6
Synthesis of *N*-Alkyl Amino Acids

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6.1
Introduction

Among the numerous reactions of nonribosomal peptide synthesis, *N*-methylation of amino acids is one of the common motifs. Consequently, the chemical research community interested in peptide synthesis and peptide modification has generated a sizeable body of literature focused on the synthesis of *N*-methyl amino acids (NMA). That literature is summarized herein.

Alkyl groups substituted on to nitrogen larger than methyl are exceedingly rare among natural products. However, medicinal chemistry programs and peptide drug development projects are not limited to *N*-methylation. While being a much smaller body of research, there is a range of methods for the *N*-alkylation of amino acids and those reports are also covered in this chapter.

The literature on *N*-alkyl, primarily *N*-methyl amino acids comes about due to the useful properties that the *N*-methyl group confers on peptides. *N*-Methylation increases lipophilicity, which has the effect of increasing solubility in nonaqueous solvents and improving membrane permeability. On balance this makes peptides more bioavailable and makes them better therapeutic candidates.

One potential disadvantage is the methyl group removes the possibility of hydrogen bonding and so binding events may be discouraged. It is notable though that the *N*-methyl group does not fundamentally alter the identity of the amino acid. Some medicinal chemists have taken advantage of this fact to deliberately discourage binding of certain peptides that can still participate in the general or partial chemistry of a peptide. A series of recent papers relating to Alzheimer's disease by Doig *et al.* [1–3] considers the use of small peptidic ligands bearing *N*-methyl amide bonds as a means of interrupting or reversing amyloid protein aggregation into toxic fibrils or lumps. Similar, related studies have been published by Gordon *et al.* [4] and Kapurniotu *et al.* [5].

Viewed from another point, the removal of the possibility of hydrogen bonding may improve the efficacy of a peptide by increasing its proteolytic resistance.

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Generally, the first event in an enzymic proteolytic event is recognition of the target amide bond by hydrogen bonding. Numerous examples of model or lead peptides acquiring increased proteolytic stability through site-specific *N*-methylation are known [6–12].

Thus, *N*-methylation and *N*-alkylation are accepted tools in peptide and peptidomimetic drug design. This leads to the requirement for methods to prepare the required monomers in forms suitable for solution and solid-phase peptide synthesis. Accordingly, in the synthetic literature summarized in this chapter attention is given, where possible, to the integrity of asymmetric centers that particular methods enjoy. A method that provides the *N*-methyl (*N*-alkyl) amino acid in high yield but as a racemate typically finds little use.

This chapter describes methods for the synthesis of *N*-methyl and larger *N*-alkyl amino acids. It addresses the synthetic challenges of *N*-methylation including regiospecific methylation, mono-*N*-methylation, and development of racemization-free chemistry. The synthetic methods reviewed reveal the difficulty that chemists have had in incorporating a single methyl group at the α-amino position and the problems encountered in applying these methods to the common 20 naturally occurring L-amino acids. Toward the end of the chapter, a specific section on *N*-alkylation where it differs from *N*-methylation is presented.

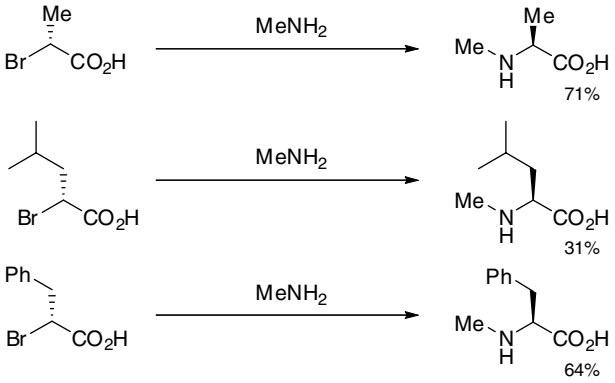
6.2
N-Methylation via Alkylation

6.2.1
S_N2 Substitution of α-Bromo Acids

The first published procedure for the *N*-methylation of α-amino acids dates back to 1915 pioneered by Emil Fischer *et al.* [13, 14]. This work provided a foundation for *N*-methyl analog synthesis utilizing *N*-tosyl amino acids and α-bromo acids as intermediates. Fischer *et al.* prepared *N*-methyl derivatives of alanine, leucine, and phenylalanine by nucleophilic displacement of optically active (*R*)-α-bromo acids (Scheme 6.1) [14]. Using this approach they made *N*-methyl derivatives of alanine, leucine, and phenylalanine with the L-configuration (Scheme 6.1).

The α-bromo acids are commonly obtained via diazotization of the parent amino acid (Figure 6.1) [15]. The reaction gives retention of configuration and this results in a "Walden inversion" [16], which forms an intermediate diazonium ion that is attacked intramolecularly, in S_N2 fashion, by the neighboring carboxylate group to form the highly reactive cyclic lactone **1** [17]. A second nucleophilic addition again in the S_N2 mode by a bromide ion provides the optically active α-bromo acids **2** with net retention of the original amino acid chirality. Consequently, substitution with excess methylamine at 0 °C provides NMAs with opposite configuration to the parent amino acids.

Izumiya and Nagamatsu extended this methodology to other amino acids such as tyrosine [15], methionine [18d], arginine [18b], and ornithine [18b]. A representative



Scheme 6.1

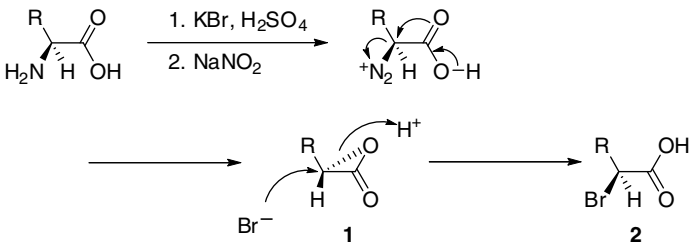
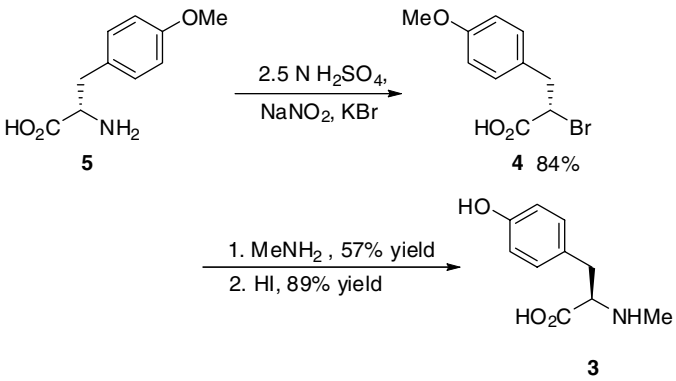


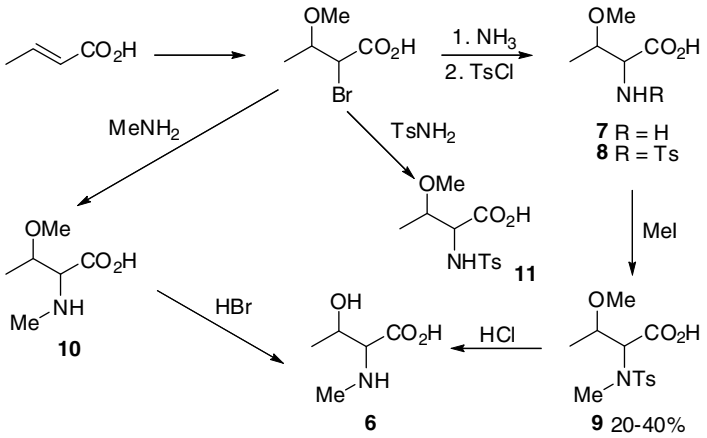
Figure 6.1 Mechanism of α-bromo acid formation via diazotization.

example is given in Scheme 6.2 in which *N*-methyl-D-tyrosine (D-surinamine) **3** is prepared by diazotization of *O*-methyl-L-tyrosine **5** to give the optically active α-bromo acid **4**. Displacement with methylamine at 100 °C in a sealed tube provided *N*-methyl-D-tyrosine **3**.

Izumiya combined both methods developed by Fischer to make NMAs [18a,c,e] of hydroxy-amino acids via α-bromo acids and *N*-tosyl amino acids. 3-Methoxy-2-bromoalkanoic acids were prepared from alkenoic acids as precursors (Scheme 6.3).



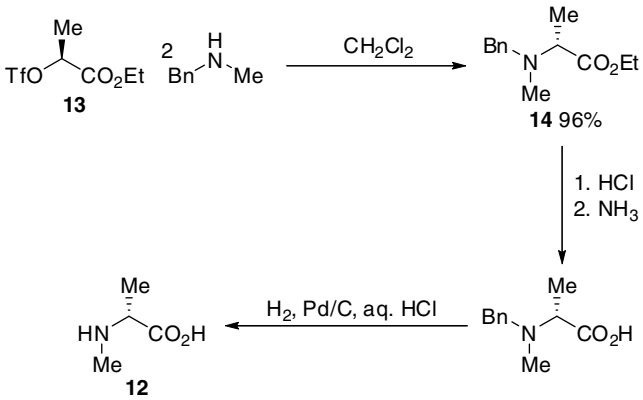
Scheme 6.2



Scheme 6.3

Izumiya describes two paths to NMAs. This is shown by the preparation of *N*-methylthreonine **6**. The first pathway involves amination with ammonia to generate *O*-methylthreonine **7**. Tosylation provides **8** and *N*-methylation with methyl iodide under basic conditions gave the *N*-methylated fully protected threonine **9**. The tosyl and *O*-methyl groups were then removed under acidic conditions to give *N*-methylthreonine **6**. The second sequence used methylamine for the amination to make *N,O*-dimethylthreonine **10** and then *O*-demethylating with HBr to provide **6**. These sequences provided racemic serine, threonine and its diastereoisomers, and β-hydroxyvaline. In a variation, the tosyl path could be made more efficient by amination with *p*-toluenesulfonamide to give **11**.

α-Bromo acids can be replaced by triflates in S_N2 displacements. Effenberger *et al.* [19] synthesized *N*-methyl-D-alanine **12** (Scheme 6.4) in this way. Ethyl-L-lactate was converted to the triflate **13** and then treatment of the triflate with *N*-benzyl-*N*-methyl amine supplied fully protected ethyl-*N*-benzyl-*N*-methyl-D-alaninate **14**. The



Scheme 6.4

excellent leaving group capability of the trifluoromethanesulfonate is the advantage of this technique even with weak amine nucleophiles at room temperature and below [19], and the fact that excess amine and high temperatures in sealed vessels are not required as in Izumiya's method (Scheme 6.2).

The synthesis of NMAs by S_N2 substitution of α-bromo acids is generally a short and simple sequence. However, it does come with limitations. The yields of product NMAs are low to moderate, the displacement using secondary amines is not reported, and epimerization is not entirely eradicated [20b]. Quitt *et al.* [20] established an epimerization-free reductive amination of a range of NMAs that revealed, by comparison of optical data, that some epimerization was occurring in the α-bromo acid substitution with the addition of methylamine at 0 °C. This approach to NMA synthesis was essentially abandoned, as Fischer and Izumiya are the sole contributors to the literature.

The alternative Effenberger *et al.* [19] approach involving triflate displacement is more mild, but suitable carboxyl protection is required. The increasing availability of lactates commercially and synthetically makes the triflate approach a far more viable procedure than the use of α-bromo acids as intermediates for NMAs as this technique was shown to provide optically pure derivatives and provides avenues to *N*-alkyl amino acids since secondary amines can also be utilized.

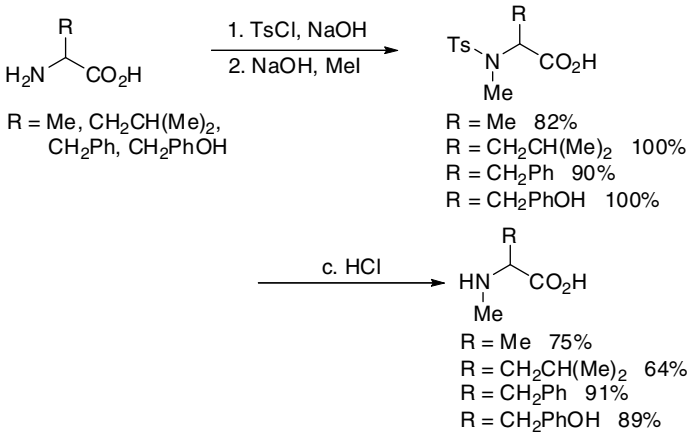
6.2.2
N-Methylation of Sulfonamides, Carbamates, and Amides

One of the common methods of *N*-methylation by alkylation is to use amide-like protection with various sulfonamides, carbamates, and (indeed) amides. Amide protection enhances NH acidity permitting deprotonation under basic conditions and in the presence of an alkylating reagent provides the NMAs, which will be discussed in three sections below. Alternatively, the Mitsunobu protocol can be employed in the synthesis of NMAs with various sulfonamide protecting groups due to the acidity of the sulfonamide nitrogen.

6.2.2.1 Base-Mediated Alkylation of *N*-Tosyl Sulfonamides

Fischer and Lipschitz [13] describe the preparation of *N*-tosyl α-amino acids (Scheme 6.5). They treated *N*-tosyl α-amino acids with sodium hydroxide at 65–70 °C and used methyl iodide as the alkylating agent. An advantage of *N*-tosyl protection is the high degree of crystallinity of the product NMAs, but a major drawback is the removal of the tosyl group, which can require vigorous conditions. The *N*-tosyl NMAs were subjected to acid hydrolysis with concentrated HCl for up to 8 h at 100 °C, to provide the free NMA. The other problem is that this method does proceed with epimerization in the methylation step in which sodium hydroxide was used at elevated temperatures. This was revealed by Quitt *et al.* [20] through comparison of optical rotation values.

The temperature is a major contributing factor to this epimerization process since the method of Hlavácek *et al.* [21, 22] revealed that *N*-tosyl amino acid isopropyl and *tert*-butyl esters of alanine and valine, when treated with sodium hydroxide and

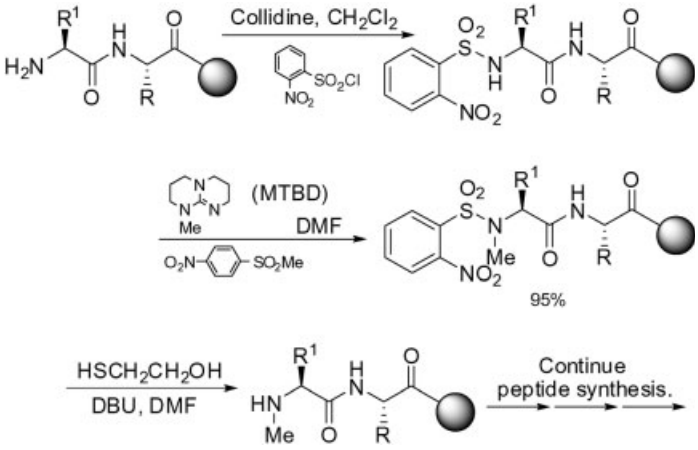


Scheme 6.5

dimethylsulfate at 0 °C, showed no epimerization and remained optically active. Isolated NMAs were assessed by comparison of optical data with that of Quitt *et al.* [20]. This was a biphasic reaction, and detergent was included to improve phase mixing and also helped in removing traces of unreacted starting materials. Pure *N*-methyl amino acid derivatives of leucine, valine, phenylalanine, alanine, and ornithine were isolated in near quantitative yields from the methylation step [22]. By treating the *tert*-butyl esters with trifluoroacetic acid (TFA) and isopropyl esters with refluxing 4 M HCl, the free acids could be obtained. Subsequent tosyl group removal was accomplished with calcium metal in liquid ammonia or with HBr at reflux in the presence of phenol.

6.2.2.2 Base Mediated Alkylation of *N*-Nitrobenzenesulfonamides

Sulfonamide protection has been used for site-selective *N*-methylation on solid support [23]. Since the sulfonamide NH is far more acidic than amide NHs, selective deprotonation of sulfonamides was achieved in the presence of amides and as a result selective methylation of sulfonamides was possible. The N-terminal amino acid (resin bound) as the free amine was protected as the *o*-nitrobenzenesulfonamide (*o*-NBS), which can be removed selectively and with milder conditions when compared to *N*-tosyl protection, using a thiol and base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The sulfonamide was treated with the guanidinium base, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), and alkylated with methyl *p*-nitrobenzenesulfonate (Scheme 6.6). This combination of sulfonamide protection, base deprotonation, and alkylation provided site-selective *N*-methylation, without methylation elsewhere in the growing peptide. It was found that the use of the guanidinium base MTBD was critical in achieving high yields and selectivity since weaker bases gave poor or no yields and stronger bases resulted in uncontrolled methylation of the amide backbone. The less vigorous conditions of methylation and deprotection with this method provide a useful alternative approach to *N*-tosyl protection.



Scheme 6.6

o-NBS protection has also been used in solution phase synthesis of NMAs as their methyl esters. Albanese *et al*. [24] alkylated the intermediate *o*-NBS amides in solution phase by treating the sulfonamides with solid potassium carbonate, triethylbenzylammonium chloride (TEBA) as phase-transfer catalyst [24] and alkyl halides providing *N*-nitrobenzenesulfonamido-*N*-alkyl amino acid esters at 25 or 80 °C. These transformations were accomplished with valine, phenylalanine, and phenylglycine in 87, 86, and 91% yields, respectively for their *N*-methyl derivatives. The use of TEBA enabled the non-nucleophilic base potassium carbonate to be utilized, whereas *N*-alkylation was considerably reduced in the absence of TEBA. Removal of the NBS group is affected by thiophenol/potassium carbonate/acetonitrile at 80 °C or potassium thiophenoxide/dimethylformamide (DMF) at 25 °C leaving the methyl ester intact. Biron and Kessler [25] solved the problem of methyl ester cleavage in their synthesis of *N*-methylated amino acids with *o*-NBS protection. They converted *o*-NBS amino acid methyl esters to the *N*-methylated analog with dimethylsulfate/DBU and then cleaved the methyl ester under S_N2 dealkylation conditions with LiI in refluxing ethyl acetate. Nuclear magnetic resonance and high-performance liquid chromatography analysis of the de-esterified products revealed no epimerization had occurred.

An even milder approach to *N*-methylating amino acid sulfonamides is under the neutral diazomethylating conditions. Di Gioia *et al*. [26a] found that by treating *N*-nosyl amino acid methyl esters with a large excess of diazomethane, the corresponding NMA esters were obtained in quantitative yield for alanine, phenylalanine, valine, leucine, and isoleucine. The *N*-nosyl group was removed with 3 equiv. of mercaptoacetic acid in the presence of 8 equiv. of sodium methoxide at 50 °C, to provide the free amines in greater than 84% yields. Treating *N*-acetyl amino acid methyl esters gave almost no *N*-methylation. Di Gioia *et al*. [26b] extended this methodology to the synthesis of several *N*-methyl-*N*-nosyl-β-amino acids.

N-Methylation by alkylating sulfonamides is advantageous in that the increased acidity of the sulfonamide nitrogen can allow for selective methylation in a

peptide [23] on a solid support or an orthogonally protected amino acid monomer. The Fischer method is undesirable since degrees of epimerization occur and the vigorous conditions for removing the tosyl group are undesirable for many sensitive amino acid residues. It is also an inappropriate protecting group in peptide synthesis since the conditions for removal also cleave peptide bonds by acid hydrolysis. The *N*-*o*-NBS or *N*-nosyl protections are significant improvements, having the advantage of mild deprotection conditions while still allowing *N*-alkylation and easy work-up in solution or solid phase. The method of Di Gioia *et al.* [26a] involving diazomethane, while elaborate, is performed under neutral conditions, but it is to be used with great caution due to the *explosive* and *toxic* nature of diazomethane! In the case of alkyl ester protection, it is not recommended to include such a protecting group that is usually removed by hydroxide or other strong bases, especially if there are no other ionizable sites in the amino acid other than the α-center where NMAs are concerned. However, the studies conducted by Biron and Kessler [25] have revealed that S_N2 dealkylation of methyl esters with LiI results in demethylation and the chiral integrity of the NMAs is retained.

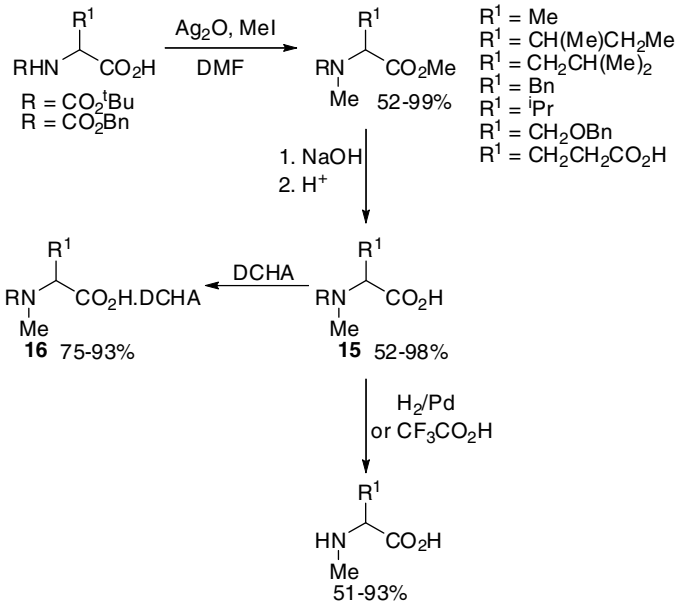
6.2.2.3 *N*-Methylation via Silver Oxide/Methyl Iodide

N-Methylation of carbamate protected peptides and their peptide bonds was first described by Das *et al.* [27]. Permethylation of peptides improved their use in mass spectrometry studies. Their intentions were purely based on the fact that oligopeptides are less volatile due to hydrogen bonding and *N*-methylation of peptide bonds alleviates the volatility problem by removing the possibility of hydrogen bonding. Their procedure involved treatment of substrate *N*-acyl peptides with excess methyl iodide and silver oxide in DMF. The final methylated products showed higher volatility and allowed mass spectral analysis at lower temperatures in the ion source.

Olsen [28] expanded the methylation procedure of Das *et al.* [27] to include carbamate protected α-amino acids. The yields of mono-*N*-methyl amino acid methyl esters like alanine and valine were routinely in the range 93–98% (Scheme 6.7). However, *N*-methylation of residues such as cysteine, arginine, methionine, aspartic acid, serine, and threonine did not provide successful candidates using this procedure.

Okamoto *et al.* [29] extended Olsen's procedure to other amino acids, and NMAs of glutamic acid and serine were successfully synthesized (Scheme 6.7). Most of the *N*-methyl amino acids **15** were isolated in crystalline form as their dicyclohexylamine salts **16** following ester saponification. However, it was found that the optical rotation data for *N*-methyl derivatives of serine and glutamic acid were lower than reported values.

The silver oxide/methyl iodide method for *N*-methylation is a mild and racemization-free process. However, the final NMAs are obtained as their methyl esters if the free acid is employed. These derivatives are then subjected to saponification if the free acid is required. This has been shown to compromise the chiral integrity of the NMAs. In addition, this method is not always reproducible since the quality of silver oxide reflects upon the conversion of amino acid to its NMA analog and therefore fresh silver oxide is necessary for good conversions. Alternatively, *N*-carbamoyl amino acids with suitable ester protection that does not require saponification for



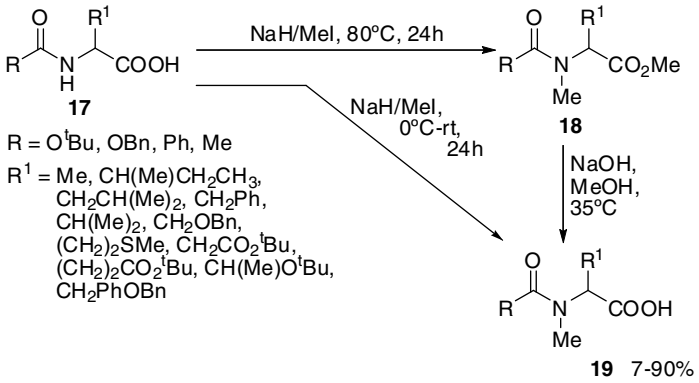
Scheme 6.7

removal should be employed in such a procedure to preclude saponification [28]. Tam *et al.* [30] synthesized *N*-methyl derivatives of α-*N*-Boc, side-chain *N*-phthaloyl-protected ornithine and lysine by protecting the carboxyl group as a benzyl ester. Silver oxide/methyl iodide-mediated *N*-methylation was achieved and the benzyl ester was removed under hydrogenolytic conditions to afford the free acids.

6.2.2.4 *N*-Methylation via Sodium Hydride/Methyl Iodide

The most broadly applied method for NMA synthesis is *N*-methylating *N*-acyl and *N*-carbamoyl amino acids with sodium hydride and methyl iodide developed by Benoiton *et al.* [31–34]. Benoiton *et al.* had synthesized a large range of NMAs using excess sodium hydride and methyl iodide. Many other contributors to the field have since utilized this method and variations thereof in producing NMAs. Benoiton *et al.* [31] initially attempted *N*-methylation employing *N*-acyl, *N*-tosyl, and *N*-carbamoyl α-amino acids **17**. Treating *N*-protected amino acids with sodium hydride and methyl iodide in tetrahydrofuran (THF)/DMF at 80 °C for 24 h produced *N*-methyl methyl esters **18**, which required a large excess of methyl iodide (8 equiv.) for optimal yields (Scheme 6.8). The methyl ester was saponified at 35 °C in methanol/THF to give the corresponding free acids **19**.

The use of alkaline conditions in the formation of the *N*-methyl group and removal of the methyl ester causes varying degrees of undesired epimerization [32–34]. Therefore, a direct route to *N*-methyl amino acids **19** was accomplished without esterification by lowering the reaction temperature to 0 °C. McDermott and Benoiton [35] found that reaction temperature was an important factor in avoiding

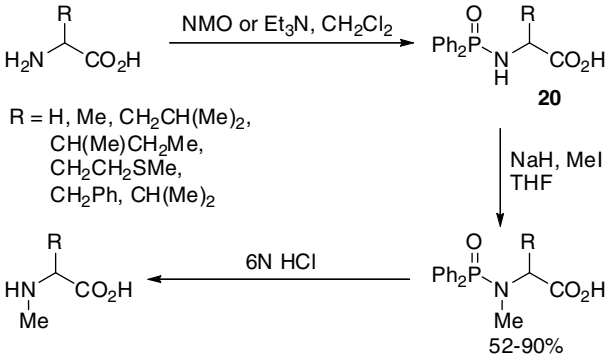


Scheme 6.8

the formation of methyl esters (Scheme 6.8) and also identified acidic reaction conditions other than basic conditions that caused epimerization of *N*-methyl amino acid-containing dipeptides. It was found the anhydrous HBr/acetic acid used for *N*-Cbz removal caused epimerization and revealed the susceptibility of NMAs to epimerize in peptide synthesis during standard peptide synthesis [34].

McDermott and Benoiton [33, 34] undertook a systematic study of the extent of epimerization of NMA residues in peptides during hydrolysis and peptide synthesis. It was concluded that appreciable epimerization occurred with aqueous hydroxide due to the absence of ionizable groups other than the α-center. Analysis of the acid-catalyzed epimerization showed that anhydrous HBr/acetic acid caused epimerization depending on several factors such as acid strength, solvent polarity, and time. It was found that including water in the acidic mixtures suppressed epimerization completely as did HCl mixtures in place of HBr mixtures. The epimerization studies were extended to include coupling reactions between NMA peptides via the mixed anhydride activation approach, and they identified factors such as ionic strength and solvent polarity as controlling epimerization during peptide bond formation via the mixed anhydride activation/coupling procedure. Polar solvents and increased ionic strength of the solvent medium due to tertiary amine salts of hydrochlorides or *p*-toluenesulfonates promoted epimerization and in the absence of these factors less epimerization was observed. Only DCC/*N*-hydroxysuccinimide as an activating agent gave stereochemically pure coupled products. Furthermore, they found that an excess of base did not promote epimerization.

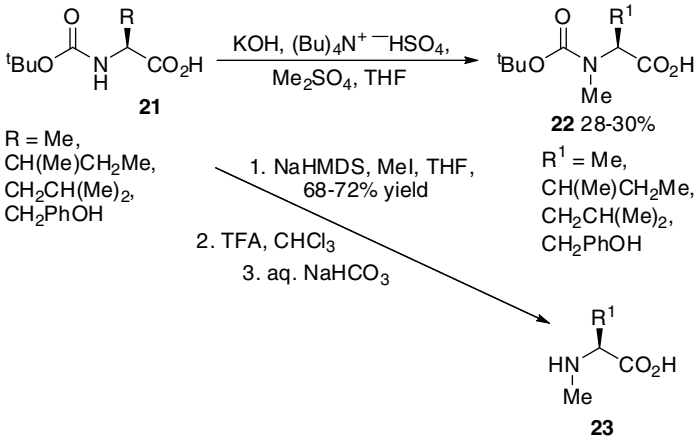
Another type of protecting group exploited yet rarely used are phosphoramides. Coulton *et al.* [36] synthesized a number of α-amino acid diphenylphosphinamides **20** (Scheme 6.9) that were methylated using the conditions of Benoiton *et al.* [31, 34, 35, 37]. The diphenylphosphinamide protecting group is acid labile and the product NMAs are highly crystalline, yet the downfall of this procedure was that the optical rotation data for the zwitterionic form did not agree well with those reported. This suggests that some epimerization may have occurred and the authors acknowledge this discrepancy, which reveals the need for further investigation of the stereochemical integrity of the product NMAs.



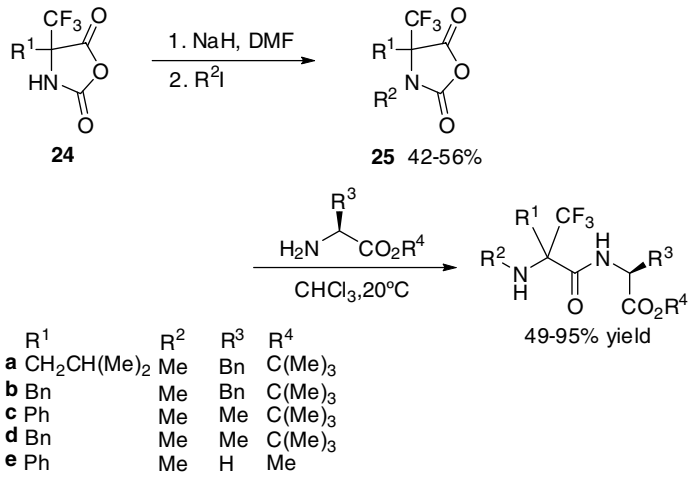
Scheme 6.9

Belagali *et al.* [38] utilized a similar approach to Benoiton with *N*-Boc-L-amino acids (Scheme 6.10), but took the *N*-Boc-L-amino acids **21** and treated them with sodium hydride/methyl iodide under the Benoiton conditions [31b]; however, they found that the yields of the *N*-methyl derivatives **22** were in the range 30–40%. Switching to more forceful conditions depicted in Scheme 6.10, by treating **21** with finely powdered potassium hydroxide, tetrabutylammonium hydrogen sulfate, and dimethylsulfate gave the *N*-methyl-*N*-Boc-L-amino acids **22** in low yields. However, utilizing sodium hexamethyldisilazide as base, the yields were greatly improved (68–72%) and the NMAs **23** were isolated after cleavage of the *N*-Boc group with TFA.

Burger and Hollweck [39], applied Benoiton's procedure to methylate 4-trifluoromethyl-1,3-oxazolidine-2,5-diones **24** known as Leuchs anhydrides (Scheme 6.11). The *N*-methylated Leuchs anhydrides **25** are activated towards nucleophilic attack and upon treatment with esterified amino acids peptide bond formation of α,α-dialkylated amino acids at the C-terminus could be achieved which is generally difficult [39].



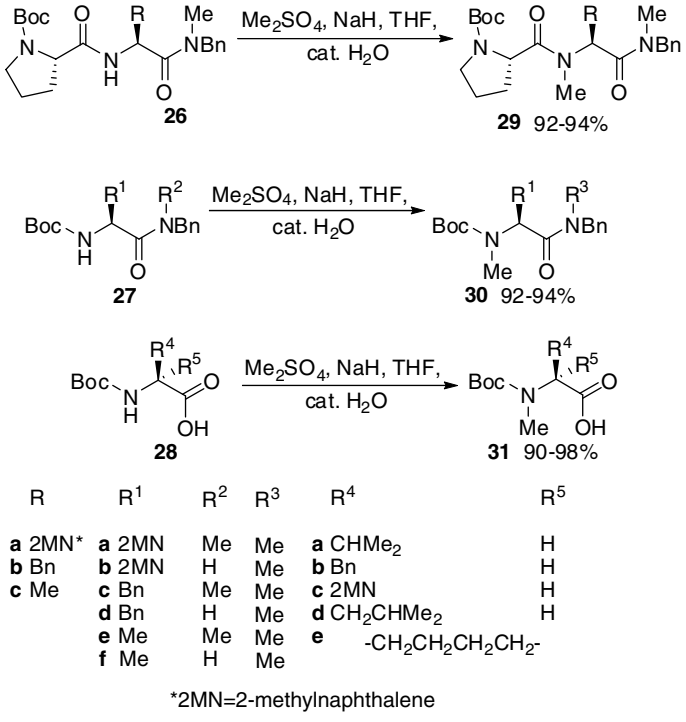
Scheme 6.10



	R^1	R^2	R^3	R^4
a	$CH_2CH(Me)_2$	Me	Bn	$C(Me)_3$
b	Bn	Me	Bn	$C(Me)_3$
c	Ph	Me	Me	$C(Me)_3$
d	Bn	Me	Me	$C(Me)_3$
e	Ph	Me	H	Me

Scheme 6.11

By slightly modifying the Benoiton method (Scheme 6.12), Prashad *et al.* [40] *N*-methylated dipeptides **26**, amino acid amides **27**, and amino acids **28**. They did this by treating the substrates with sodium hydride in THF and then methylated the resulting anion with dimethylsulfate, in the presence of catalytic amounts of water. The



R	R^1	R^2	R^3	R^4	R^5
a 2MN*	**a** 2MN	Me	Me	**a** $CHMe_2$	H
b Bn	**b** 2MN	H	Me	**b** Bn	H
c Me	**c** Bn	Me	Me	**c** 2MN	H
	d Bn	H	Me	**d** CH_2CHMe_2	H
	e Me	Me	Me	**e** $-CH_2CH_2CH_2CH_2-$	
	f Me	H	Me		

*2MN=2-methylnaphthalene

Scheme 6.12

authors found that higher yields of *N*-methylation were achieved, since the addition of water produces dry sodium hydroxide that has better solubility in THF compared to sodium hydride and consequently makes for excellent yields of **29**, **30**, and **31**.

A number of NMA derivatives have been synthesized by the sodium hydride/methyl iodide method developed by Benoiton and NMAs manufactured by this method have been employed in a number of natural product syntheses. This method has generally been accepted as a mild and practical procedure that enables the *N*-methylation of a number of *N*-acyl and *N*-carbamoyl amino acids that are readily available. In the case of Fmoc-protected amino acids this method is not applicable due to the base lability of this protecting group. To avoid esterification, low temperatures are required in the methylation and epimerization is not entirely avoided [31–35]. As Prashad *et al.* [40] noted, sodium hydride does not have high solubility in THF and the sodium salt of the substrate amino acid formed by treatment with sodium hydride has low solubility, as is the case with Boc-Ala-OH. Twice the volume of organic solvent is required due to precipitation during the reaction otherwise the reaction is incomplete [31]. The addition of phase transfer catalysts and catalytic amounts of water to increase the solubility of reagents and intermediates has been a successful strategy to overcome some problems of this method.

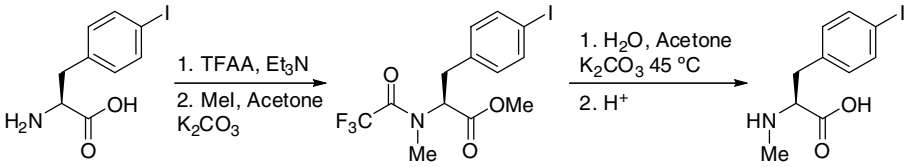
6.2.2.5 *N*-Methylation of Trifluoroacetamides

The trifluoroacetamide is a protecting group that is scarcely used in amino acid protection. There are several advantages with this group in that it is easily introduced and very mild conditions are used to remove it (aqueous potassium carbonate). One other advantage is the increased acidity it confers on the NH proton. Liu *et al.* [41] exploited this property and synthesized *N*-methylphenylalanine analogs under mild conditions (Scheme 6.13). The *N*-methylation step proceeded in anhydrous acetone and potassium carbonate with methyl iodide as the alkylating agent. This produced the methyl ester. Both protecting groups were then removed with aqueous potassium carbonate.

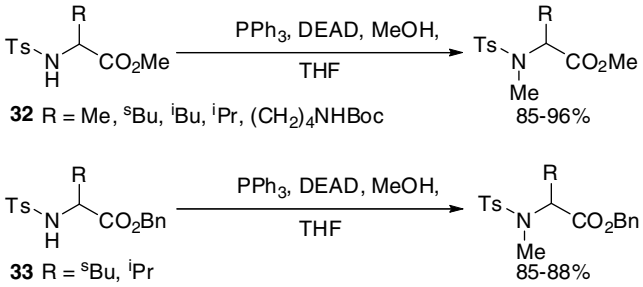
6.2.2.6 *N*-Methylation via the Mitsunobu Reaction

Alkaline reagents can cause varying degrees of epimerization, particularly if the N- and C-termini are protected, making the α-center the most acidic site and prone to enolization. One variation on this approach was to exploit *N*-tosyl amino acids for use in the Mitsunobu reaction due to the acidity of the NH that the tosyl group bestows.

Papaioannou *et al.* [42] used the Mitsunobu protocol [43] to *N*-alkylate *N*-tosyl amino acid esters **32** and **33** (Scheme 6.14) without epimerizing the products for the



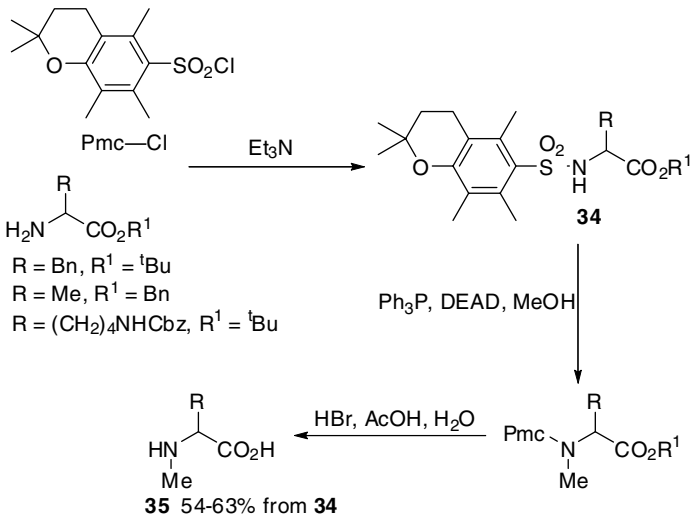
Scheme 6.13



Scheme 6.14

methylation step. Papaioannou *et al.* saponified *N*-methyl-*N*-tosyl-L-valine methyl ester to evaluate the degree of epimerization. They found that saponifying with sodium hydroxide in methanol at room temperature produced up to 44% of the D-enantiomer. Alternatively, deprotection with iodotrimethylsilane effectively removed the methyl ester without epimerization. This reagent, however, is nonselective in that many other protecting groups are susceptible to cleavage with iodotrimethylsilane [44]. Alternatively, the S_N2 dealkylation method of Biron and Kessler [25] would be well suited. The benzyl esters were removed under hydrogenolytic conditions, which did not epimerize the NMAs and were the preferred choice for carboxyl protection in this case. The tosyl group was cleaved with sodium in liquid ammonia providing optically active NMAs.

Wisniewski and Kolodziejczyk [45] used the 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) group, which has increased lability to acid conditions compared to *N*-toluenesulfonamides, to protect the amino acid nitrogen. The *N*-Pmc-protected amino acid *tert*-butyl and benzyl esters **34** (Scheme 6.15) were subjected to



Scheme 6.15

Mitsunobu conditions yielding, after deprotection of the Pmc group with HBr/AcOH/H_2O (conditions reported by Benoiton *et al*. [32–34] to suppress epimerization), three NMAs **35** in 54–63% yield from **34**.

Yang and Chiu [46] applied a strategy similar to Miller and Scanlan to synthesize Fmoc-*N*-methyl amino acid forms of alanine, valine, phenylalanine, tryptophan, lysine, serine, and aspartic acid that were preloaded on 2-chloro-trityl resin with yields ranging from 86 to 100%. Yang and Chiu [46] *N*-methylated the corresponding 2-NBS under Mitsunobu conditions or with finely powdered potassium carbonate and methyl iodide, and noted that alcohols other than methanol could be used to provide the *N*-alkyl amino acids under Mitsunobu conditions [46]. The sulfonamide group was removed with sodium thiophenoxide and the free amine was carbamoylated with Fmoc-Cl/diisopropylethylamine and then cleaved from the resin with 0.5% TFA/dichloromethane to provide the Fmoc-*N*-methyl amino acids, which were generally isolated in greater than 90% yield. The methylated amino acids thus isolated were found to be racemization free [46].

The Mitsunobu protocol for *N*-methylating *N*-sulfonyl amino acids is an effective racemization-free method for NMA synthesis. The use of *N*-nosyl protection over *N*-tosyl has provided a means for ready introduction and removal of sulfonamide type protection and the neutral conditions of the Mitsunobu reaction permit a variety of protecting groups that can be included in an orthogonal protection scheme. It would be preferable to limit this procedure to solid-phase synthetic schemes since the monomeric amino acid requires carboxyl protection as it will also be alkylated and excess reagents can be effectively washed away.

6.3
N-Methylation via Schiff's Base Reduction

6.3.1
Reduction of Schiff's Bases via Transition Metal-Mediated Reactions

An alternate method of alkylation for introducing methyl groups to the α-amino position is through reductive amination. This simple method is quite flexible in that groups other than methyl can be introduced by varying the carbonyl source. There are several methods developed for reducing the intermediate Schiff's bases that involve transition metal-catalyzed hydrogenation, borohydride reduction, and the Leuckart reaction. Borane reduction of formamides has also been included at the end of this section since it involves reduction. Schiff's base reduction is particularly attractive since the Schiff's base formation is a straightforward process performed by simply combining the aldehyde and the amine together in an appropriate solvent, and then reducing the intermediate imine that forms. *N*-Alkylation of amino acids by the Schiff's base approach works well for aldehydes other than formaldehyde [47–50], since steric hindrance conferred by the alkyl group and amino acid side-chains helps to minimize or prevent dialkylation. This steric limitation does not apply to formaldehyde. In reported attempts to mono *N*-methylate amino acids with

formaldehyde, a combination of *N,N*-dimethylation, *N*-monomethylation, and starting material results [48, 51]. This can be rationalized by the fact that secondary amines are more nucleophilic than primary amines. When the Schiff's base intermediate is reduced to the *N*-methyl species, this species can form another Schiff's base or iminium ion with formaldehyde, since it is the smallest aldehyde. Therefore, equivalent amounts of formaldehyde will result in the mixtures observed, as was the case for Keller-Schierlein *et al.* [51] who synthesized N^{α}-methyl-N^{δ}-benzyloxycarbonyl-L-ornithine from N^{δ}-benzyloxycarbonyl-L-ornithine. When treating N^{δ}-benzyloxycarbonyl-L-ornithine with formalin and reducing the mixture with sodium borohydride, a crude mixture of di- and mono-*N*-methyl amino acids and starting material was recovered. After chromatographic purification, N^{α}-methyl-N^{δ}-benzyloxycarbonyl-L-ornithine was obtained in only 35% yield.

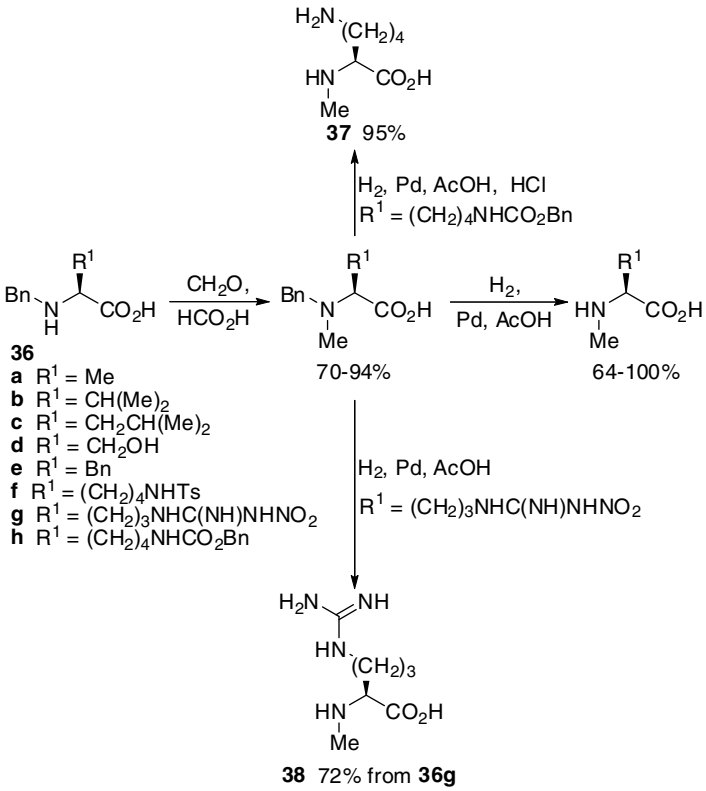
In a series of papers, Bowman *et al.* [52–54] describe the *N,N*-dimethylation of amino acids with formalin over palladium-on-charcoal catalyst under hydrogenolytic conditions. The work in this paper was concerned with dimethylation, and provided quantitative yields of the *N,N*-dimethyl amino acids of alanine, valine, leucine, phenylalanine, tyrosine, cysteine, aspartic acid, and glutamic acid. It was noted that the *N,N*-dimethyl derivative of aspartic acid was epimerized in aqueous solution at 100 °C [52]. Ikutani [55] applied the method of Bowman to synthesize *N,N*-dimethyl amino acids of glycine, alanine, leucine, phenylalanine, and tyrosine, which were then converted to *N*-oxides with peroxide. This was also the approach Poduska [56] used in dimethylating lysine derivatives.

The second paper [53] extends the methodology to the mono *N*-alkylation of valine, leucine, and phenylglycine with various aldehydes in ethanol or aqueous ethanol. In this case *N,N*-dialkylglycine can also be produced, whereas amino acids other than glycine were only mono-*N*-alkylated [53]. The last paper [54] describes the reductive alkylation of peptides for identifying the N-terminal amino acid in the chain, employing the same protocols as the two previous papers [54].

The *N,N*-dimethylation and mono-*N*-alkylation of amino acids performed via palladium catalysis is a cheap, effective, and epimerization-free route to these alkylated derivates. As mentioned, monomethylation is impractical with this method as dimethyl amino acids and starting material are byproducts that require tedious purification for their removal.

6.3.2
Reduction of Schiff's Bases via Formic Acid: The Leuckart Reaction

The Leuckart reaction is a method involving the reduction of imines in the presence of formic acid. The procedure developed for amino acid *N*-methylation heats *N*-benzyl amino acids in formic acid in the presence of formalin until CO_2 ceases to effervesce from the solution. This is the only type of reductive amination with formic acid/formalin to produce NMAs; no other variations have been described in the literature so far (Scheme 6.16). This method developed by Quitt *et al.* [20] reveals the variety of different functional groups that tolerate these conditions for *N*-methylating *N*-benzyl amino acids. The two amino acids, lysine and arginine, that

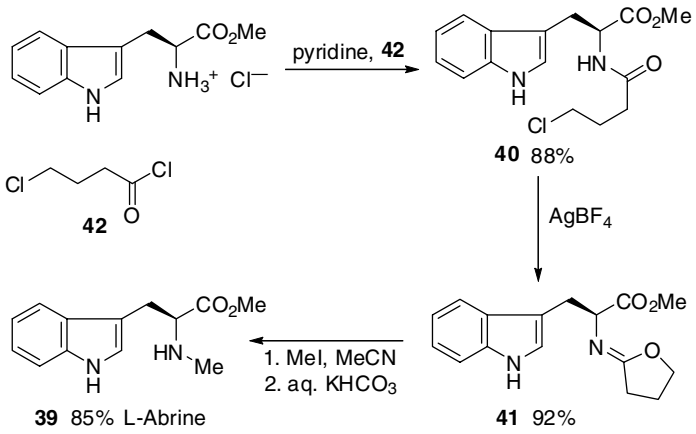


Scheme 6.16

present difficulties for some other methods were successfully *N*-methylated via reductive amination with formaldehyde and formic acid to give structures **37** and **38**, respectively. To date, the physical data obtained from these derivatives have provided a benchmark for the comparison of synthetic NMAs due to the mildness of this epimerization-free method. Ebata *et al.* [57] extended the methodology to other amino acids such as aspartic acid, isoleucine, threonine, and glycine with success, albeit the reactions were low yielding. Various other groups have also used this methodology to prepare *N*-methyl amino acid derivatives as part of synthesis [58] and other studies [59].

6.3.3
Quaternization of Imino Species

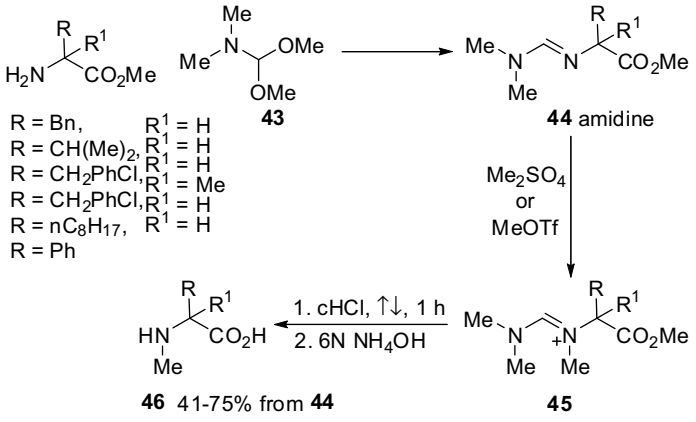
Another less-common method for NMA synthesis is forming quaternary iminium salts. This approach for amino acid monomethylation is appealing in that the imino group can only be alkylated once and this prohibits possible dialkylation. This procedure was applied by Eschenmoser *et al.* [60] in the formation of *N*-methyltryptophan (L-abrine) **39**, in which the *N*-chlorobutyroyl amide **40** was treated with silver



Scheme 6.17

tetrafluoroborate resulting in the iminolactone **41** (Scheme 6.17). Treating the imine with methyl iodide followed by hydrolysis with aqueous potassium carbonate provided the *N*-methyltryptophan **39**. The conversions of **40** through to **39** can be performed in one pot in 85% yield and, notably, the process was epimerization free.

Amidines of amino acid esters generated by reaction with DMF dimethyl acetal **43** have been utilized as intermediates in the formation of NMAs [61]. Methylsulfate or methyltriflate quaternization of the resulting amidine **44** gives an iminium salt **45**, which when hydrolyzed gives the *N*-methyl amino acid **46** (Scheme 6.18). It was found that the amidines were more reactive than simple alkyl Schiff's bases since amidines are more basic and the amidines that were prepared directly from the free amino acid and DMF dimethylacetal in refluxing toluene were epimerized. By simply utilizing amino acid esters enabled lower temperatures and reaction times for the formation of the amidines resulting in stereochemical integrity being intact. The amidine esters also enabled the alkylation with methyltriflate or dimethylsulfate



Scheme 6.18

under more mild conditions and this was tested with phenylglycine. The amidine of phenylglycine methyl ester was reacted with methyltriflate in dichloromethane at room temperature and after hydrolysis gave optically active *N*-methylphenylglycine. It was noted that these conditions are particularly mild as phenylglycine is prone to racemization.

6.3.4 Reduction of Schiff's Bases via Borohydrides

Borohydride reductions are alternative approaches to transition metal-catalyzed reduction of Schiff's base intermediates; however, borohydrides such as potassium, sodium, and lithium borohydride are seldom used to reduce Schiff's base intermediates since yields are compromised by competing side-products, particularly the direct reduction of the aldehyde [62]. Borohydrides such as sodium cyanoborohydride are more suited to this application especially in the *N*-alkylation of amino acid esters with aldehydes [48, 51, 63], and triacetoxyborohydride has been recommended as a replacement reducing agent to sodium cyanoborohydride since less-toxic side-products are formed and better yields and reproducibility of results can be obtained with this mild reducing agent [49, 50].

The reductive amination of proteins with formaldehyde in the presence of sodium cyanoborohydride to produce *N*,*N*-dimethylated proteins has been described [62]. The reaction was regiospecific, with methylation occurring only at the N-terminus and at lysyl side-chains and was a means of "labeling" the protein for further studies. Jentoft and Dearborn [62] discuss the superiority of sodium cyanoborohydride over sodium borohydride in its mildness and specificity for reductive amination.

Polt *et al.* [47] have utilized *N*-diphenylmethyl imine (ketimine) esters of amino acids and in a one-pot procedure reduced the intermediates with sodium cyanoborohydride to *N*-diphenylmethyl amino acid esters and then condensed these secondary amines with excess formaldehyde or other aldehydes in the presence of excess sodium cyanoborohydride providing *N*-diphenylmethyl-*N*-methyl amino esters. The fully protected NMAs were hydrogenolyzed over palladium catalyst to afford the *N*-methyl amino acids. In this way tryptophan was monoalkylated without competing Pictet–Spengler cyclization nor was there any mention of methylation occurring at the indole nitrogen [47]. This procedure was applied to alanine, serine, threonine, leucine, and tryptophan, and is closely related to the approach of Quitt *et al.* [20] One important note is that it was generally observed that 5–19% of unmethylated *N*-diphenylmethyl amino acid esters were recovered along with the starting ketimine [47].

Kaljuste and Undén [64] reported the mono-*N*-methylation of resin-bound terminal amino acid residues on solid phase. The authors make use of the acid-labile 4,4′-dimethoxydiphenylmethyl (4,4′-dimethoxydityl) group for nitrogen protecting terminal amino acid residues [65]. *N*-Methylation was performed with formaldehyde, acetic acid and sodium cyanoborohydride in DMF. This reaction proceeded in yields in the range 56–99% for most common amino acids. One of the problems associated with the procedure is that up to three methylation cycles were required for some amino acids in order to complete the methylation. It was noted that side-chain

functionalized amino acids needed longer reaction times that then lead to undesirable side-products that could be avoided by decreasing the reaction time, but then incomplete methylation occurred.

6.3.5 Borane Reduction of Amides

Although the reduction of amino acid amides to *N*-alkyl amino acids [66–68], diverges from the parent topic title of Schiff's base reductions, its inclusion in this section is warranted due to its similarity with borohydride reductions of imine intermediates. Krishnamurthy [67] made use of the selective reduction of various formanilides and some alkyl formamides with excess borane/dimethylsulfide complex ($BH_3{\cdot}SMe_2$). The two-step process gave high purity *N*-methyl anilides in 80–100% yield. The method allows for mono-*N*-methylation without the problems associated with dimethylation and no methylation of imines. Chu *et al.* [69] exploited this strategy by reducing *N*-formyl-D-tryptophan methyl ester with $BH_3{\cdot}SMe_2$. The reduction gave, after work-up, *N*-methyl-D-tryptophan methyl ester in 56% yield.

Hall *et al.* [70] reduced amino acid amides in solution and on solid support with diborane in THF, and then treated the product with iodine to promote oxidative cleavage of the borane-amine adducts. In this fashion, amino acid formates coupled to Wang resin were reduced with diborane in greater than 72% yield and greater than 75% purity for the amino acids alanine, valine, serine, and phenylalanine.

The reduction of Schiff's base intermediates is a very mild and racemization-free process. Quitt's method [20] of reductive amination of *N*-benzyl amino acids is to date an efficient cheap and mild method for the synthesis of most NMAs, and has been used frequently for comparison of physicochemical data. A similar approach, employing sodium cyanoborohydride reduction of *N*-diphenylmethyl amino acid ester Schiff's base intermediates in solution and solid phase was described by Polt *et al.* [47] and Kaljuste and Undén [64], respectively. Their work revealed the efficacy of this approach as applied to a wide variety of amino acids, albeit on a small scale. Although in principal this technique is similar to Quitt's method, there are more manipulations involved and the C-terminus must be protected, and excessive amounts of formaldehyde and reducing agent are required to force complete methylation. However, it was shown in the work of Polt *et al.* [47] that small degrees of incomplete methylation were observed.

Reductive amination involving transition metal hydrogenolysis is somewhat limited to dimethylation with formaldehyde, but monoalkylation with aldehydes other than formaldehyde is possible [52–54].

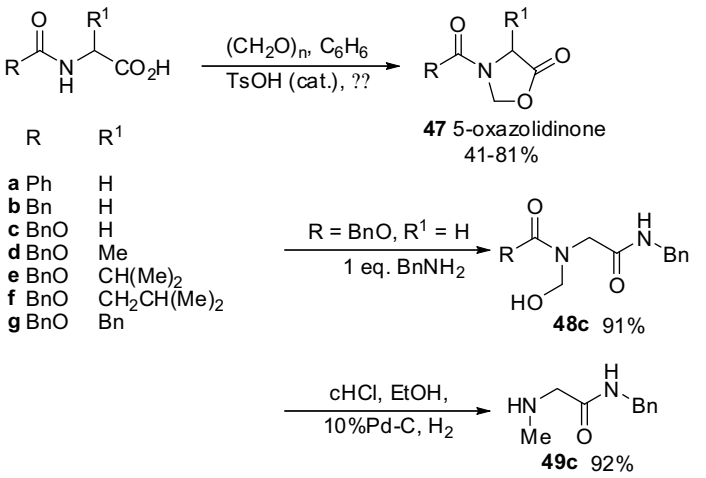
One uncommon technique is the reduction of *N*-formyl amino acids. This approach is obvious since monoformylation of amino acids is readily achieved and therefore concerns of dialkylation and the need for multistep syntheses are eradicated. The problem is the carboxylic acid needs protection since the borane can reduce the acids to alcohols. The technique is further limited to amino acids without other amide groups (i.e., asparagine and glutamine) that may also be reduced.

6.4
N-Methylation by Novel Methods

The following section is a compilation of more elaborate methods for the synthesis of *N*-methyl amino acids. While some of the methods use techniques discussed previously for installing the *N*-methyl group, the methods in this section were devised to prepare especially unusual NMAs required typically for natural product syntheses. These techniques devised for unusual NMA syntheses in most cases were applicable for certain *N*-methylated derivatives and are often not appropriate for other NMAs.

6.4.1
1,3-Oxazolidin-5-ones

Ben-Ishai [71] reported the synthesis of oxazolidin-5-ones **47** (Scheme 6.19) by refluxing *N*-Cbz-protected amino acids with paraformaldehyde in the presence of an acid catalyst. The five-membered heterocyclic intermediates **47** resemble *N*-hydroxymethyl amides and display distinct carbonyl stretches in the infrared region between 1790 and 1810 cm^{-1}. The oxazolidin-5-one ring is susceptible to nucleophilic attack. Amines open them to form amides [71, 72] and alcohols to form esters [73]. Ben-Ishai established this nucleophilic susceptibility by treating the 1,3-oxazolidin-5-one **47c** with an equivalent amount of benzyl amine in alcohol to afford the *N*-hydroxymethyl amide **48c**. Hydrogenation of the *N*-hydroxymethyl intermediate provided *N*-methylglycine (sarcosine) **49c**. It was noted that treating the *N*-hydroxymethyl amide **48c** with an extra equivalent of benzyl amine affects the removal of the *N*-hydroxymethyl moiety to provide *N*-Cbz-glycine benzyl amide. The reductive cleavage of oxazolidin-5-ones to NMAs was not realized until the work of Freidinger *et al*. [74] (see below).

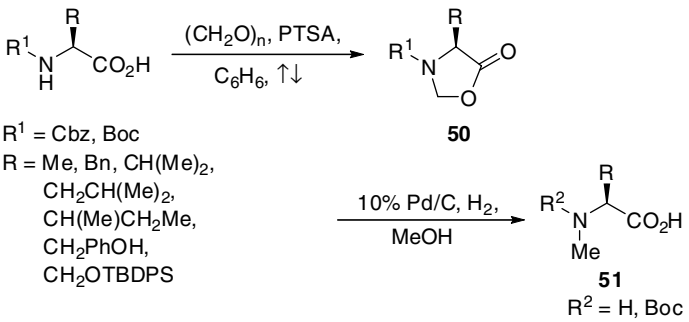


Scheme 6.19

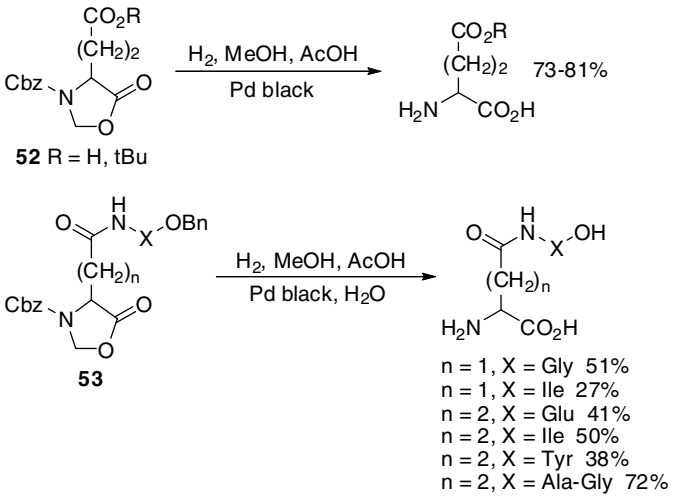
Auerbach *et al.* [75] have shown that *N*-hydroxymethyl (or *N*-methylol) amides analogous to structure **48** could be reduced with triethylsilane/TFA in chloroform to the *N*-methyl amide. Their reduction proceeds by hydride transfer from the silane to an acyliminium ion derived from the *N*-hydroxymethyl amide under the acidic conditions and also showed that this reduction proceeds via a palladium-catalyzed hydrogenation in the presence of TFA [75].

Freidinger *et al.* [74] recognized the potential of oxazolidin-5-ones as stable lactones that are analogous to methylols and could be converted to *N*-methylated derivatives under the conditions described by Auerbach *et al.* [75]. By using Fmoc-protected amino acids, they extended the range of substrates that can be converted to 1,3-oxazolidin-5-ones with alkanals including paraformaldehyde. Treating these substrates with triethylsilane/TFA gave the expected *N*-Fmoc-*N*-methyl amino acids and also some *N*-alkyl derivatives. This sequence was applied to Fmoc-protected alanine, valine, methionine, phenylalanine, lysine, serine, and histidine. Freidinger *et al.* [74] also conducted epimerization studies on the technique using nuclear magnetic resonance analysis of the ^{13}C satellites of the methoxyl signal as internal reference peaks of D- and L-methyl-*N*-Fmoc-*N*-methyl-*O*-benzylserinate, and observed that no detectable epimerization occurred in the reductive cleavage reaction. This technique has also been applied to the TFA-stable *N*-Cbz-protected amino acids and a large range of *N*-Cbz-*N*-methyl amino acids have been synthesized [76, 77].

This technique was further extended to *N*-Boc-protected amino acids by Reddy *et al.* [78], who prepared 1,3-oxazolidin-5-ones **50** with *N*-Cbz and *N*-Boc protection (Scheme 6.20). They applied a different approach to the reduction of the oxazolidin-5-ones by hydrogenation over palladium catalyst under neutral conditions. The *N*-Cbz compounds were converted to NMAs with concomitant removal of the *N*-Cbz group **51** ($R^2 = H$) and the *N*-Boc derivatives were reduced to the corresponding *N*-Boc-*N*-methyl amino acids **51** ($R^2 =$ Boc). This was the first report of success in the use of hydrogenation of *N*-Boc-protected oxazolidin-5-ones as a means of producing the *N*-methyl group directly. However, Itoh [72] reported that the 1,3-oxazolidin-5-one ring becomes reactive by removal of the *N*-protection and this was also the experience of Aurelio *et al.* [77], in the case of *N*-Cbz protected 1,3-oxazolidin-5-ones. Itoh [72] studied the reactions of *N*-Cbz 1,3-oxazolidin-5-ones and, in particular, the



Scheme 6.20



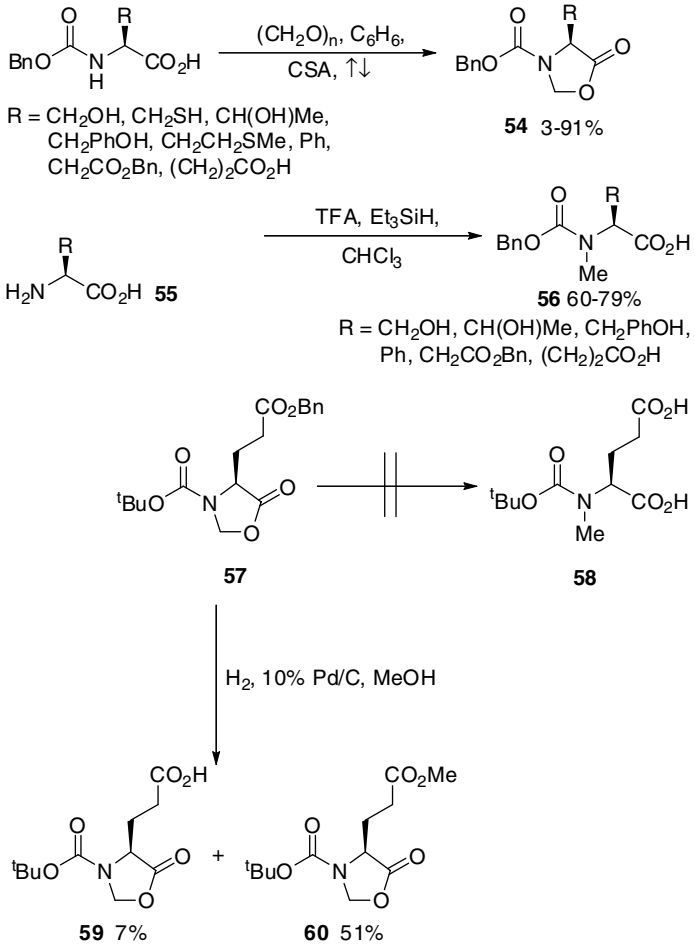
Scheme 6.21

hydrogenolyzes of the derivatives **52** and **53** (Scheme 6.21). These conversions did not produce *N*-methyl amino acids, but instead the methylene carbon was cleaved entirely from the lactone substrate, providing the parent amino acids. Williams and Yuan [79] also observed this result.

Aurelio *et al*. [77] prepared the *N*-Cbz-oxazolidin-5-ones **54** of a variety α-amino acids (Scheme 6.22). Substrates with reactive side-chains were included in the oxazolidin-5-one formation with varying degrees of success. Threonine and serine, in particular, were prone to oxazolidinine formation as was cysteine in forming *N*-Cbz-thiazolidines by reaction with the side-chain hydroxyl and thiol, respectively. Side-chain protection was thus necessary for oxazolidin-5-one formation of these amino acids as well as amino acids with basic side-chains [77c]. Amino acids like tyrosine, glutamic acid, and methionine were converted to the corresponding oxazolidin-5-one, and reduction of several of these substrates by catalytic hydrogenation gave varying amounts of the free α-amino acid **55** in accord with Itoh [72]. Resorting to the conditions applied by Freidinger *et al*. [74], triethylsilane/TFA provided the NMAs **56**. Use of the hydrogenolytic conditions of Reddy *et al*. [78], to reduce *N*-Boc oxazolidin-5-ones **57**, did not result in any of the expected NMA **58** [32]. Instead, two products, **59** and **60**, were recovered.

One reported successful reduction of *N*-Boc-oxazolidin-5-one of methionine in triethylsilane/TFA mixture was achieved by Willuhn *et al*. [80] in the synthesis of *N*-methylhomocysteine derivatives. The reduction under these conditions provided the NMA of methionine with concomitant removal of the Boc group.

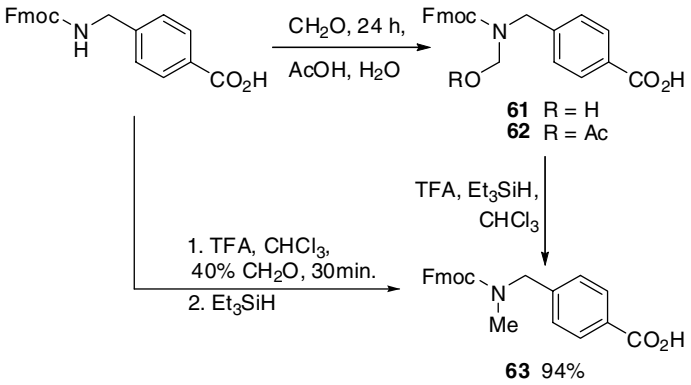
A similar protocol to that of Freidinger was applied to Fmoc-protected *p*-aminomethylbenzoic acid substrates (Scheme 6.23) [81]. The methylol derivatives **61** and **62** were isolated after work-up with varying degrees of decomposition back to starting material when the starting Fmoc-*p*-aminomethylbenzoic acid was treated with formaldehyde in acetic acid. By treating the methylol derivatives with a triethylsilane/TFA



Scheme 6.22

mixture, the corresponding *N*-Fmoc-*N*-methyl amino acids **63** were isolated. This was an unpredictable route due to degrees of reversion to starting materials and so a one-pot process was developed which did not involve the isolation of the often unstable methylol intermediate. The substrate was exposed to TFA and 40% formaldehyde solution for 30 min and then treating the intermediate methylol with triethylsilane providing good to excellent yields (up to 92% yield) of *N*-methylated product.

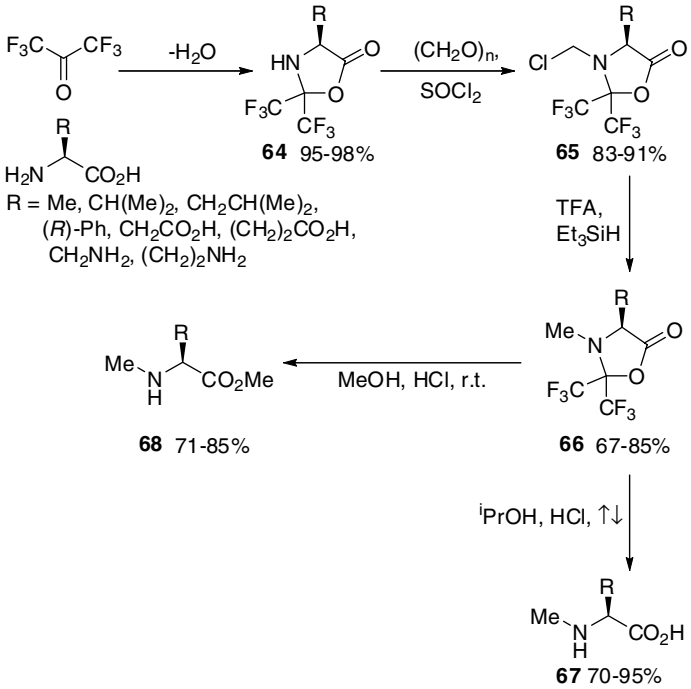
A variation on the theme of 1,3-oxazolidin-5-ones employed 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones **64** as cyclic aminals by condensing amino acids with hexafluoroacetone (Scheme 6.24) [82]. The 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones **64** were used as a means of protecting the carboxyl group and providing a single valence on the α-nitrogen for the desired reaction. The aminal **64** was chloromethylated with paraformaldehyde in the presence of thionyl chloride providing the



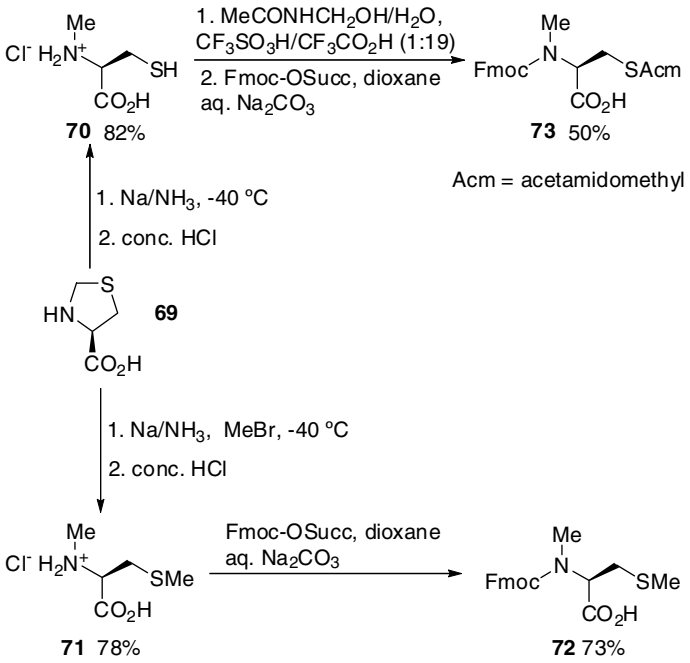
Scheme 6.23

chloromethyl amine **65** which was converted to the *N*-methyl-oxazolidin-5-one **66** with triethylsilane and TFA. Acidolysis of the *N*-methylated derivatives **66** with isopropanol or methanol allows for the isolation of either the NMA **67** or the NMA methyl ester **68**, respectively.

Treating cysteine with formalin provides thiazolidine **69** (Scheme 6.25) which was employed as an intermediate for *N*-methylcysteine in the synthesis of



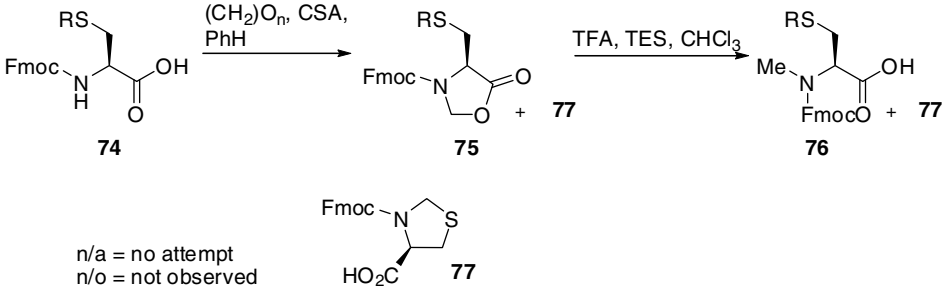
Scheme 6.24



Scheme 6.25

[1-(*N*-methyl-hemi-L-cysteine)]-oxytocin [83]. Reduction of the thiazolidine intermediate with sodium in liquid ammonia gave *N*-methylcysteine that was treated in the same pot with an equivalent amount of benzyl chloride providing the *N*-methyl-*S*-benzyl-L-cysteine in 90% yield (the addition of 1 equiv. of water is crucial in suppressing dimerization) [83]. Final *N*-protection with CbzCl afforded *N*-Cbz-*N*-methyl *S*-benzyl-L-cysteine in 84% yield. Liu *et al.* [84] used the same protocol in making Fmoc derivatives of *N*-methyl-L-cysteine (Scheme 6.26). The thiazolidine **69** [85] was reduced to provide *N*-methyl-L-cysteine **70**. *In situ* treatment with methyl bromide provides the *S*-methyl derivative **71** that was treated with Fmoc-succinimide to give the NMA **72**. Alternatively, treatment of **70** with *N*-hydroxymethyl acetamide and a TFA/trifluoromethanesulfonic acid mixture provided an *S*-acetamidomethyl intermediate that was converted to the Fmoc derivative **73**.

The synthesis of *N*-methylcysteine is a challenging task and, in particular, an appropriate derivative for Fmoc solid-phase application available by a small number of manipulations is desirable. Ruggles *et al.* [86] synthesized *N*-Fmoc-*N*-methyl-Cys (*S*-*t*Bu)-OH **76g** (Scheme 6.26) from the commercially available *N*-Fmoc-Cys (*S*-*t*Bu)-OH **74g** via an oxazolidin-5-one intermediate that was reduced with a triethylsilane/TFA mixture. The authors conducted a study into various classical methods for installing the *N*-methyl moiety with discouraging results. By resorting to the 1,3-oxazolidin-5-one method, it was found that most conversions of a series of derivatives **74a–g** were accompanied by the thiazolidinine **77** formation, even in the reductive step. It was found that the acid-stable *tert*-butylthio protecting group



		% of **77**		% of **77**
74a R = Trt	**75a 76%**	**n/o**	**76a n/o**	**54**
74b R = Mob	**75b 55%**	**42**	**76b 64%**	**34**
74c R = Meb	**75c 85%**	**15**	**76c n/a**	**n/a**
74d R = Bn	**75d 98%**	**2**	**76d n/a**	**n/a**
74e R = tBu	**75e 41%**	**59**	**76e n/a**	**n/a**
74f R = Acm	**75f 20%**	**80**	**76f n/a**	**n/a**
74g R = StBu	**75g 99%**	**11**	**76g 89%**	**n/o**

Scheme 6.26

(*S*-*t*Bu) was the highest yielding in both steps and it was amenable to their synthetic protocol for construction of *N*-methylated small molecule mimics of cyclocystine [86].

Arvidsson *et al.* [87] have studied the reduction of Fmoc-protected 1,3-oxazolidin-5-ones and 1,3-oxazinan-6-ones with different Lewis acids in place of TFA. The authors found that 2 equiv. of aluminum chloride could replace TFA and the reaction time was reduced nearly to a sixth under standard conditions. It was also shown that lactonization and reductions could be performed under microwave irradiation. Several minutes were required for both manipulations, improving yields considerably in most cases.

The oxazolidin-5-one intermediate offers an advantage over the direct alkylation procedures in that the methylene bridge between the α-nitrogen and carboxyl groups offers simultaneous N- and C-terminal protection, and thus side-chain manipulations are possible. Furthermore, the methylene bridge can be smoothly converted to the NMA by reduction under acidic conditions. Although the triethylsilane/TFA combination is a versatile choice for reduction [77], the expense of these reagents and problems in removing trace amounts of TFA make the Lewis acid reduction an enticing practical improvement.

The synthesis of *N*-methylcysteine via reduction of the thiazolidine intermediate is a cost-effective and scalable procedure for making the *N*-methyl derivative. The manipulations involved are trivial and the added advantage is the fact that regioselective alkylation of the thiol group facilitates synthesis of a variety of cysteine derivatives. The recent approach by Ruggles *et al.* [86] utilizing commercially available *N*-Fmoc-Cys(*S*-*t*Bu)-OH for oxazolidinone formation and reduction to the NMA provides a derivative amenable to Fmoc solid-phase synthesis in only two steps.

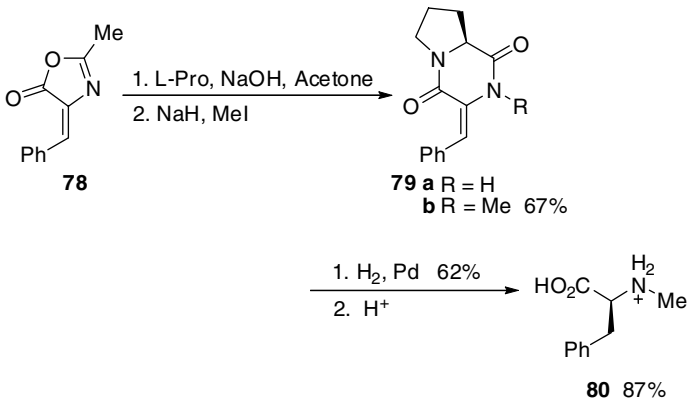
6.4.2
Asymmetric Syntheses

Few contributors to the field have constructed NMAs by methods that require the α-center be created. The common reason for this is that the methodologies enable the synthesis of quite unusual NMAs with unnatural side-chains. The following section involves diverse methodologies that incorporate chiral auxiliaries that confer the required asymmetry on the α-carbon under construction.

A simple technique that utilizes L-proline as an auxiliary was reported by Poisel and Schmidt [88], in the synthesis of *N*-methylphenylalanine (Scheme 6.27). Azlactone **78** is readily prepared from *N*-acetyl-glycine and benzaldehyde under basic conditions. It is then treated with L-proline to form an arylidenedioxopiperazine **79a**. The chiral dioxopiperazine is methylated with classical sodium hydride/methyl iodide conditions providing **79b**. Subjecting **79b** to standard hydrogenation conditions with palladium metal catalyst gives *N*-methyl-L-phenylalanine-L-proline diketopiperazine in 90% e.e. The diketopiperazine was hydrolyzed under acidic conditions affording the free *N*-methylphenylalanine **80**.

Pandey *et al.* [89] condensed *N*-benzylsarcosine **82** and L-prolinol **83** and then through an intramolecular photosensitized electron transfer cyclization formed the chiral auxiliary **84** (93% d.e., Scheme 6.28). The intermediate ether **84** is formed through an iminium ion **81** and upon treatment with Grignard reagents yields *N*-methyl amino acid-L-prolinol dipeptides **85**. It was also shown that Lewis acid-mediated alkylation was possible and provided higher stereoselectivity than the Grignard approach. Hydrolysis of the dipeptides **85** with either aqueous HCl or methanolic HCl provided the corresponding *N*-benzyl-*N*-methyl amino acids or esters **86**, respectively, and L-prolinol **83**, which was recovered in 96%.

Agami *et al.* [90, 91] constructed various NMAs using the chiral morpholine **87** as a template (Scheme 6.29). By condensing *N*-methyl-D-phenylglycinol, glyoxal, and thiophenol, the morpholine **87** was obtained as a single stereoisomer [90]. Treating the morpholine **87** with organometallic reagents displaces the thiophenyl ether

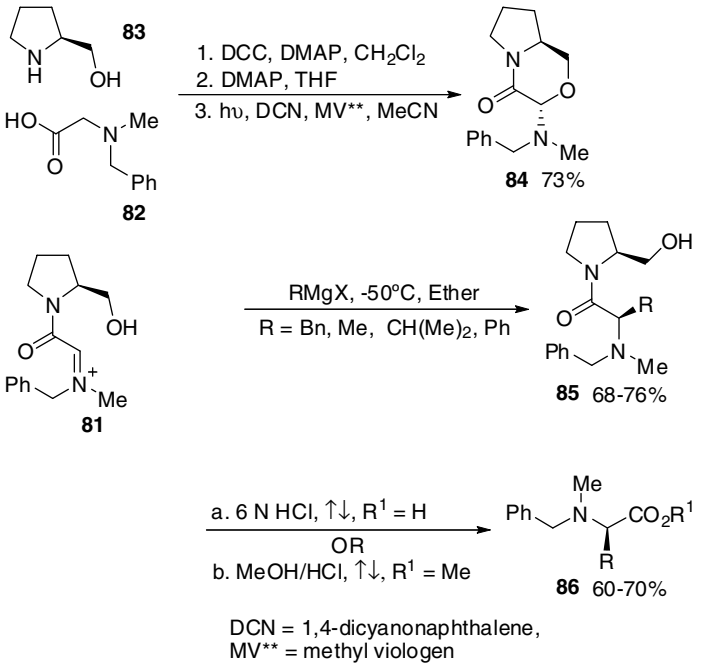


78

79 a R = H
b R = Me 67%

80 87%

Scheme 6.27

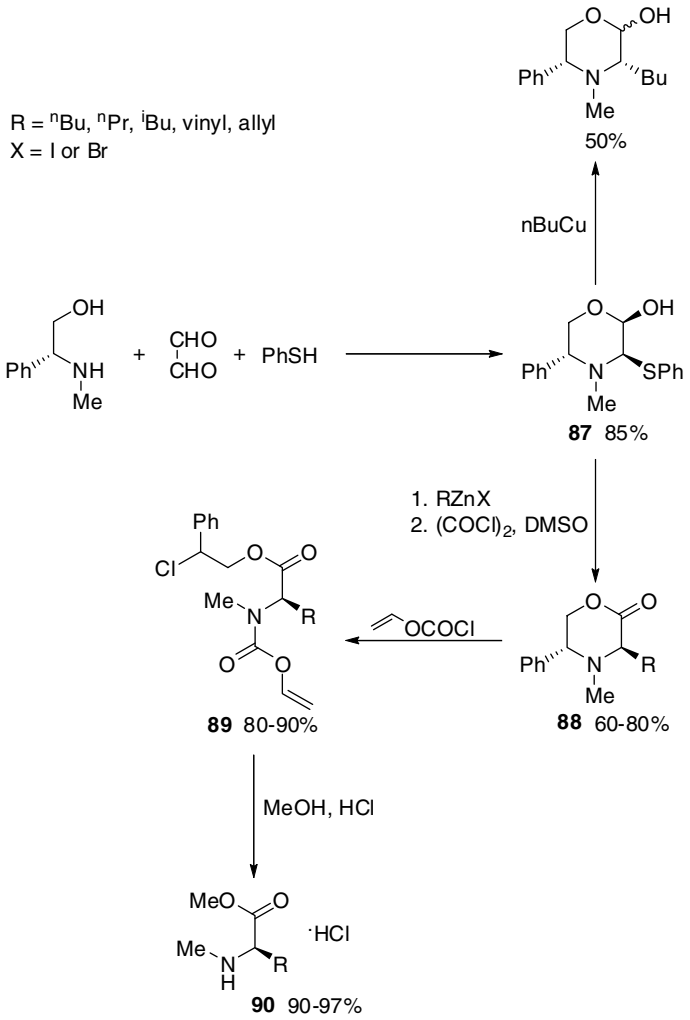


Scheme 6.28

moiety in a stereocontrolled fashion with excellent control, giving in most cases above 98% e.e. Organozincates displaced with retention of configuration and organocuprates displaced with inversion of configuration. Oxidation of the hemiacetal under Swern conditions affords the lactone **88**, which can be completely epimerized with potassium *tert*-butoxide at 40 °C. The NMA was isolated by treating the lactone with vinyl chloroformate to give the acyclic carbamate **89**. Hydrolysis with methanolic HCl cleaves the carbamate and transesterifies the chlorophenethyl ester to the corresponding methyl ester **90**.

Oppolzer *et al.* [92] utilized acylated camphorsultams as auxiliaries in the production of NMAs. Selective hydroxamination of the enolate **91** enabled the monomethylation under reductive alkylation conditions with methanolic formaldehyde, providing the precursors **92** with enantiomeric excesses greater than 99% (Scheme 6.30). Reduction of **92** with zinc dust provided the (*N*-alkylamino)acylsultams **93** which were hydrolyzed under basic conditions to afford the (*S*)-configured NMAs **94** in high yields (90–100%). By applying the same synthetic sequence to the camphorsultam of opposite configuration, (*R*)-configured *N*-methyl α-amino acids can be synthesized with equal efficiency. One advantage of this versatile technique is that the diversity of side-chains in the final NMAs can be made by simply altering the acyl function attached to the camphorsultam auxiliary.

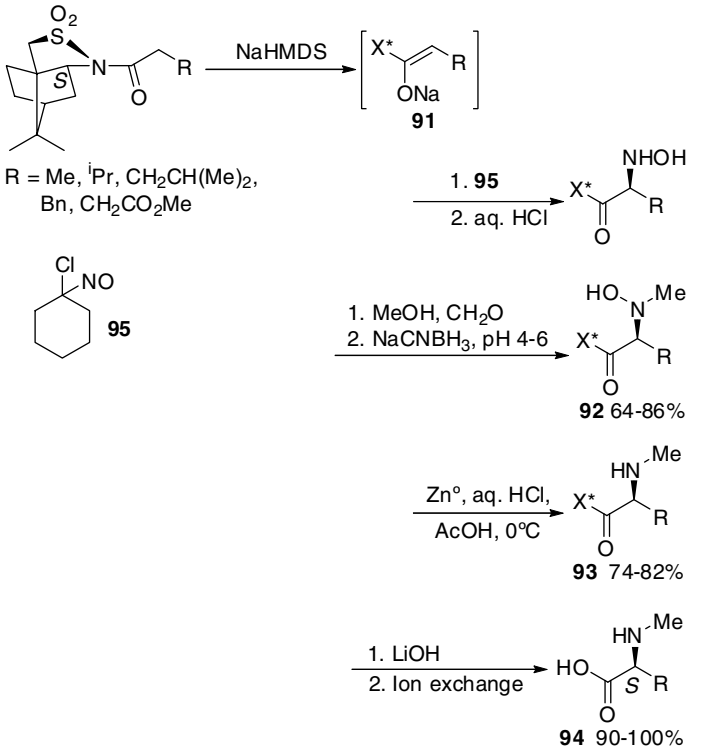
Pseudoephedrine has made its way as a chiral auxiliary into the asymmetric synthesis of NMAs as described by Myers *et al.* [93]. By amidating sarcosine with (*R,R*)-pseudoephedrine, the chiral auxiliary **96** was used in the synthesis of amino



Scheme 6.29

acids and *N*-methyl amino acids (Scheme 6.31). Lithiation of **96** forms the intermediate enolate **97** that was quenched with alkyl halides providing the NMA derivatives **98** with good stereocontrol. Where R = Bn, the alkylation product **98** (*N*-methylphenylalanine) was isolated in 93% yield and 88% d.e. in the crude state and the diastereomeric excess was improved to 99% by recrystallization. Where the alkyl substituent was an ethyl group, the product **98** was isolated in 77% yield with 94% d.e. after purification.

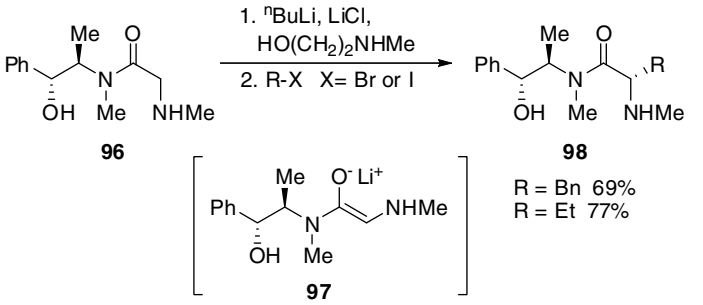
An imaginative approach to NMAs was applied by Grieco and Bahsas [94] in the synthesis of a variety of NMAs. Amino acid esters and amides were treated with formaldehyde and the intermediate iminium ion was trapped with excess cyclopentadiene via an aza-Diels–Alder pericyclic reaction as 2-azanorbornenes **100**



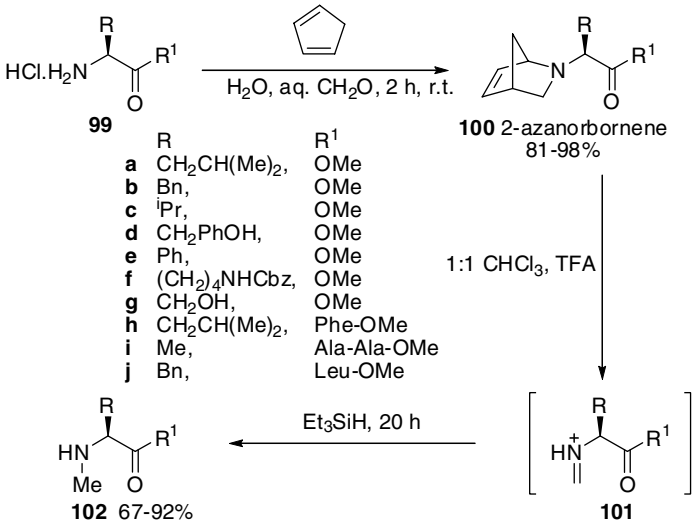
Scheme 6.30

(Scheme 6.32). In the presence of TFA, cycloreversion occurs and the intermediate iminium ion **101** is intercepted by silane affording the NMA esters and amides **102** in yields ranging from 67 to 92%.

The reductive alkylation of optically active scalemic azides **103** has found use providing intermediates in the synthesis of several NMAs (Scheme 6.33). Dorow and Gingrich [95] treated several azido acids, esters, and amides with dimethylbromoborane providing the NMAs. The synthetic sequence was subjected to an



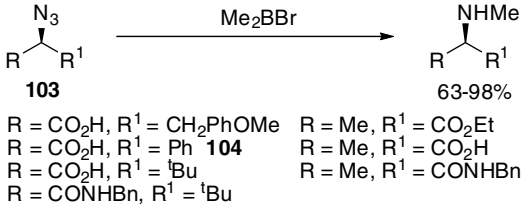
Scheme 6.31



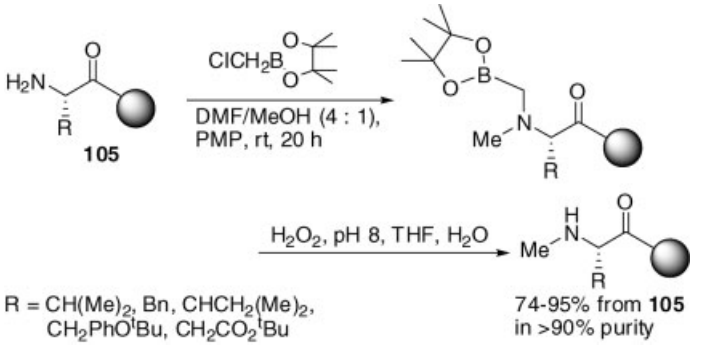
Scheme 6.32

epimerization test with 2-azidophenylacetic acid **104** (99% e.e.), a precursor to *N*-methylphenylglycine, a standard used in epimerization studies of NMA syntheses. It was found that treatment of **104** with dimethylbromoborane at 40 °C gave the product *N*-methylphenylglycine in 68% yield with 38% e.e. When the same conditions were applied to **104** at 20 °C, (*S*)-*N*-methylphenylglycine was obtained in 99% yield, but the enantiomeric excess was not revealed and it was hypothesized that the increased temperature contributed to the possibility of enolization. The lower temperatures used suppressed enolization, providing optically active NMAs.

A clever method for *N*-methylating α-amino acids was devised by Laplante and Hall [96]. Amino acids bound on solid support were treated with pinacol chloromethylboronic ester under basic conditions with the highly hindered base, 1,2,2,6,6-pentamethylpiperidine (PMP) (Scheme 6.34). Peroxide treatment of the aminomethylboronic ester adduct provides the free NMA. To date this is the only procedure that utilizes amino acids in an unprotected form by which mono-*N*-methylation is achieved. The *N*-methylation is based on a 1,2-carbon-to-nitrogen migration of boron in α-aminoalkylboronic esters. The free amine **105** bound to either Wang or SASRIN resin (an acronym coined from super acid sensitive resin) was treated with an excess of the boronic ester (5 equiv.) that achieves dialkylation.



Scheme 6.33



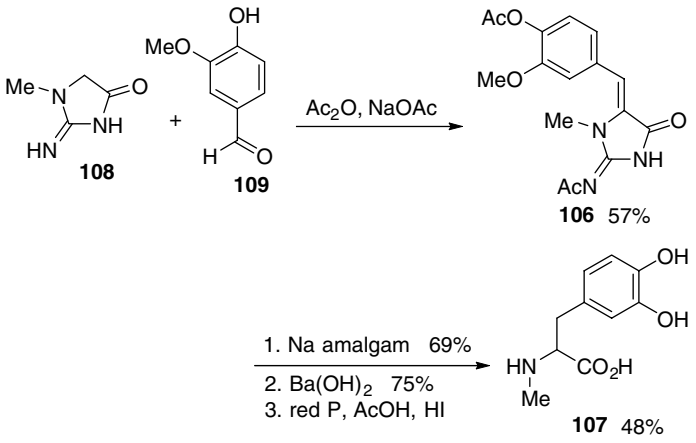
Scheme 6.34

This is followed by hydrogen peroxide treatment in a pH 8 buffered solution and was designated as a "repair mechanism" that removes over alkylated sites. The dialkylation/peroxide process provided NMAs with greater than 90% purity. It was shown that using equivalent amounts of the boronic ester always resulted in varying degrees of alkylation. However, there are limitations to this procedure in that oxidizable candidates such as methionine were not suitable for these *N*-methylation conditions.

6.4.3
Racemic Syntheses

Up until now the processes reviewed for *N*-methylation of α-amino acids have focused on chiral methodologies whether they include optically active amino acids as starting materials or construction of optically active NMAs through asymmetric synthesis. One obvious facet of NMA chemistry is the propensity of NMAs to epimerize through certain reactions and the majority of the synthetic routes discussed thus far have been developed in order to eliminate this problem. Racemic amino acids are rarely employed in synthetic applications but have been evaluated as potential therapeutics [97]. One obvious disadvantage of racemic mixtures is that if single enantiomers are required, a resolution process must follow. However, one advantage of racemic substrates is that conditions which usually racemize amino acids and, in particular NMAs, are compatible with racemic syntheses.

The earliest account of NMA synthesis via azlactam intermediates was reported by Guerrero *et al*. [98] who employed intermediate **106** in the synthesis of *N*-methyl-3,4-dihydroxyphenylalanine (DOPA) **107** (Scheme 6.35) as opposed to the azlactone asymmetric synthesis developed by Poisel and Schmidt [88] several decades later. Creatinine **108** and vanillin **109** were condensed under classical azlactone conditions with acetic anhydride (dehydrating source) and fused sodium acetate (base) to provide the azlactam **106**. By utilizing creatinine **108** the *N*-methyl group is already in place. Reduction of the benzal group with sodium amalgam also results in concomitant removal of the acetate. Hydrolysis with barium hydroxide removes the formamidine moiety, and final reduction with red phosphorus and hydroiodic acid provided racemic *N*-methyl-DOPA **107**.

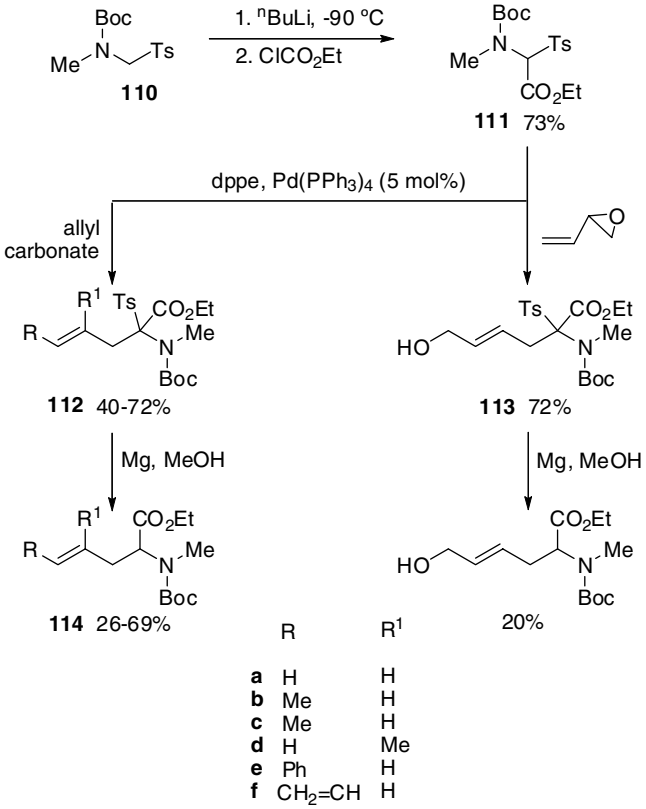


Scheme 6.35

Racemic unsaturated alkyl side-chain NMAs have been synthesized through a sulfone intermediate applied by Alonso *et al*. [99]. The *N*-Boc-*N*-methylsulfone **110** (Scheme 6.36) was lithiated and quenched with ethyl chloroformate providing the *N*-Boc-NMA ester **111**. The intermediate **111** was used to synthesize various unsaturated NMAs via two paths. One path involved the palladium catalyzed allylation with various allyl carbonates and the other involved epoxide ring opening of 2-vinyloxirane, affording α-tosyl-γ,δ-unsaturated-*N*-methyl amino acids **112** and **113**, respectively. The sulfone derivatives **112** and **113** were then treated with magnesium powder in methanol which caused desulfonylation at room temperature, as these intermediates were unstable. It was revealed that the nucleophilic substitutions were highly regioselective and completely stereoselective for compounds **114b**, **c**, **e**, and **f**, affording only the *E*-stereoisomers.

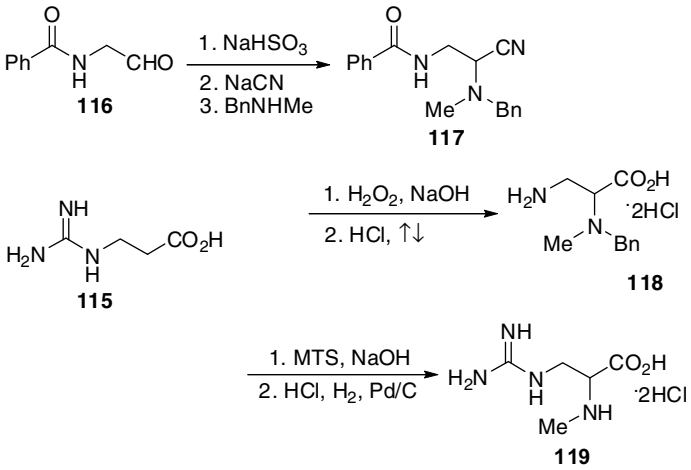
A novel guanidine-based NMA was synthesized by Larsen *et al*. [97] based on analogs of the antidiabetic/antiobesity agent, 3-guanidinopropionic acid **115** (Scheme 6.37). The racemic aminonitrile **117** was synthesized from the starting aldehyde **116**, and then oxidized to the carboxylic acid and hydrolyzed with HCl to the dihydrochloride salt **118**. The dihydrochloride salt **118** was derivatized with the guanilating agent 2-methyl-2-thiopseudourea sulfate and the *N*-benzyl group was removed under standard hydrogenation conditions to provide the NMA **119**.

As mentioned in the introduction to this section, if single enantiomers are required from a racemic synthesis then a resolution of racemate is to follow. Groeger *et al*. [100] synthesized a variety of racemic *N*-methylaminonitriles by condensing various aldehydes with methylamine and hydrogen cyanide in yields ranging from 79 to 89% (Scheme 6.38). Hydrolysis of the nitriles to the carboxylic acids and chloroacetylation provided the *N*-protected NMAs, that were resolved by the *N*-acyl-L-proline-acylase specific for (*S*)-configured NMAs. A complete loss of activity was observed if the substrate had α-substituents that were longer than two carbons or branched.



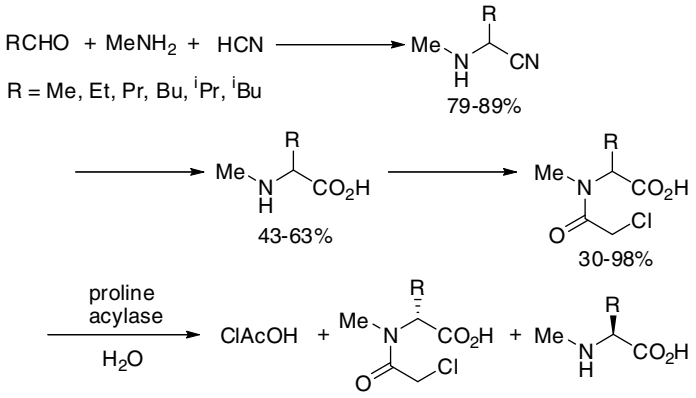
dppe=1,2-bis (diphenylphosphine) ethane

Scheme 6.36



MTS=2-methyl-2-thiopseudourea sulfate

Scheme 6.37



Scheme 6.38

6.5 *N*-Alkylation of Amino Acids

The following sections are devoted to the synthesis of *N*-alkyl α-amino acids with alkyl chain lengths longer than one carbon unit. One of the first methods for synthesizing various *N*-alkyl α-amino acids was reported in 1949 by Gal [101], who treated various racemic α-bromo acids with alkyl amines. Many of the methods described earlier for *N*-methylating α-amino acids are applicable for *N*-alkylation and in particular the techniques described in Section 6.3. *N*-Methylation via Schiff's base reduction is most pertinent to this topic. The work of Bowman [52–54] described in Section 6.3, has shown the ease with which mono *N*-alkylating α-amino acids with various aldehydes is compared to mono *N*-methylation under palladium catalyzed hydrogenation conditions. One should note that the area of *N*-alkylation has not been studied in as great detail as *N*-methylation since these substituents are rarely seen in natural products; however, it is an attractive functional group in materials and peptidomimetic chemistry. Some *N*-alkylated amino acids are used as *N*-protecting groups and in particular the benzyl-type groups (dityl and trityl also) are used in *N*-methylation procedures due to their ease of removal (see Section 6.3). The following sections are broken down by the type of technique employed to install the alkyl substituent rather than by *N*-alkyl α-amino acid since most authors employ a range of alkyl groups in a technique.

6.5.1 Borohydride Reduction of Schiff's Bases

This section comprises the majority of techniques that are used to synthesize *N*-alkyl α-amino acids. This simple procedure of adding an aldehyde to an amino acid in basic, acidic, or neutral media and reducing the resultant Schiff's base with a borohydride reducing agent offers the chemist a practical means to prepare *N*-alkyl α-amino acids by using simple zwitterionic amino acids without carboxyl protection.

Again, dialkylation is not problematic since steric hindrance does not allow for this to occur.

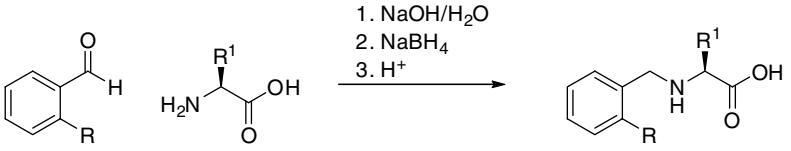
6.5.1.1 Sodium Borohydride Reductions

Preparation of *N*-benzyl α-amino acids is readily accomplished by the simple expedient of forming the Schiff's base of the amino acid and the appropriate benzaldehyde in aqueous base or alcoholic aqueous base mixtures [20, 102]. After stirring for a period of time to complete the Schiff's base formation, the intermediate is reduced with excess sodium borohydride in portions providing the *N*-benzyl α-amino acids in yields ranging from 40–90% and high purities. This simple procedure allows for excess benzaldehyde to be used without the problem of dialkylation occurring and there is no need for protecting the acid as an ester (Scheme 6.39).

6.5.1.2 Sodium Cyanoborohydride Reductions

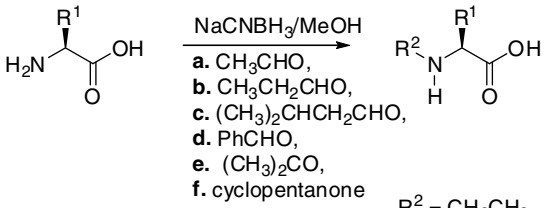
In comparison to other reducing agents, sodium cyanoborohydride is the most frequently used borohydride in the reduction of Schiff's bases to form *N*-alkyl α-amino acids. Ohfune *et al.* [48a] used a variety of aldehydes and ketones to form Schiff's bases with five amino acids (methionine, phenylalanine, valine, serine, and glutamic acid) and these were reduced in one pot with sodium cyanoborohydride (Scheme 6.40). Methionine was used as a model compound for optimization of the reaction conditions. It was found methanol was the best solvent to use with 0.7 equiv. of sodium cyanoborohydride to affect complete reduction to the *N*-alkyl species. The products precipitated from the reaction media as the zwitterion and were simply washed with methanol providing essentially pure compound in yields ranging from 51 to 96%. Ando and Shioiri [103] applied the same protocol as Ohfune *et al.* [48a] in the synthesis of *N*-alkyl amino acids and methyl esters. In the case of methyl esters, acetic acid was added to the medium until pH 6 was reached.

Bitan *et al.* [104] synthesized a range of N^{α}-functionalized alkyl amino acids as building units for *N*-backbone cyclic peptides. Aldehydes of varying chain lengths containing heteroatoms are condensed under the conditions of Ohfune *et al.* [48a]. In



R = OH, R^1 = gly	R = H, R^1 = ala
R = OH, R^1 = ala	R = H, R^1 = val
R = OH, R^1 = aib	R = H, R^1 = leu
R = OH, R^1 = val	R = H, R^1 = phe
R = OH, R^1 = his	R = H, R^1 = ser
R = OH, R^1 = tyr	R = H, R^1 = lys(Tos)
R = OH, R^1 = trp	R = H, R^1 = lys(Cbz)
	R = H, R^1 = arg(NO_2)

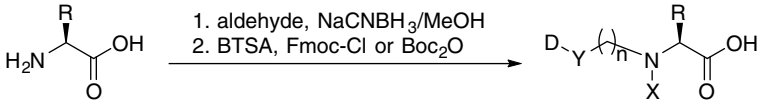
Scheme 6.39



R^1 = met
R^1 = phe
R^1 = val
R^1 = ser
R^1 = glu

$R^2 = CH_2CH_3$
$R^2 = CH_2CH_2CH_3$
$R^2 = CH_2CH_2CH_2(CH_3)_2$
$R^2 = CH_2Ph$
$R^2 = CH_2(CH_3)_2$
R^2 = cyclopentyl

Scheme 6.40



R = gly, glu, ile, leu, lys, met, phe, ser, trp, tyr, val.
BTSA = *N*,*O*-bis(trimethylsilyl)acetamide

Y	D	n	X
NH	Boc	2,3	Fmoc
CO_2	^{t}Bu	4	Fmoc
S	Bzl	2-4,6	Boc, Fmoc

Scheme 6.41

this fashion a number of orthogonally protected *N*-alkyl α-amino acids suitable for Fmoc solid-phase synthesis were produced (Scheme 6.41).

6.5.1.3 Sodium Triacetoxyborohydride Reductions

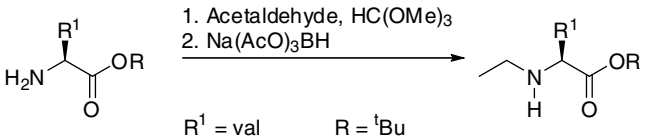
Ramanjulu and Joullié [49] synthesized various *N*-alkyl amino acid esters employing various aldehydes and reducing the imine thus formed with sodium triacetoxyborohydride. The authors state that better yields and reproducibility of results are obtained with this reducing agent compared to the cyanoborohydride. Rückle *et al.* [50] sought to improve on this technique by synthesizing various *N*-ethyl amino acids using excess acetaldehyde in the dehydrating solvent trimethyl orthoformate (Scheme 6.42). After 30 min imine formation was complete, and the excess acetaldehyde was removed by concentration and then the imine was reduced with excess triacetoxyborohydride in yields ranging from 57 to 85%.

6.5.2 *N*-Alkylation of Sulfonamides

The reader should consult Section 6.2.2 as the techniques described there are related to the alkylation protocol described here.

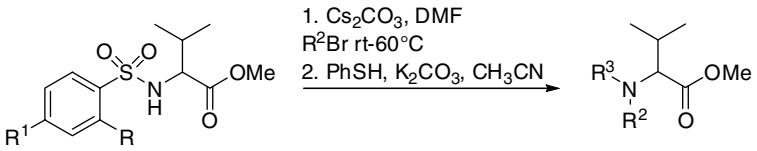
6.5.2.1 Base-Mediated Alkylation of Benzene Sulfonamides

In 1995, Fukuyama *et al.* [105] reported the *N*-alkylation of nosyl-protected amines via alkylation with alkyl halides and Mitsunobu reaction with alcohols. The nosyl



R^1 = val	R = ^{t}Bu
R^1 = val	R = Me
R^1 = leu	R = ^{t}Bu
R^1 = phe	R = ^{t}Bu
R^1 = lys(Cbz)	R = ^{t}Bu
R^1 = thr	R = ^{t}Bu
R^1 = thr	R = Bn
R^1 = thr(OBn)	R = Bn
R^1 = thr(O^tBu)	R = ^{t}Bu

Scheme 6.42



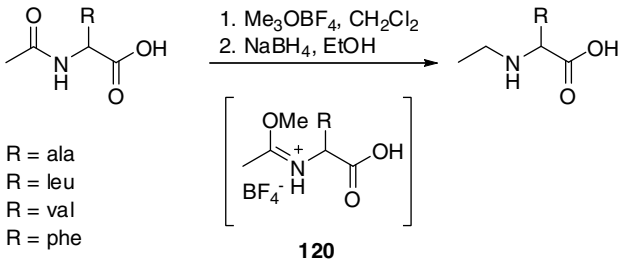
R = NO_2	R^1 = H	R^2 = allyl	R^3 = H
R = NO_2	R^1 = H	R^2 = benzyl	R^3 = H
R = NO_2	R^1 = H	R^2 = butyl	R^3 = H
R = NO_2	R^1 = H	R^2 = 4-pentenyl	R^3 = H
R = H	R^1 = NO_2	R^2 = 4-pentenyl	R^3 = H
R = CN	R^1 = H	R^2 = allyl	R^3 = 4-CNPhSO_2
R = CN	R^1 = H	R^2 = butyl	R^3 = 4-CNPhSO_2

Scheme 6.43

protection protocol has many applications in amino acid synthesis, due to its ease of introduction and removal (see Section 6.2.2). Bhatt *et al.* [106] exploited this with their synthesis of oxopiperazines, and Bowman and Coghlan [107] revealed the ease with which unsaturated alkyl groups can be installed by using D- and L-valine methyl esters as models (Scheme 6.43). The authors describe two sets of conditions used to install the alkyl groups as "mild" in which the alkylation takes place at room temperature and "vigorous" when taking place at 60 °C. The 4-cyanobenzenesulfonyl group was also utilized in the protocol to overcome the sluggish allylation and butylation in the nosyl series. Although the alkylations were rapid and high yielding the conditions to remove the nosyl derivatives (PhSH, K_2CO_3, CH_3CN) did not remove the 4-cyanobenzenesulfonyl group and resulted in decomposition [107].

6.5.3
Reduction of *N*-Acyl Amino Acids

The reader should consult Section 6.3.5 as some of the methods described include examples of the *N*-alkyl amino acids from the acylated precursors; in particular,



Scheme 6.44

the borane reduction of amides by Hall *et al.* [70] in solution and solid phase producing *N*-ethyl and *N*-propyl amino acid derivatives.

6.5.3.1 Reduction of Acetamides

The pioneering work of Benoiton *et al.* [31–34] in the *N*-methylation of carbamates and amides using sodium hydride and methyl iodide has been exploited in the synthesis of many natural products, and has been accepted as a mild procedure for *N*-methylating amino acid derivatives. Chen and Benoiton [66] have also devised a mild room temperature reduction of acetamides using Meerweins reagent [108] (trimethyloxonium tetrafluoroborate, Scheme 6.44). By treating the acetamides with trimethyloxonium tetrafluoroborate an imino ether fluoroborate intermediate **120** forms that is reduced to the alkyl substituent with sodium borohydride. In this fashion *N*-ethyl-D,L-amino acids were isolated in 41–55% yield. One chiral amino acid *N*-Ac-L-Leu-OH was submitted to the reaction conditions and the isolated *N*-ethyl-L-Leu-OH showed an optical rotation similar to a reported value, yet no other information on the chiral purity of this derivative was communicated.

6.5.4 Novel Methods for *N*-Alkylating α-Amino Acids

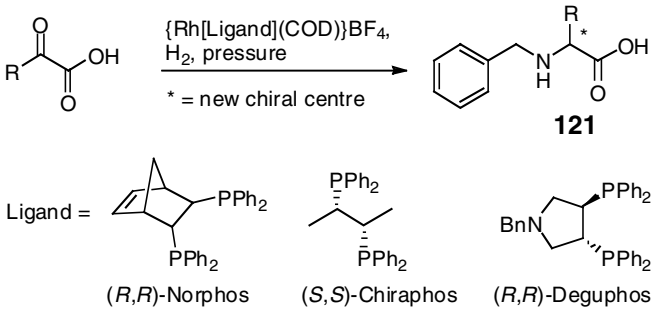
Only a few reports on the synthesis of *N*-alkyl amino acid synthesis by novel methods have been published and the reader is urged to refer to Section 6.4 as, again, some of the methods there are applicable to *N*-alkylation.

6.5.4.1 Asymmetric Synthesis of *N*-Alkyl α-Amino Acids

One report by Kadyrov *et al.* [109] describes the asymmetric synthesis of *N*-benzyl amino acids by condensing different α-keto acids with benzyl amines and reducing the imines enantioselectively with rhodium catalysts under pressure in a hydrogen atmosphere (Scheme 6.45). After optimization of the reaction conditions and utilization of suitable chiral ligands (Scheme 6.45) a range of chiral (*R*) amino acids **121** were produced in good yield and up to 98% e.e.

6.5.4.2 *N*-Alkylation of 1,3-Oxazolidin-5-ones

The 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones (Scheme 6.24) employed by Spengler and Burger [82] in the synthesis of *N*-methylamino acids were utilized by

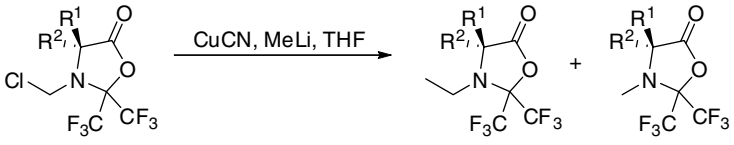


R = $PhCH_2$, Me, Ph, $HOOCCH_2CH_2$, $HOOCCH_2$, $PhCH_2CH_2$, Me_2CHCH_2, Me_3CCH_2

Scheme 6.45

Schedel and Burger [110] in the synthesis of *N*-ethylamino acids (Scheme 6.46). By treating the 1,3-oxazolidin-5-ones with Cu(I) cyanide and 2 equiv. of methyl lithium the authors found that 20–50% of the NMA was formed along with the *N*-ethyl species. By reducing methyl lithium to one equivalent, high yields of the *N*-ethyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones were isolated and only trace amounts of the *N*-methyl derivative were detected. It was also shown that the free *N*-ethylamino acid could be isolated by treating the oxazolidin-5-one with dilute HCl or hydroxamates by treatment with hydroxylamine and dipeptide amides by exposure to amino acid amides.

It is well documented that the synthesis of *N*-methylamino acids is accompanied by difficulties that arise by installing a single methyl unit at the α-nitrogen. On the other hand, *N*-alkylation with more than one carbon unit has been shown to be relatively straightforward and less transformations are involved, particularly with reductive amination reactions as described by Ohfune *et al.* [48a]. The area of *N*-alkylation is not as broadly studied as *N*-methylation and this can be attributed to the fact that *N*-methylamino acids are highly prominent in natural products compared to *N*-alkylamino acids.



$R^1 = CH_3$	$R^2 = H$
$R^1 = CH(CH_3)_2$	$R^2 = H$
$R^1 = CH_2CH(CH_3)_2$	$R^2 = H$
$R^1 = H$	$R^2 = Ph$
$R^1 = Ph$	$R^2 = H$

Scheme 6.46

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