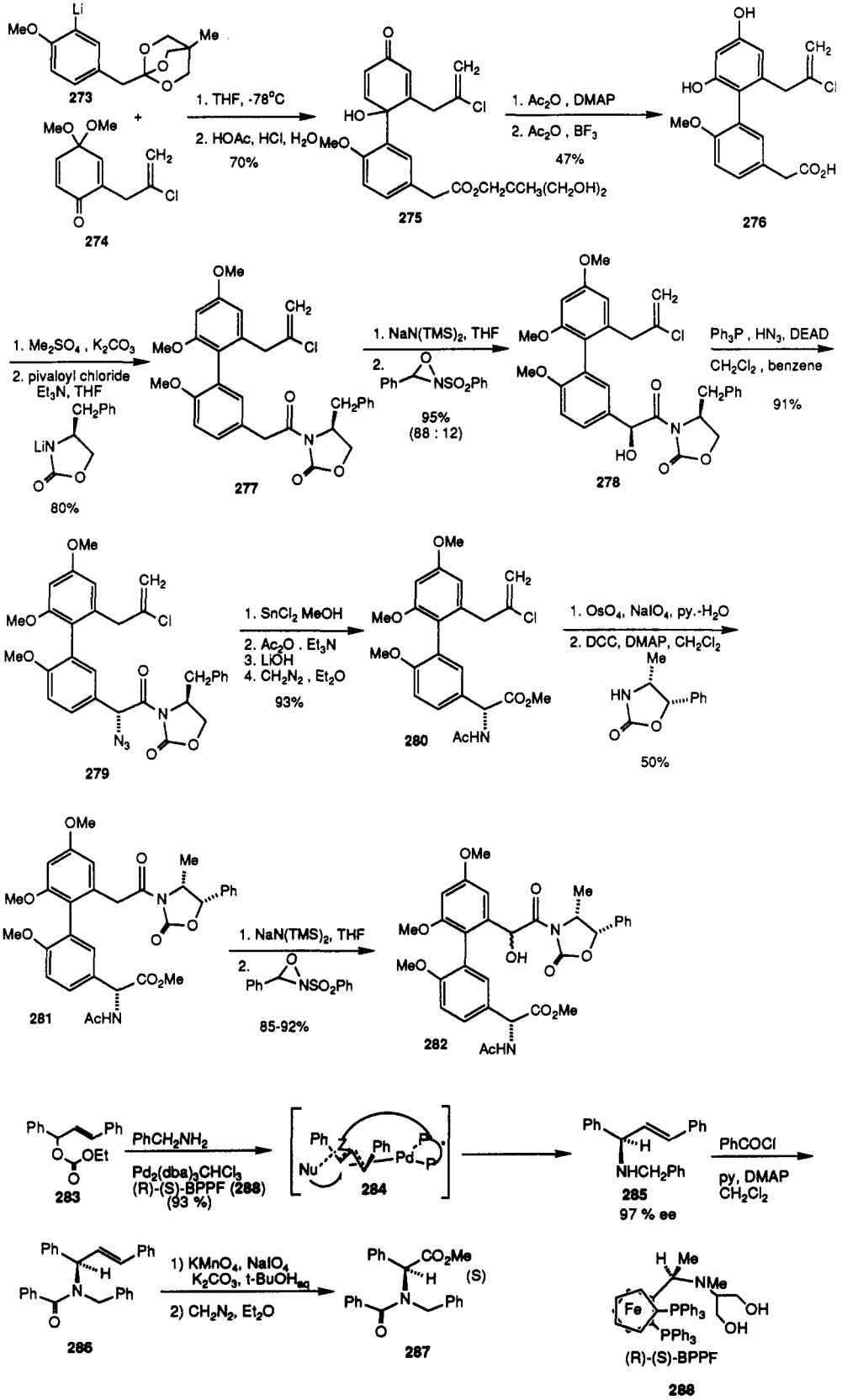


the allyl ether furnished **264**.

The authors report an optimized set of cyclization conditions involving 10 equiv of thallium trinitrate in 5:1 THF/methanol at 1 mM concentration containing 3 equiv of pyridine per equivalent of TNN. Thus, cyclization of **257** under these conditions furnished the *p*-quinol **265** which is reduced in situ with excess $CrCl_2$. The macrocycle **266** was obtained in 42% overall yield. In the case of **264**, cyclization was performed under similar conditions, only the solvent employed was 1:1 methanol/methylene chloride. In this instance, the methoxylated macrocycle **268** was obtained in 48% overall yield following reduction of the incipient *p*-quinol **267**. The authors note that the displacement of the aryl bromine by methanol (in contrast to the reaction from **257**) is presumably due to steric crowding at the para position of the intermediate leading to **267** and further dictates the order of assemblage of the macrobicyclic substance **272** (Scheme 59).

The BOC group is removed from **257** with TFA and the resulting amine **269** is condensed with the acid **270** derived from **262**. The hexapeptide **271** is then sub-

Scheme 60

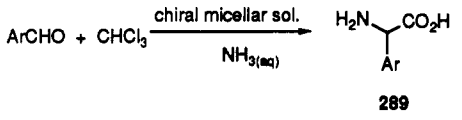


Scheme 61

jected to allyl ether cleavage and cyclization as above, to afford the macrobicyclic substance **272** in 37% overall yield.

Many difficult problems remain in constructing the vancomycin molecule. Among the most formidable include, the establishment of the correct axial chirality of the mono-chlorinated β-hydroxytyrosine residues; the construction of actinoidic acid (lower left biaryl 5/7 macrocyclic portion), the incorporation of this unit, also with the correct axial chirality, into a synthetic stratagem, and the attachment of the disaccharide unit. The above synthetic approaches to vancomycin are extremely impressive and demonstrate significant progress toward the vancomycin structure and the

Scheme 62

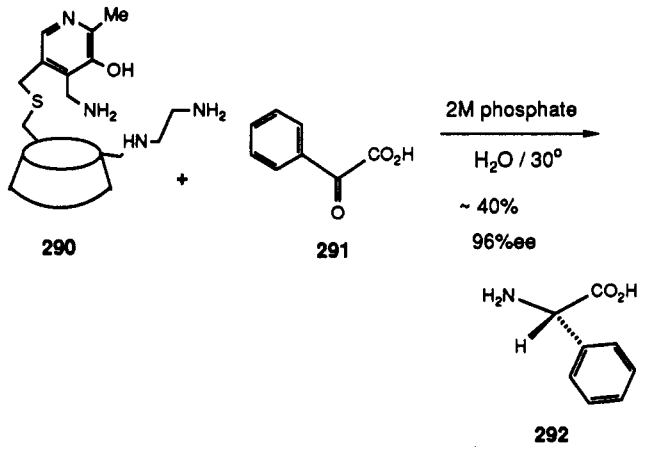


289

Table 18

Ar	% yield	Ar	% yield
Ph	93	4-$MeOC_6H_4$	33
4-ClC_6H_4	48	4-MeC_6H_4	15
3-ClC_6H_4	19	3-MeC_6H_4	18
4-BrC_6H_4	72		

Scheme 63



290 291 292

power of the methodologies under development. However, this molecule continues to provide one of the most challenging and difficult set of stereochemical and functional group complexities in arylglycine construction specifically and in natural products synthesis in general.

Evans and Morrissey[78] have embarked on the asymmetric synthesis of actinoidic acid as shown in Scheme 60. The general strategy embraces construction of the biarylacetic acid units and subsequent asymmetric amination. The two phenylacetic acid units are differentiated so as to allow for the unambiguous introduction of the correct absolute configuration at each α-amino acid subunit. Thus, biaryl acid **276** is assembled by coupling the lithiated OBO (2,6,7-trioxabicyclo[2.2.2]-octane) ester **273** with vinyl chloride **274**. Methylation of the phenols and acylation of the acid provides carboximide **277**. Enolate generation and oxidation affords α-hydroxy acid **278** in excellent yield as an 88:12 ratio of diastereoisomers; the desired 2*S* isomer (**278**) was isolated by chromatography in 80% yield. Mitsunobu reaction of **278** with hydrazoic acid afforded the α-azido carboximide in excellent yield. Sequential reduction of the azide, acylation, removal of the chiral auxiliary, and esterification provided arylglycine **280** in high yield. Next, the vinyl chloride was unmasked to furnish the ephedrine carboximide **281**. This was then subjected to enolate hydroxylation to give the α-hydroxy acids **282**. The author notes that two separable atropisomers of **279** were each subjected to the reaction sequence depicted. The "higher R_f" isomer of **281** gave a 94:6 diastereoselection (85% yield) while the "lower R_f" isomer gave a 66:33 diastereoselection (92% yield).

In a recent publication, Hayashi and co-workers[79] reported a unique method for the synthesis of a phenylglycine derivative using an asymmetric palladium-catalyzed allylic amination as the key step. The authors reported the use of a chiral ferrocenylphosphine catalyst (**288**) which forms a palladium complex in situ when reacted with $Pd(dba)_3CHCl_3$. This chiral complex forms a π-allylpalladium complex (**284**) with the diphenylpropenyl substrate (**283**). Directed nucleophilic attack by an attractive interaction with the functional group of the pendant side chain yields the desired diphenyl benzylamine **285** in 97% ee. The diphenyl benzyl amine **285** can be converted to a phenylglycine derivative via an oxidative route. Thus, **285** was first N-acylated with benzoyl chloride followed by the oxidation of the olefin with $KMnO_4/NaIO_4$, yielding the acid which was immediately esterified with diazomethane yielding the desired protected phenylglycine derivative (**287**, Scheme 61).

Zhang and Li[80] reported the use of a chiral surfactant to obtain asymmetric induction. In this one-step synthesis, aqueous micelles were formed from the chiral surfactant, *N*-hexadecyl-*N*-methylephedrine bromide. The benzaldehyde derivatives were captured in a rigid enzyme-like layer where CCl_3^- attacked the aldehyde in the presence of NH_4OH. Very few details on this interesting reaction are available, but the authors

Scheme 64

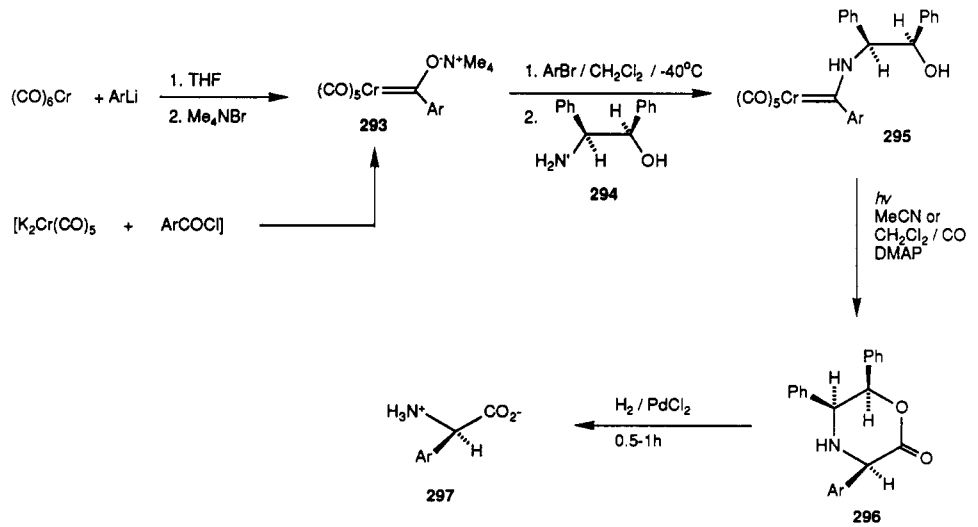


Table 19

entry	Ar	293 (%)	295 (%)	296 (crude %)	de (ratio)	296 (%)[a]	297 (%)[b]	% ee
A	Ph	62	79	80	64 (82:18)	67	69 (23)	94
B	*p*-MeOPh	78	81	82	76 (88:12)	72	91 (41)	96
C	*p*-ClPh	64	73	73	60 (80:20)	59	81 (22)	84
D	*p*-FPh	62	77	77	72 (86:14)	69	80 (26)	98
E	*p*-F_3CPh	80	84	84	60 (80:20)	73	86 (42)	98
F	*o*-MeOPh	80	86	78	76 (88:12)	61	unstable	
G	2,6-F_2Ph	63	62	62	64 (82:18)	63	95 (23)	64
H	1-naphthyl	75	51	76	62 (81:19)	66	40 (10)	56
I	3-thienyl	52	55	75	66 (83:17)	62	-	-

[a] Yield of purified, single diastereomer. [b] Yield in parentheses refers to overall yield of **297** from **293**.

do report that they obtained the arylglycine products **289** in moderate yields and in approximately 28% ee (Scheme 62, Table 18).

In a unique approach, Breslow and co-workers[81] used an artificial enzyme system **290** to perform a chiral amino transfer reaction to phenyl keto acid **291** to produce phenylglycine **292**. In this procedure, pyridoxylamine is bound to a modified β-cyclodextrin which contained both a binding domain and an amine group. The researchers observed that the aromatic keto acid **291** would bind inside the cyclodextrin pocket and then the stereoselective transamination occurred yielding L-phenylglycine **292** in modest chemical yield but in 96% ee (Scheme 63). The high % ee of phenylglycine clearly indicates that the conditions of the reaction are very mild and do not promote racemization.

Hegedus and co-workers[82] have developed a very interesting and unusual approach to the synthesis of α-amino acids and have very recently been able to embrace the arylglycine manifold. As shown in Scheme 64, chromium hexacarbonyl is condensed with a variety of aryllithium reagents furnishing the chromium carbene tetramethylammonium salts **293**. Acylation and exchange with diphenyl amino alcohol **294** furnishes the aminocarbene complexes **295** in high overall yields. These substances are then photolyzed which induces a CO insertion and cyclization on the incipient ketene complex which provides the oxazinones **296** in reasonably high diastereoselectivity. The diastereomers of **296** are separated during the requisite chromatographic removal of the DMAP-chromium residual complex and can be obtained as single syn-diastereomers in pure form. Catalytic hydrogenation surprisingly cleaves only the desired benzylic bonds without overreducing the arylglycine product producing the arylglycines **297** in good to excellent % ee's (Table 19). The mechanism for the critical diastereofacial protonation reaction is not evident, but a reasonable explanation might involve protonation from the least hindered face of an enolized form of the lactone giving as a major product, the observed syn diastereomer. It should also be noted that the related oxazinones produced by Williams' approach[57] which provides the corresponding N-protected anti diastereomers, do not cleanly reduce to the arylglycines under H_2/Pd reduction conditions in all cases (see Scheme 37). The all-syn stereochemistry of **296** must therefore play a critical role in presenting the labile C–N and C–O bond the catalyst surface; the selectivity remains remarkable.

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