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Amino acid chlorides

A journey from instability and racemization towards broader utility in organic synthesis including peptides and their mimetics[Ψ]

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[Ψ] *Dedicated to Professor Padmanabhan Balaram, Indian Institute of Science, Bangalore on the occasion of his superannuation*

Abstract

The review provides a broad overview of amino acid chlorides in peptide chemistry, classified into different sections comprising reagents, *N*-protected amino acid chlorides (preparation and properties), coupling employing various protocols and applications in difficult and hindered couplings. The recent developments include their applications in synthesis of various amino acid derivatives, peptidomimetics, heterocycles and biologically active molecules.

Contents

1. Introduction

Acid chlorides as peptide coupling agents has its origin in Emil Fischer's era with the first report of *N*-protected dipeptide of glycine synthesis emerging in 1903 by Emil Fischer.[1] Soon the octadecapeptide [Leu-$(Gly)_3$-Leu-$(Gly)_3$-Leu-$(Gly)_9$-OH, 1907] of Emil Fischer[2] and the nonadecapeptide of Abderhalden and Fodor[3] were successfully obtained by the same method. Their journey until 1980's has been roller coaster where upon acid halides were considered as overactivated species and labeled as "obsolete" in peptide chemistry. The incompatibility of acid halide activation with the protecting groups,[4] as well as conditions of coupling which may lead to racemization were majorly due to dearth of technologies to overcome those limitations and were quite exaggerated. Though newer techniques were blossomed in the hands of peptide chemists, these didn't address the concerns related to the acid halide activation strategy for a very long time. Also acid halide activation faced severe competition and criticism due to the availability of myriad fancy reagents. With seminal contribution of Louis Carpino on acid chlorides of Fmoc amino acids, the inertia surrounding the stability aspect of acid halides as coupling agents was brushed away by the isolation of shelf stable Fmoc amino acid chlorides and their successful application in peptide bond formation.[5] In fact, the so called "over activation" is turned out to be a boon in the synthesis of sterically hindered peptides in the years followed. Since then, the acid halides have been at the forefront of armamentarium of peptide chemists in difficult synthesis from being redundant.

Subsequently amino acid fluorides were developed and found to be sufficiently stable to tertiary bases and can also be employed in coupling in absence of a base effectively.[6-10] Oxazolone formation was scant or absent in the presence of a tertiary base. Acid fluorides were efficient in both solution and solid phase synthesis of peptides incorporating even acid labile protecting groups. However for the coupling of highly hindered substrates utility of acid chlorides prevail on to that of acid fluorides. Though the acid fluorides are of significance as evidenced by their utility in critical synthesis of some bioactive peptides, a broad discussion of their chemistry is out of the scope of this review.

Amino acid bromides are highly reactive species which are more reactive than acyl chlorides towards amines (up to two orders of magnitude). Acid bromides have been utilized successfully for the synthesis of peptides containing α–trifluoromethyl (α–Tfm) or α–

difluoromethyl (α–Dfm) amino acids and *N*-Me-amino acids.[11-17] However acid bromides are underutilized thus far. This is mainly because of the non availability of suitable brominating reagent, even for their generation in situ.

The pronouncement of acid chloride method as 'overactivation' (as illustrated by Brenner)[18] or unattractive (as summarized by Bodanszky)[19] or obsolete (as concluded by Jone)[20] has been quite overstated. What is needed is the following: both the conditions for preparation of acid chlorides as well as coupling required to be compatible with nature of N^{α}, C^{α} and side chain protecting groups. In other words, choosing appropriate protocol is a must for obtaining the target molecules with chiral homogeneity.

With the advent of in situ acid halide generating reagents such as bis(trichloromethyl)carbonate,[21] 1-chloro-*N*,*N*,2-trimethyl-1-propen-1-amine,[22] *N*-[chloro(dimethylamino)methylene]-*N*-methylmethanaminium chloride (TMUCl Cl),[23] simplified work up and purification procedures were developed which offer quite a solution to the problems pertaining to reactivity and difficult coupling as faced by peptide community over a long period. Acid halides have turned out to be the most efficient coupling strategy in terms of chemistry and atom economy. Also acid halides have been the trouble shooter in some of latest relevant peptide syntheses. Thus today, acid halides are the most bankable coupling activation strategy particularly for the assembly of difficult peptide sequences. The acid halides have now grown from mere peptide coupling agents to valuable candidates for a variety of difficult acylation reactions.

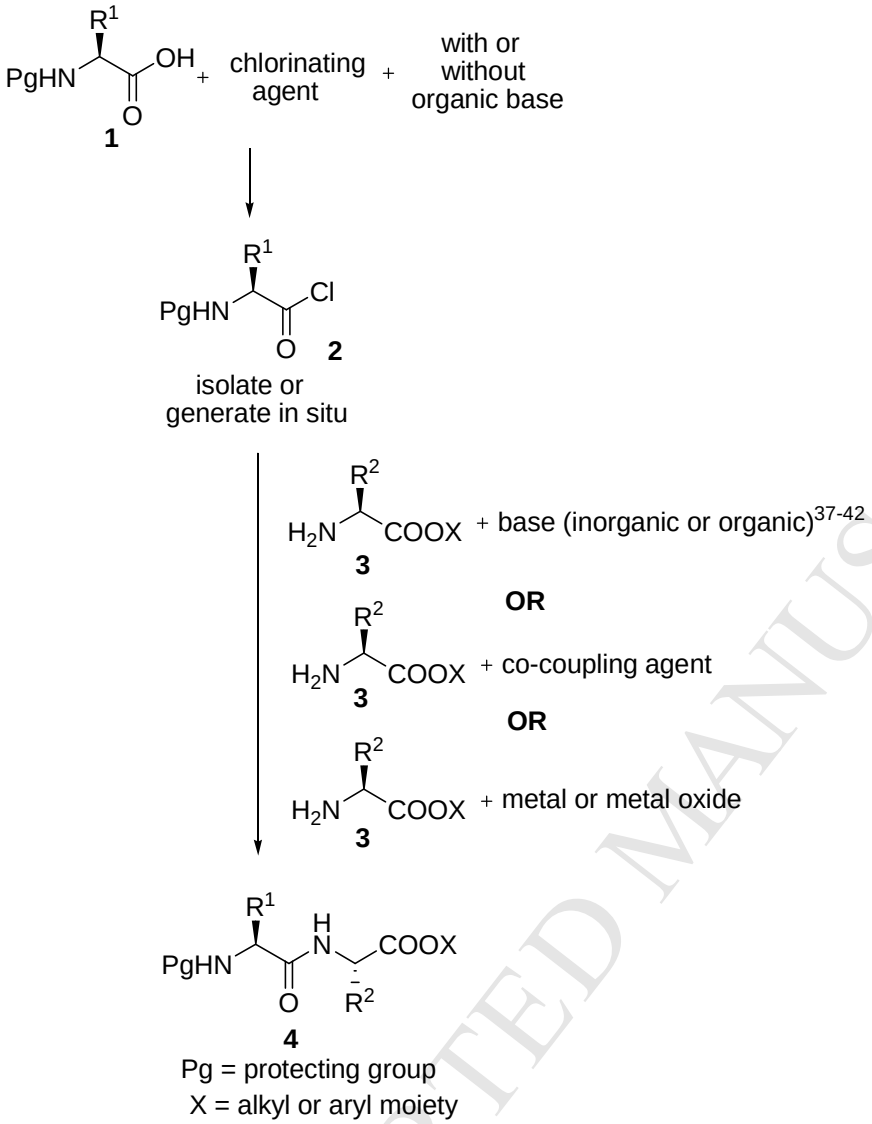
The last review on the topic has been Louis Carpino's work in which he had summarized primarily his group's contributions in an account in 1996.[24] Also, not a comprehensive coverage is found in the chapters regarding acid halides in various books.[19, 25-30] Various reviews[31-36] have been published on peptide coupling reagents, however without the essential depth in acid halide activation. The applications of acid halides have generated impressive number of publications in recent past (i.e., after Louis Carpino's account) and there is no update in the review literature regarding the recent developments in critical applications of acid chloride activation in the assembly of biologically active molecules. Thus, there is a need of a review encompassing the origin, significance and relevance of acid halides in peptide chemistry, which could be termed as a "black swan event" being revolutionized by Louis Carpino. The present review focusses on

essentials of origin and development of acid chloride chemistry, as well as contributions after Louis Carpino's account surveyed till 2014 and thus in all the journey of acid chlorides over a century.

The objectives of the review are to provide broad overview of acid chloride activation in peptide chemistry, which has not been dealt with the requisite attention thus far and a full pledged article on this topic has been elusive in the literature. The review covers wholesome aspects of acid chlorides in peptide chemistry classified into different sections comprising reagents, *N*-protected amino acid halides, coupling employing various protocols and applications in difficult and hindered couplings. In addition to synthetic methodology and coupling protocols, the review highlights diverse applications which include synthesis of peptidomimetics, biologically active drugs, natural products and as chiral auxiliaries in synthesis of enantiopure intermediates. Total synthesis of various biologically active cyclic peptides including cyclosporins O and A, omphalotin A, and petriellin A possessing *N*-methyl amino acids in their core structure involved in situ acid chloride activation as an important feature. Distinct advantages of acid halides over a range of peptide coupling reagents in terms of hindered couplings have been utilized in recent significant contributions, which gave them decisive edge over other methods.

With our expertise in acid halides, we want to put forth the legacy details as well as the growth of the acid chloride chemistry and highlight their relevance in today's synthetic peptide chemistry.

A broad picture of several protocols available for both the preparation as well as the coupling using acid chlorides is furnished in scheme 1.



Scheme 1. Various protocols employed for the preparation as well as the coupling using acid chlorides.

Unlike active ester and anhydride methods, the preparation of acid chlorides itself require attention. Altogether, the following criteria are very significant with respect to the use of acid chloride method in peptide chemistry.[37-44]

(1) selection of chlorinating agent: conditions required for the formation of acid chloride, i.e., temperature, quantity of reagent, duration of conversion, properties of other products (eg., CO_2, SO_2, $POCl_3$, etc) and their complete removal.

(2) the necessity of base and of course, its nature for preparation of acid chlorides

(3) shelf stability of acid chlorides for storage which in turn depends on nature of N^{α}-protecting group. Parallelly the acid chloride can be generated in situ for immediate use.

(4) coupling conditions chosen play extremely key role in terms of oxazolone formation (or otherwise) which can lead to racemization. In essence, the coupling being carried out using (i) an equimolar quantity of an organic base or ii) under Schotten-Baumann conditions or iii) mediated by non Schotten-Baumann conditions determines the oxazolone formation.

(5) the use of either an equimolar quantity of an organic base or Schotten-Baumann conditions for coupling and the properties of N^{α}-protecting group; in particular, when the coupling duration need to be extended (for insertion of sterically hindered amino acids/residues). The use of base labile group and the coupling under basic conditions lead to the premature deblocking of N^{α}-protecting group.

(6) monitoring of coupling eg., polarity of 9-fluorenylmethoxycarbonyl (Fmoc)-amino acid chloride vs the product are almost similar in many cases.

To summarise, it is to understand that the optimum conditions need to be chosen for both efficient as well as practical utility of the acid chloride method. Suffice to point out that this primarily depends on the nature of the target molecule itself.

2. Chlorinating reagents

Acid chlorides provide simple and economical way to accomplish activation of a carboxylic group towards acylation. This makes the carbonyl group highly electrophilic and reactive towards both nitrogen as well as oxygen nucleophiles. Numerous reagents have been developed over the years to bring about acyl chloride formation. Thionyl chloride, oxalyl chloride, phosphorous trichloride, phosphorous oxychloride, phosphorous pentachloride, pivaloyl chloride, phthaloyl dichloride, phosgene are the commonly employed reagents for the preparation of acid chlorides in organic synthesis (Fig. 1).[45-51] The harsh conditions including elevated temperatures employed during acid chloride preparation using PCl_5 or $SOCl_2$ leads to side reactions. The isolation of pure products in case of reagents PCl_5, $POCl_3$ is also cumbersome. However, $SOCl_2$ is the most frequently used one in amino acid chemistry. The formation of undesired product HCl in the above cases is detrimental for acid sensitive Boc, Cbz and ^{t}Bu protecting groups; thereby dictating the selection of reaction condition to be chosen for preparation involving acid sensitive functionalities. The use of iminium chloride reagent *N,N*-

dimethylchloroformimidinium chloride has been limited primarily in phthaloyl and Cbz chemistry.

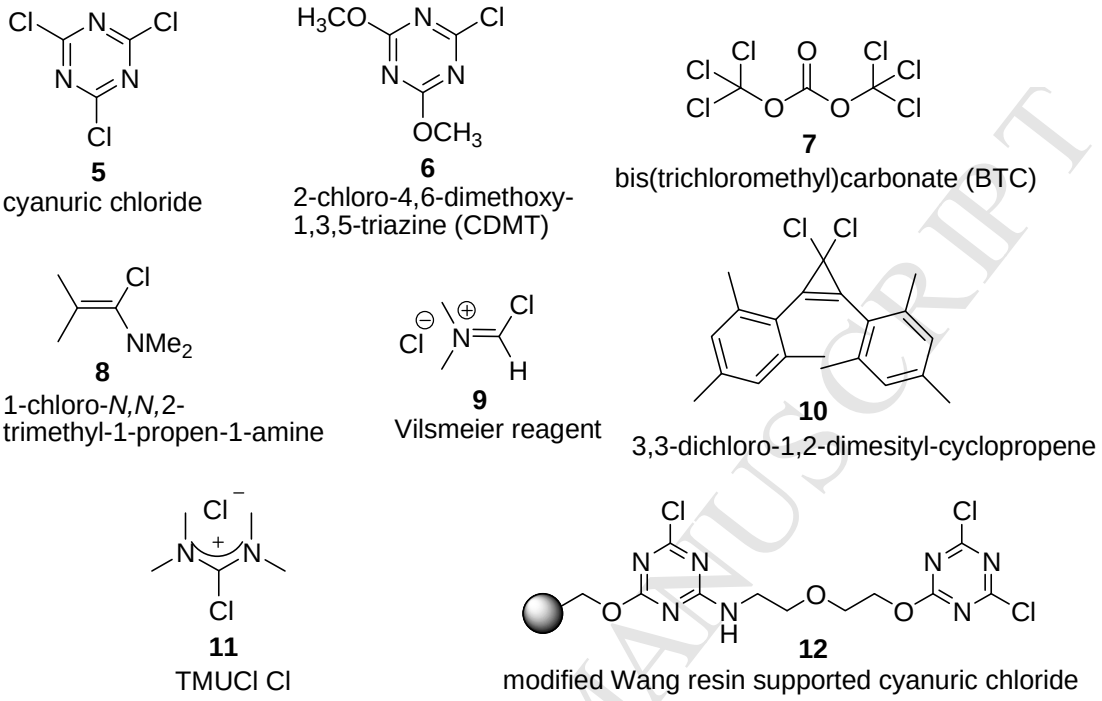


Figure 1. Chlorinating reagents employed in peptide chemistry.

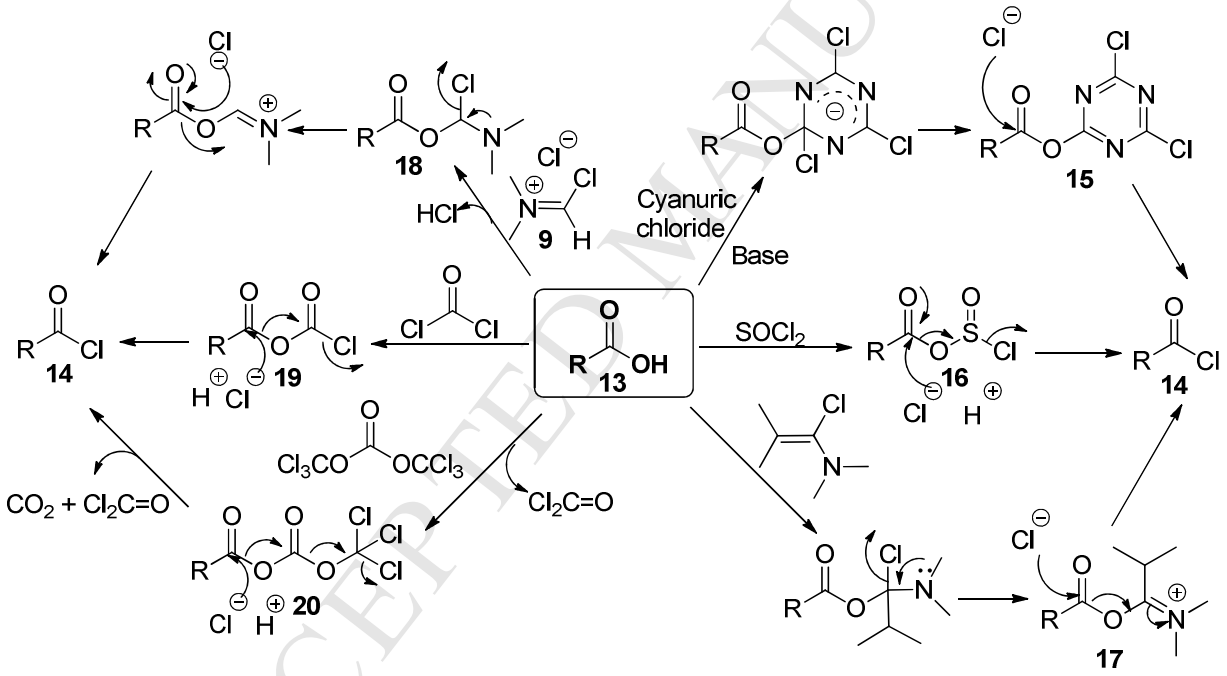
Cyanuric chloride **5**[52] and 2-chloro-4,6-dimethoxy-1,3,5-triazine **6** (CDMT, Fig.1),[53] are useful halogenating reagents which give rise to neutral side products thereby compatibility with the ^{t}Bu side chains in amino acid chemistry is achieved. Due to weak basicity of the triazine moiety, the byproduct cyanuric acid and excess coupling reagent present, if any, can be removed by simple filtration followed by washing with diluted acids.

Bis(trichloromethyl)carbonate **7** (BTC or triphosgene)[21] was employed by Falb et al. as in situ chlorinating agent in combination with collidine as a base at 50 ^{o}C in inert solvents such as tetrahydrofuran (THF), 1,4-dioxane to obtain Fmoc amino acid chlorides containing acid labile side chains (both proteinogenic and *N*-alkyl amino acids). BTC in combination with diisopropylethylamine (DIEA) and collidine is exceptionally useful for coupling of sterically hindered *N*-alkyl amino acids in the synthesis of hinderd polypeptides.

Devos et al. developed an extremely benign reagent system tetramethyl-α-chloroenamine **8** (1-chloro-*N*,*N*,2-trimethyl-1-propen-1-amine),[22] devoid of formation of HCl in acid chloride preparations. This will concord the presence of acid sensitive ^{t}Bu groups and wide range of other

protecting groups. Vilsmeier reagent **9** was employed as an efficient chlorinating agent which can be prepared by combination of *N*,*N*-dimethylformamide (DMF) with phosgene or $SOCl_2$ or $(COCl)_2$. 1-Chloro-*N*,*N*,2-trimethyl-1-propen-1-amine **8**[22] as well as Vilsmeier reagent **9**[54] have been employed for the in situ generation of amino acid chlorides (Scheme 2).

Recently in an interesting study, Hardee et al. employed 3,3-dichloro-1,2-dimesitylcyclopropene **10** for generation of acid chlorides in presence of DIEA by aromatic cation activation.[55] *N*-[Chloro(dimethylamino)methylene]-*N*-methylmethanaminium chloride **11** (TMUCl Cl) was developed by Albericio et al. for the solid phase preparation of anilides from carboxylic acids.[23] Also a modified Wang resin supported cyanuric chloride **12** has been demonstrated for amidation of Boc amino acids through acyl chloride route albeit with complete racemization.[56]



Scheme 2. Commonly employed reagents for acid chloride formation and the mechanism of activation.

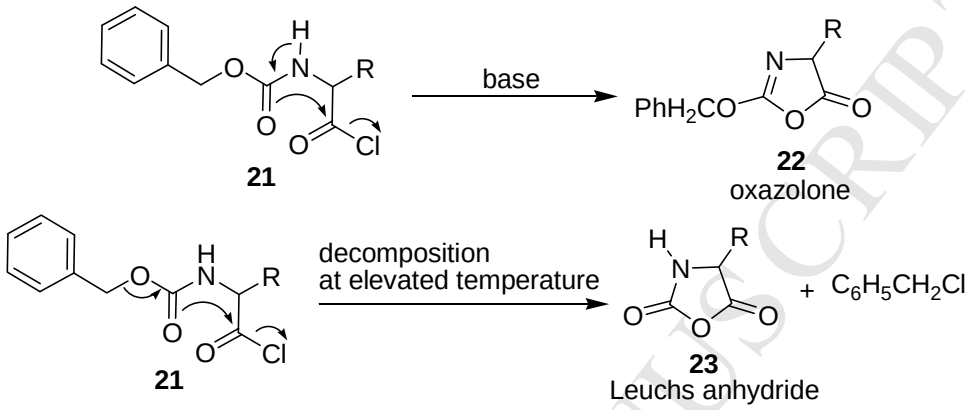
3. Preparation and properties

3.1. Urethane protected amino acid chlorides

3.1.1. Cbz- and Boc-chemistry

The general synthesis of benzyloxycarbonyl (Cbz)-amino acid chlorides **21** is primarily marked by the instability as well as the loss of stereochemical integrity through base catalyzed oxazolone formation **22** (Scheme 3).[57-60] Stable Cbz-amino acid chlorides **21** can be prepared at

low temperatures using PCl_5, however get converted to the corresponding *N*-carboxyanhydrides **23** (NCAs) slowly on shelf (Scheme 3). Also the removal of unwanted product $POCl_3$ from the acid chloride product is known to be tedious.[61] $SOCl_2$ usually gives acid chlorides at high temperature, hence considered unsuitable for the synthesis of Cbz-amino acid chlorides **21**.



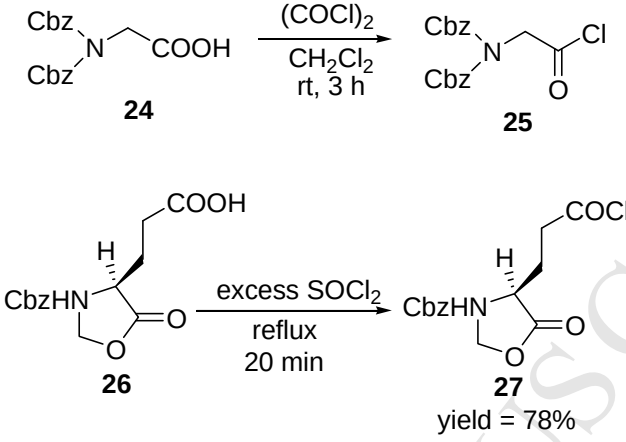
Scheme 3. Formation of oxazolone and Leuch's anhydride from Cbz-amino acid chloride.

The use of 1 : 1 mixture of $SOCl_2$: benzotriazole permits the preparation of acid chlorides at room temperature.[62] This procedure seems attractive for the synthesis of stable Cbz-amino acid chlorides at room temperature thereby alleviating the high temperature conditions which will lead to their decomposition to NCAs **23**.[63] Of course, the resulting acid chlorides need to be utilized soon after its preparation which circumvents their decomposition on shelf storage.

NCAs were first discovered by Leuchs and coworkers, when they tried to purify *N*-ethoxycarbonyl or *N*-methoxycarbonyl amino acid chlorides by distillation.[64-66]

Schmidt et al. developed a simple protocol for in situ generation of acid chlorides from Cbz-amino acids as well as Cbz-oxycarboxylic acids at 0 ^oC by employing 1-chloro-*N*,*N*-2-trimethyl-1-propen-1-amine **8**.[67,68] The acid chlorides thus formed were free from tertiary bases, HCl and their salts. The byproduct *N*,*N*-dimethylisobutyramide was separated from the crude desired product by distillation or by silica gel chromatography. Matsuda et al. employed dicyclohexylammonium (DCHA) salts of Cbz-protected amino acids for in situ generation of acid chlorides at room temperature using $SOCl_2$ and pyridine within one min.[69] But the study involved Ala, Phe, Val, Leu, Glp and Glu(OEt) only. In other examples involving Cbz group, bis-Cbz-glycyl chloride **25** (*N*,*N*-bisbenzyloxycarbonyl-glycyl chloride) was prepared in situ by

reaction of oxalyl chloride on *N*,*N*-bis-Cbz-Gly **24** and was utilized directly without isolation (Scheme 4).[70] Also Cbz-Glu protected as oxazolidinone **26**, was refluxed with excess $SOCl_2$ to obtain the corresponding γ-acid chloride **27**.[71,72]



Scheme 4. Synthesis of bis-Cbz-glycyl chloride and γ-acid chloride of Cbz-Glu protected as oxazolidinone.

As in the case of Cbz chemistry, preparation of *tert*-butoxycarbonyl (Boc) amino acid chlorides posed problems concerning both stability and stereomutation. There are only a couple of reports regarding the synthesis of Boc-amino acid chlorides.[73] The attempts to prepare Boc-Phe-Cl using modified Wang resin-supported cyanuric chloride **12** had met with limited success.[56]

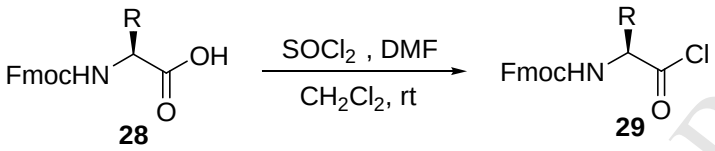
Interestingly, recent attempts with the use of 3,3-dichloro-1,2-dimesitylcyclopropene **10** as a chlorination reagent in presence of DIEA as the base is quite promising with encouraging prospects.[55] Recently, the reagent is used for the conversion of carboxylic acids to their acid azides, which are later converted into ureidopeptides through Curtius rearrangement.[74]

3.1.2. Fmoc chemistry

The first illustration of Fmoc amino acid chloride **29** was evidenced in a tertiary amide bond formation as reported independently by Cohen[75a] and by Pass et al.[75b] But neither they were isolated nor characterized by them. Finally in 1984, Carpino successfully applied $SOCl_2$ method to Fmoc amino acids **28** leading to the isolation of corresponding acid chlorides **29**.[5] A 0.1 eq of DMF as catalyst accelerated the conversion which was complete within 1 h at room temperature. The participating chlorinating agent here is *N*,*N*′-formamidinium chloride. All the Fmoc-amino acid chlorides from proteinogenic amino acids were isolated as crystalline solids, none of them

were found as oils (Table 1). They were found to be shelf stable, could be stored for months in a desiccator at room temperature without perceptible decomposition. Fmoc-amino acid chlorides show characteristic vibrational stetching band (KBr) at around 1790-1810 cm^{-1}.

Table 1 List of Fmoc-protected amino acid chlorides



Amino acid	Yield (%)	mp (^oC)	Amino acid	Yield (%)	mp (^oC)
Gly	95.4	108-109	Lys(Cbz)	88.3	67-68
Ala	80.6	112-114	Phe	95.8	120-121
Ile	87.3	103-104	D-Phe	92.5	119-120
Pro	78.6	93-94	Leu	96.0	80-81
Val	85.3	111-112	Tyr(Bn)	91.2	114-115
Met	90.3	118-119	Ser(Bn)	90.8	96-98
Cys(Bn)	95.2	104-105	Asp(Bn)	89.3	50-53

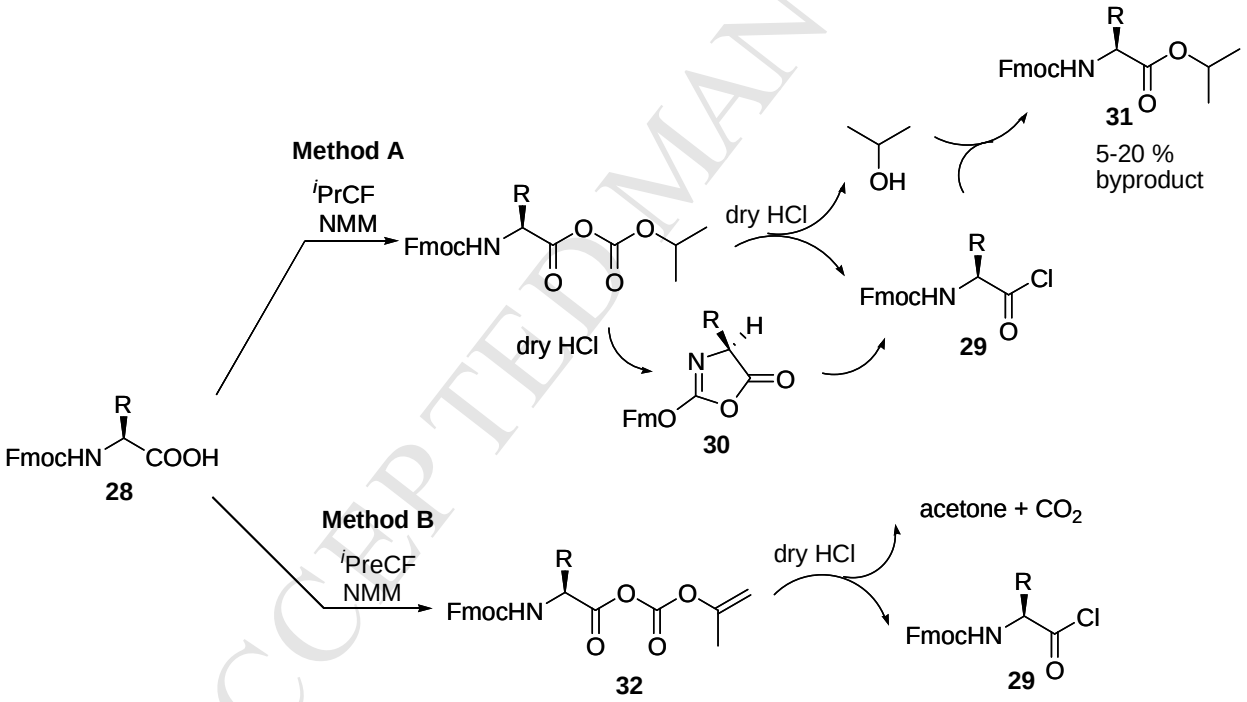
* Yields given are of the pure isolated chlorides following recrystallization from CH_2Cl_2-hexane.

Several Fmoc-*N*-methylamino acid chlorides, Fmoc-dialkylamino acid chlorides were also reported by employing $SOCl_2$ method at room temperature in moderate to good yields.[76] All these compounds were obtained as solids and were shelf stable under anhydrous conditions. Although not isolated, Fmoc-δ-aminovaleryl chloride (Fmoc-δ-Ava-Cl) was also prepared.[77-79] The synthesis of Fmoc-amino acid chlorides[80] **29** has been found to be accelerated by ultrasonication at room temperature, and corresponding acid chlorides could be obtained in 25-55 min in good yields and purity.[81,82]

Benoiton et al. demonstrated that mixed anhydrides of Fmoc-amino acids could be converted into corresponding acid chlorides by anhydrous HCl in contrast to that of Cbz- as well as Boc-protected amino acid mixed anhydrides which will convert into corresponding NCAs.[83] Activation of Fmoc amino acids with isopropyl chloroformate (^{i}PrCF) followed by treatment with anhydrous HCl (Scheme 5; method A) provided corresponding acid chlorides along with 5-20% of ester byproduct **31** depending on the amino acid employed. However, Fmoc-Phe-$OCO_2{}^i$Pr and Fmoc-Val-$OCO_2{}^i$Pr gave ester free acid chlorides in good yields. The *tert*-butyl

esters and *tert*-butyl carbamido groups did not survive, though varying percentages of intact ether function were obtained from Fmoc-Ser(^{t}Bu)-OH and Fmoc-Thr(^{t}Bu)-OH. Also depending on the nature of the alkyl group varied amounts of ester was obtained as side product. The side reaction could be eliminated by employing isopropenyl chloroformate (^{i}PreCF; Scheme 5; method B), as acetone is generated by the liberated alkoxy group. The optical integrity of the Fmoc-Val-Cl (chosen as a model substrate) obtained by mixed anhydride method was established by reacting it with HCl·H-Val-OEt/NMM followed by determination of the epimeric content of the products by RP-HPLC, where it showed <1% of D-isomer.

The list of Fmoc-amino acid chlorides made include Leu (yield = 78%), Phe (yield = 78%), Ile (yield = 74%), Lys(Cbz) (yield = 83%), Glu(Bn) (yield = 80%), Ser(^{t}Bu) (yield = 82%) and Thr(^{t}Bu) (yield = 82%).



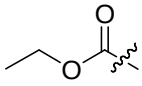
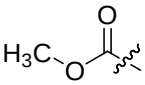
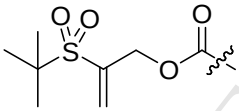
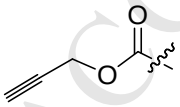
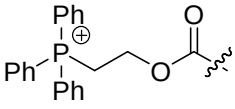
Scheme 5. Synthesis of Fmoc-amino acid chlorides from mixed anhydrides.

Significantly, the in situ generation of Fmoc-amino acid chlorides using BTC lead to the conversion of Met, Arg(Pmc) (Pmc = 2,2,5,7,8-pentamethylchroman-6-sulfonyl), Asp/Glu(O^{t}Bu), Cys(Trt) (Trt = trityl), Gly, L/D-Lys(Boc), Ser-/Thr-L/D-Tyr(O^{t}Bu), Trp(Boc) to the corresponding acid chlorides. However, the attempts with respect to Fmoc-His(Trt) and Fmoc-Asn(Trt) were futile.[84]

3.1.3. Other urethane protecting groups

Several other reported urethane protected amino acid chlorides include 2-(*tert*-butylsulfonyl)-2-propenyloxycarbonyl (Bspoc) amino acid chlorides,[85] and propargyloxy carbonyl (Poc) amino acid chlorides,[86] {[2-(tri-phenylphosphonio)ethyl]oxy}carbonyl (Peoc) amino acid chlorides[87] and Etoc-amino acid chlorides.[88-90] Their preparation and properties are enlisted in the table 2.

Table 2 Other urethane protected amino acid chlorides: Preparation and properties

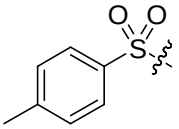
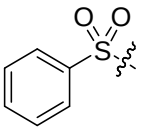
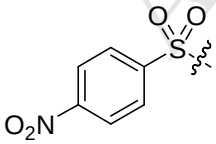
Entry	Protecting group	Reagent/Reaction condition	Amino acid chlorides
1	 Etoc	$(COCl)_2$, DMF, 0 °C[88,91,92]	Ala (97%, yellow oil)[54,93] Val (98%, colourless oil)[54] Pro (98%, colourless oil)[54] Phe[94] *N*-MeAla[95,96]
	 MeOCO	$(COCl)_2$ in CH_2Cl_2, 0 °C to room temperature[95,96] PCl_5 in ether, 0 °C	Ala[95]
2	 Bspoc	$SOCl_2$ in CH_2Cl_2, room temperature[85]	Phe (82%, mp = 100-100.5 °C) Gly (91%, mp = 61.5-62.5 °C)
3	 Poc	$SOCl_2$ in CH_2Cl_2, room temperature[86]	Phg, Phe, Ala (Acid chlorides were found stable and storable at room temperature under anhydrous conditions for several days.)
4		$(COCl)_2$ in CH_2Cl_2 at 0 °C to room temperature[87]	Val, *O*-Peoc-hydroxyisovaleroyl chloride (Peoc-Hyiv-Cl)[97]

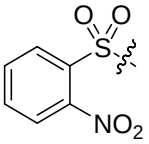
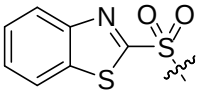
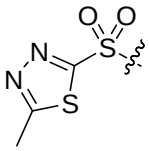
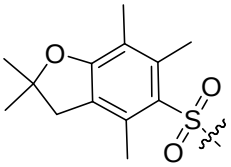
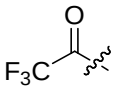
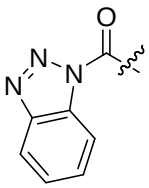
Peoc

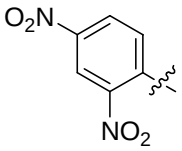
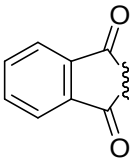
3.2. Non-urethane protected amino acid chlorides

Several sulfonyl protecting groups including 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf), *ortho*-nitrobenzenesulfonyl (*o*-Nbs), benzothiazole-2-sulfonyl (Bts),[98] and 5-methyl-1,3,4-thiadiazole-2-sulfonyl (Ths) have been used to prepare stable amino acid chlorides which find utility, particularly when highly reactive coupling agent is required. Sulfonamide linkage is completely stable to the conditions employed for both the preparation of acid chlorides as well as their use as coupling agents. However their deprotection is quite cumbersome due to requirement of harsh conditions. A list of sulfonyl as well as other non-urethane protected amino acid chlorides and their properties are compiled in table 3.

Table 3 Non-uretharne protected acid chlorides: Preparation and properties*

Entry	Protecting group	Reaction condition	Amino acid chloride	Remarks
1	 Tos	(a) $SOCl_2$ in $CHCl_3$ at 45 ^oC for 15 min.	L-Phg (mp = 134-137 ^oC)[99] D-Phg (mp = 133-136 ^oC)[99] Phe (mp = 124-126 ^oC)[100] Cys(SBn) (45.5 %, mp = 112-114 ^oC),[101] Pro,[102] Ala[103]	Recrystallized as crystalline solids.[104]
		(b) PCl_5 in dry ether, 0 ^oC to room temperature	pyroglutamyl chloride (Glp) (90%, mp = 71-74 ^oC)[105]	
		$SOCl_2$ in dry benzene at room temperature to reflux for 3 h	Ala[103,106]	
2	 Nosyl (Ns)	$SOCl_2$ in CH_2Cl_2 at reflux for 30 min[106,107]	L-Phe, D-Phe, Leu, Ile, Val, L-Ala, D-Ala[103,106]	Yellowish solids obtained in quantitative yields.

3	 o-Nbs	1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, collidine[108,109]	Ala	
4	 Bts	$SOCl_2$ in CH_2Cl_2 at reflux for 2 h[110]	Phg, Leu, Val, L-Ala, D-Ala[110,111]	
5	 Ths	$SOCl_2$ in CH_2Cl_2 at reflux for 2 h[111]	Phg[111]	
6	 Pbf		*N*-Me-Aib[112]	
7	 TFA	(a) Vilsmeier reagent in *n*-BuOAc at -10 to -12 °C for 3 h[54,113-116]	Phe, Lys[54,117]	Acid chlorides found stable for at least 24 h when maintained at -10 °C in EtOAc, BuOAc and CH_2Cl_2 whereas in DMF significant racemization was observed.
		(b) $(COCl)_2$ in dry benzene, pyridine (3 drops) at reflux for 15 min[54]	Ile, Met, Tyr, Pro[54,117]	
		(c) $(COCl)_2$ in CH_2Cl_2, DMF (0.5 mL/0.1 mL) at room temperature for 2 h[117]	Pro[118]	
8		$SOCl_2$ in CH_2Cl_2 at room temperature, 24 h or reflux for 1 h	Val, Leu, Phe, D-Phg[119-122]	

	Btc			
9		$SOCl_2$ at reflux for 1 h	Gly (92.5%, mp = 129-130 ^oC), Ala[123-125]	Recrystallized using benzene as crystalline solids.
	2,4-DNP			
10		PCl_5 in dry benzene at 50-55 ^oC (boiling water bath)	Ala (93%, mp = 55 ^oC) Phe (87%, mp = 86 ^oC) Phg (85%, yellow oil)[126-130]	
	Pht		Gly (mp 84-85 ^oC)[131]	
11	Tos/phenyl/2-methyl-5-nitrophenyl/4-methyl-3-nitrophenyl/sulphonyl	$SOCl_2$, reflux, 1 h	glutamic acid dichloride[132]	

*selected amino acid derivatives listed

3.3. Azido acid chlorides

Meldal et al. has proposed azido acid chlorides as highly efficient coupling agents with small size amino protecting group.[133] Several proteinogenic amino acids could be converted into α-azido acid chlorides with triflylazide (TfN_3), followed by treatment with $SOCl_2$. The acid chlorides of hindered α-azido acids can be obtained using excess of $SOCl_2$ at 50 ^oC. Weigelt and Sewald reported ^2H labeled α-azidoisobutyryl chloride (D_6-Aib-Cl) as Aib equivalent building block from acetone cyanohydrin-D_6 in six steps in good yield (61%) and high degree of deuteration for solid phase peptide synthesis (SPPS).[134] The percentile deuterium incorporation was found to be more than 90 according to NMR and MS data. D_6-Aib equivalent can be incorporated into peptides for determination of three dimensional structures of peptides.

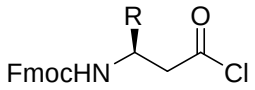
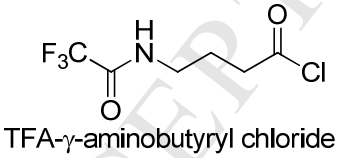
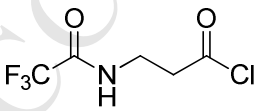
The last, but not the least ones are amino acid chloride hydrochlorides.[135-139] An amino acid in acetyl chloride on treatment with PCl_5 gives amino acid chloride hydrochloride. However, they are used sporadically.

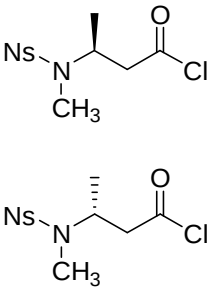
3. 4. β- and γ-Amino acid chlorides

β- and γ-Amino acid chlorides were also prepared employing reagents $SOCl_2$ and oxalyl chloride and most of which have been used as such and not isolated (Table 4).

Table 4

Preparation of β- and γ-amino acid chlorides

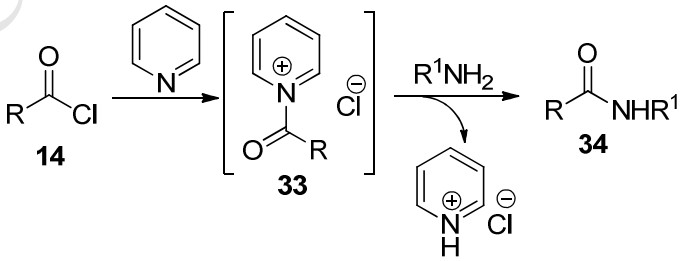
Entry	Amino acid chloride	Reaction condition	Remarks
1	 R = CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$	$SOCl_2$ in CH_2Cl_2 at reflux for 2 h[140]	The chemical and optical purity of these acid chlorides was determined spectroscopically after their conversion into methyl esters.
2	 TFA-γ-aminobutyryl chloride  TFA-β-alanyl chloride	$(COCl)_2$ in dry benzene, pyridine (three drops) at reflux for 15 min[141]	Obtained as clear yellow liquid. Acid chloride was diluted immediately with dry CH_2Cl_2 and used without further purification.

3		$SOCl_2$ in dry ethanol-free $CHCl_3$ at reflux for 20-30 min[107]	Obtained in quantitative yield as yellowish amorphous solids.

4. Coupling

Availability of plethora of coupling protocols tempts the practitioners of peptide chemistry to opt for a so called 'racemization free protocol'. There is a risk of racemization associated with acid chlorides as coupling agents unless otherwise two aspects are appropriately addressed, (i) nature of N^{α}-protecting group versus reagent/method used for acid chloride formation and (ii) conditions employed for coupling. However, undoubtedly, the acid chlorides are the reagents of choice, particularly in the assembly of sterically hindered as well as difficult peptide sequences. Their utlity in acylation of weak nucleophilic amines has been found widely useful in organic synthesis.

The aminolysis of the protected amino acid chloride with the desired amine will generate an amide bond and HCl is released as the undesired product. Thus it's essential that the amide bond formation be carried out in presence of a base, to trap the hydrogen chloride liberated. Otherwise, protonation of amino component by HCl will hamper both the rate of coupling and yield of the product significantly. Dry conditions can be employed in presence of a non-nucleophilic base such as *N*-methylmorpholine (NMM), triethylamine (TEA), collidine or DIEA to trap the HCl.[142] This reaction is found to be accelerated by catalytic amount of pyridine or DMAP.[143] The acyl pyridinium intermediate **33** is proposed for the observed catalytic action (Scheme 6).



Scheme 6. Catalytic role of pyridine in amide bond formation via acyl pyridinium salt intermediate.

However, the use of base has undesired effect on the conversion, leading to the formation of oxazolones, which naturally aminolize at a slower rate. Thus racemization *via* oxazolone formation, premature deprotection of protecting groups in case of base labile protecting groups and other side reactions including *N*-carboxyanhydride formation initially hindered the use of protected-amino acid chlorides in peptide coupling. In a strategy to overcome these difficulties, two phase system employing 5% $NaHCO_3/CH_2Cl_2$ or $CHCl_3$ i.e., Schotten-Baumann condition has been successfully developed and utilized which minimizes the contact of acid chloride with the base.[5] In a deviation to conventional solution phase methods, even soild supports such as poly-4-vinylpyridine (P4PVy) (copolymer of 4-vinylpyridine with divinylbenzene) have been proposed as HCl acceptors.[144] In a nutshell, several strategies are envisaged to ensure rapid acylation with stability as well as circumvention of oxazolone formation with concomitant loss of chirality.

In other methods, metal and metal oxides have been used to mediate coupling reactions. In these reactions, corresponding metal halide is the byproduct. MgO has been employed by Katsoyannis and Du Vigneaud in the coupling of tosyl amino acid chlorides with free amino acids.[145] Though various reports have emerged on metal mediated amide bond formation, their application in peptide chemistry is limited. Some of the successful results include the use of zinc dust,[146] indium,[147] and CuO[148] mediated peptide coupling.

Various co-coupling agents/additives such as potassium salts of 1-hydroxybenzotriazole and 7-aza-1-hydroxybenzotriazole (KOBt **71a** and KOAt **71b** respectively) in place of tertiary amine have been utilized to circumvent the necessity of use of equimolar quantity of base during coupling and thus, instead of HCl, KCl is formed as other product.[149,150] The use of 1-(t-butyldimethylsilyloxy)benzotriazole **72** (TBDMS-OBt), results in the formation of t-butyldimethylsilyl chloride (TBDMS-Cl) which is completely soluble in organic solvent.[151,152]

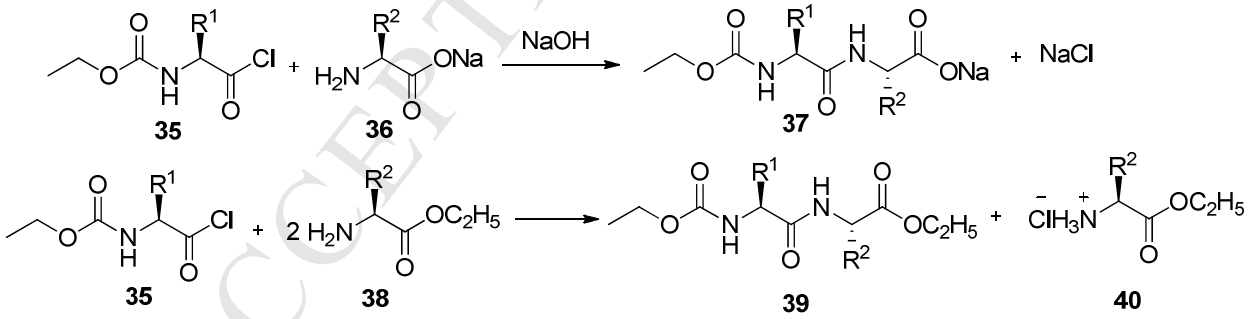
Another strategy involved the use of *N*-allyloxycarbonyl (Alloc) amino acid methyl esters **70**, which were sequentially treated with $Pd/PhSiH_3$ and acid chlorides to obtain peptides.[153,154] In all these protocols, peptide bond formation can be achieved in organic solvent without necessity of either organic or inorganic base.

4.1. Solution phase synthesis

Several attempts have been made in the earlier stages of peptide synthesis to make use of acid chlorides, due to their highly reactive nature. One of the very first attempts by Emil Fischer involved demonstration of the feasibility of the use of amino acid chloride hydrochlorides[135-138] as coupling agents with simultaneous carboxyl activation as well as amino protection.[139] Ethyl L-alanylglycinate was obtained by coupling L-alanyl chloride hydrochloride with ethyl glycinate.[135-138] Several of peptides including L-alanyl-glycine, leucylglycylleucine, leucyltriglycine, L-prolyl-L-phenylalanine, L-tryptophylglycine were made albiet with lesser purity.[88-90,135,155] However in solution, a part of the amino acid chloride hydrochloride undergoes deprotonation and the acylation of free amine leads to a mixture of products.

4.1.1. Schotten-Baumann conditions

The only activation method compatible to accomplish coupling in water (i.e., Schotten-Baumann conditions) is the acid chloride method. As is well known, in general, the acylation of amines using acid chlorides has been accomplished employing Schotten-Baumann conditions. Emil Fischer demonstrated coupling employing Etoc-amino acid chlorides **35** under Schotten-Baumann conditions as well as in non-aqueous media.[1] In one of these studies, 2 eq of amino acid ester **38** was employed, wherein additional equivalent of amino acid ester served as a HCl acceptor (Scheme 7). Obviously, the use of an additional molar quantity of amino acid ester is not practiced, due to the escalation in the cost of the protocol.

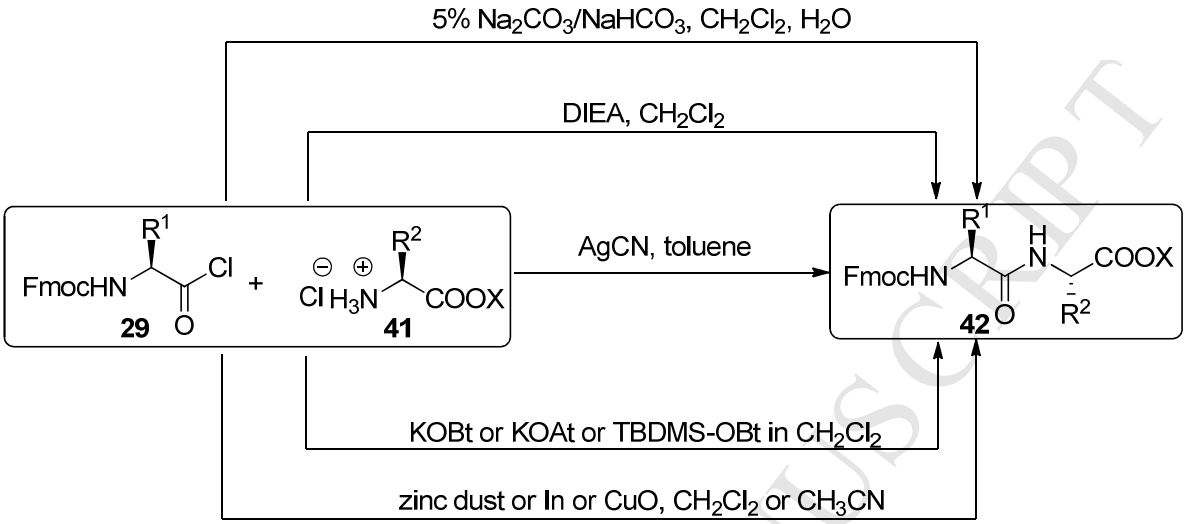


Scheme 7. Coupling employing Etoc-amino acid chlorides under Schotten-Baumann conditions and in non-aqueous media.

4.1.1.1. Fmoc Chemistry

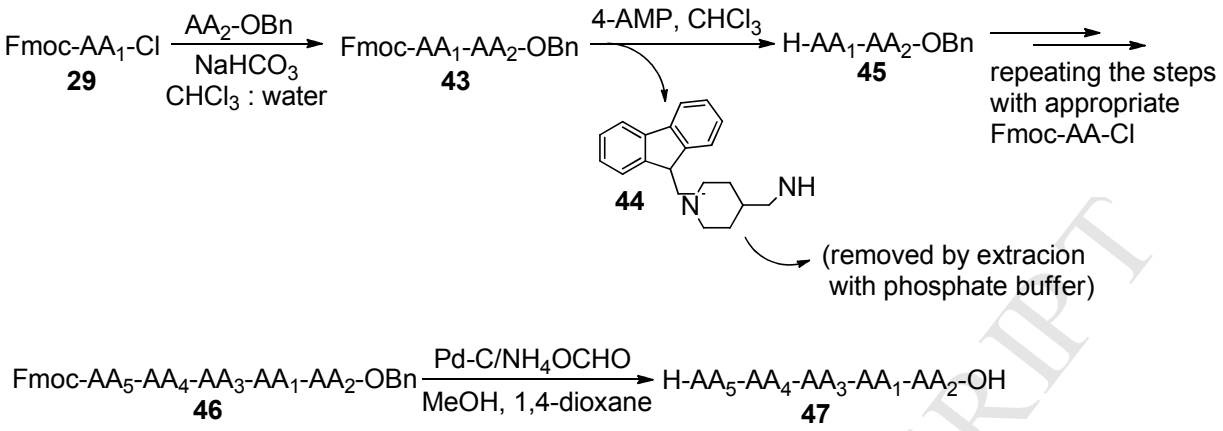
Due to the base lability of Fmoc moiety, there is a feasibility of premature deblocking of the Fmoc group. Consequently, coupling methods evolved in two pathways involving two phase

system with mild inorganic base in aqueous layer to minimize contact with the acid chloride as well as in homogeneous solution assisted by a HCl acceptor (Scheme 8).



Scheme 8. Various protocols employed for coupling of Fmoc-amino acid chlorides.

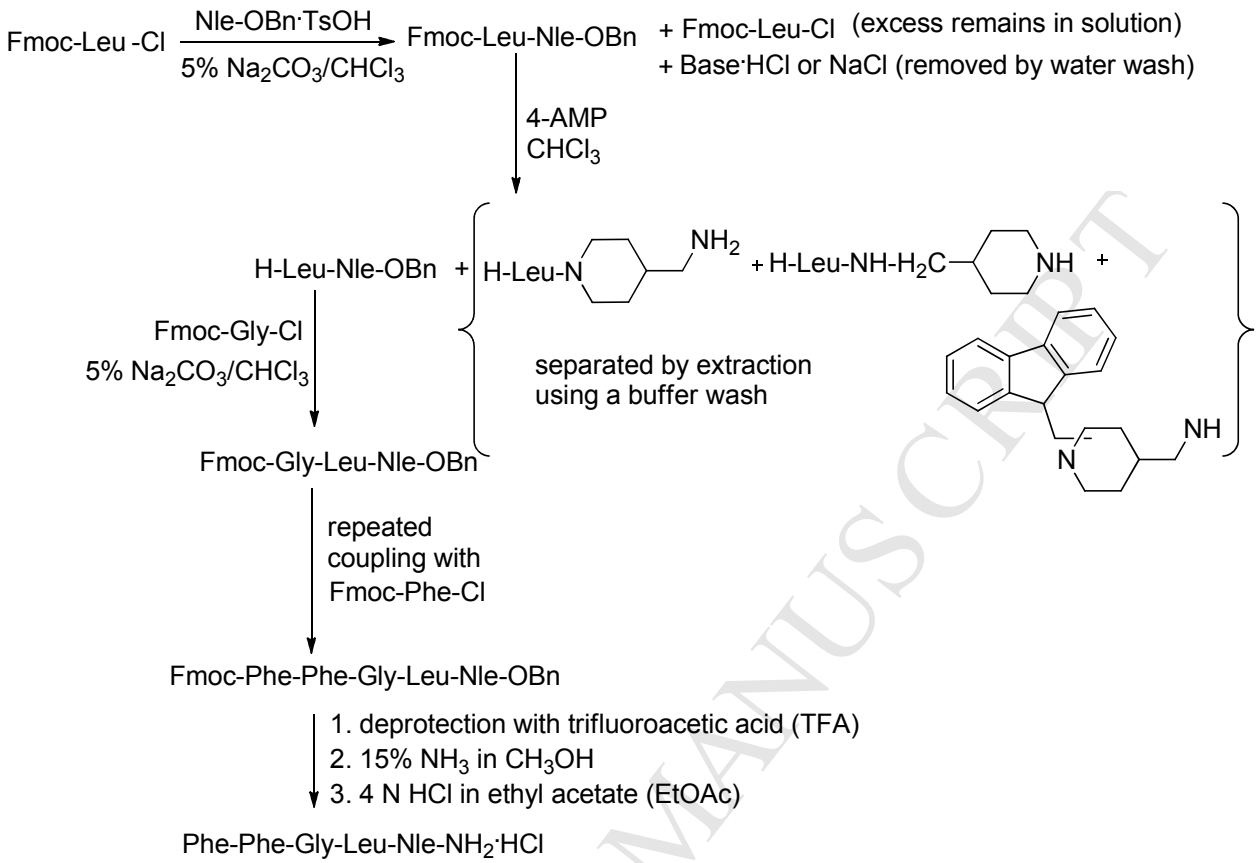
It was envisioned by Louis Carpino that Fmoc chemistry and the acid chloride method are compatible with each other with simple modifications in coupling conditions without racemization[156] (Scheme 9). Carpino's group succeeded in rapid synthesis of short peptide segments using Fmoc-amino acid chlorides as coupling agents in biphasic medium.[5] The method involved a two-phase system consisting of CH_2Cl_2 or $CHCl_3$ with a mild inorganic base (5% Na_2CO_3 or 10% $NaHCO_3$) in the aqueous layer to minimize contact with the acid chloride. The excess acid chloride was scavenged by addition of *N*-methylpiperazine and deblocking was carried out by 4-(aminomethyl)piperidine (4-AMP). A phosphate buffer (pH 5.5) extraction ensures the separation of dibenzofulvene (DBF) adduct of 4-AMP **44** (Scheme 9). [Leu^5]Enkephalin (Tyr-Gly-Gly-Phe-Leu) was synthesized[77,157-159] on a ten mmol scale within 4 h in 50-55% yield and the overall racemization at the Phe residue, was found to be less than 0.1%, as determined by measuring the ratio of D, L, LL diastereomers of *N*-methylbenzoyl phenylalanylleucinate.



Scheme 9. Rapid synthesis of short peptide segments using Fmoc-amino acid chlorides in biphasic medium.

4.1.1.1.1. Continuous solution phase synthesis

Beyermann et al. reported the synthesis of C-terminal tachykinin and N-terminal substance P and neurokinin B sequences in an improved protocol employing Fmoc amino acid chlorides.[77] Continuous solution synthesis of peptides in a sequential process up to the heptapeptide stage has been carried out, wherein both removal of the excess acid chloride as well as deblocking step was accomplished by the use of 4-AMP. DBF adduct of 4-AMP **44** and the byproducts were removed by extraction with phosphate buffer (pH 5.5) and the growing peptide chain was retained in the organic phase. Using this rapid protocol, a pentapeptide H-Phe-Phe-Gly-Leu-Nle-NH_2 was prepared in 79% overall yield (Scheme 10). In earlier synthesis, the premature deblocking of the Fmoc group by *N*-methylpiperazine and complete extraction of piperazides derived from hydrophobic amino acids had lead to around 20-30% yield of the pentapeptide H-Phe-Phe-Gly-Leu-Nle-NH_2. A combination of Fmoc amino acid chlorides and 4-AMP as deblocking/scavenging agent has been conveniently employed for the continuous synthesis of eight peptides, while corresponding pentafluorophenyl esters were employed wherever required, albiet as less reactive substitutes (Table 5).



Scheme 10. Continuous solution synthesis of pentapeptide H-Phe-Phe-Gly-Leu-Nle-NH_2.

Table 5 List of peptides synthesized by Fmoc-amino acid chloride/4-AMP coupling-deprotection strategy[77]

Entry	Compound	Yield (%)
1	H-Phe-Phe-Gly-Leu-Nle-NH_2·HCl	79
2	H-Lys(Cbz)-Phe-Phe-Gly-Leu-Met-NH_2·2HCl	73
3	H-Phe-Phe-Val-Gly-Leu-Met-NH_2	29
4	H-δ-Ava-Phe-Phe-Gly-Leu-Nle-NH_2	40
5	Boc-Gln¦-Glu(OBn)-Phe-Phe-Gly-Leu-Nle-OBn	47
6	H-Lys-Pro-Lys-Pro-$NHC_{12}H_{25}$·HCl	47
7	Cbz-Arg(NO_2)¦-Pro-Lys(Cbz)-Pro-OH	84
8	H-Arg-Pro-Lys-Pro¦-δ-Ava-Phe-Phe-Gly-Leu-Nle-NH_2	57.6

* pentafluorophenyl ester (entries 5 & 7) or the mixed anhydride method (entry 8) was employed at the bond indicated by ¦ .

In a subsequent improvement of continuous solution phase synthesis, 4-AMP was replaced with tris(2-aminoethyl)amine (TAEA). The use of TAEA simplified the workup during buffer extraction, whereas 4-AMP/DBF adducts lead to the formation of emulsions or precipitate with certain sequences in CH_2Cl_2 as a solvent. Also synthesis can be carried out in monophasic

medium in CH_2Cl_2 as demonstrated by coupling of Fmoc-D-Phg-Cl to H-Phe-OMe·HCl in presence of TEA (Table 6).[160]

Table 6 List of peptides synthesized by Fmoc-amino acid chloride/TAEA coupling-deprotection strategy[160]

Entry	Peptide	Yield (%)
1	Fmoc-Gly-Gly-Phe-OBn	69.6
2	Fmoc-Tyr(Bn)-Gly-Gly-Phe-Leu-OBn	45.8
3	H-Lys-Pro-Lys-Pro-NH-$C_{12}H_{25}$	60.9
4	H-Phe-Phe-Val-Gly-Leu-Met-OBn	40.0
5	H-Phe-Phe-Val-Gly-Leu-Met-NH_2	32.4

4.1.1.2. Other protecting groups

Bspoc amino acid chlorides were employed in two phase using $CH_2Cl_2/H_2O/NaHCO_3$ system and silica tethered secondary amine 4-aminomethyl piperidine (4-AMP) silica as deblocking agent (Table 7). The high reactivity (high acylating activity) of acid chloride diminishes the attack of amine donor at the second electrophilic center, the Michael acceptor. The protocol was illustrated with efficient synthesis of Fmoc-NH-[Leu^5]enkephalin in a continuous solution assembly without isolation of any of the intermediates (with exception of Fmoc-Tyr(Bn)-Cl for the final coupling step) in overall yield of 30%.[85]

Table 7 List of peptides prepared through other urethane protected amino acid chlorides

Entry	Peptide	Yield (%)
1	Bspoc-Phe-Phe-O^{t}Bu	94.3
2	Bspoc-Phe-Phe-Phe-O^{t}Bu	75
3	Poc-Ala-Ala-OCH_3	83
4	Poc-Phe-Phe-OCH_3	88
5	Poc-Phg-Phg-OCH_3	86
6	Poc-Phg-Phe-OCH_3	88
7	Poc-Phg-Ala-OCH_3	83

Poc amino acid chlorides were employed as coupling reagents employing H_2O-Na_2CO_3 (6 eq)-CH_2Cl_2 system at -5 to 0 ^oC to assemble few Poc protected dipeptides in solution phase within 15 min in high yields as crystalline solids.[86] The peptides were found to be diastereomerically pure as determined by the use of chiral shift reagent in ^1H NMR as well as chiral HPLC.

Vedejs group claimed Bts and Ths amino acid chlorides as practical reagents for difficult solution phase couplings and other applications wherein the high reactivity of acid chloride is desirable (Fig. 2). Thus Bts and Ths protected amino acid chlorides[110,111] were reported for peptide coupling reactions including the ones involving sensitive phenylglycine (Phg) residues as well as hindered amino acids in the absence of any organic additive with the ease of product purification involving no chromatography or crystallisation. In this study Bts-Phg-Cl was coupled to amino acid esters (Ala-OCH_3, Phe-O^{t}Bu, Aib-OCH_3) in bi-phasic medium (aqueous Na_2CO_3/$NaHCO_3$ and CH_2Cl_2; 0-5 ^oC; 15 min) and products were isolated in high yields. The diastereomeric purity of peptides **48** was satisfactory with a maximum of 0.1% racemization of the Phg (phenylglycine) subunit (≥ 99.8% retention). Deprotection of diastereomers using inexpensive reagents zinc/AcOH-EtOH or 50% H_3PO_2 resulted in peptides with no change in diastereomeric ratio. Also Ths-Phg was utilized via acid chloride coupling yielding peptides **49** with similar results. Thus Ths-Phg-Phe-$OC(CH_3)_3$ and Ths-Phe-Ala-OCH_3 were prepared in ≥ 99.8% de.

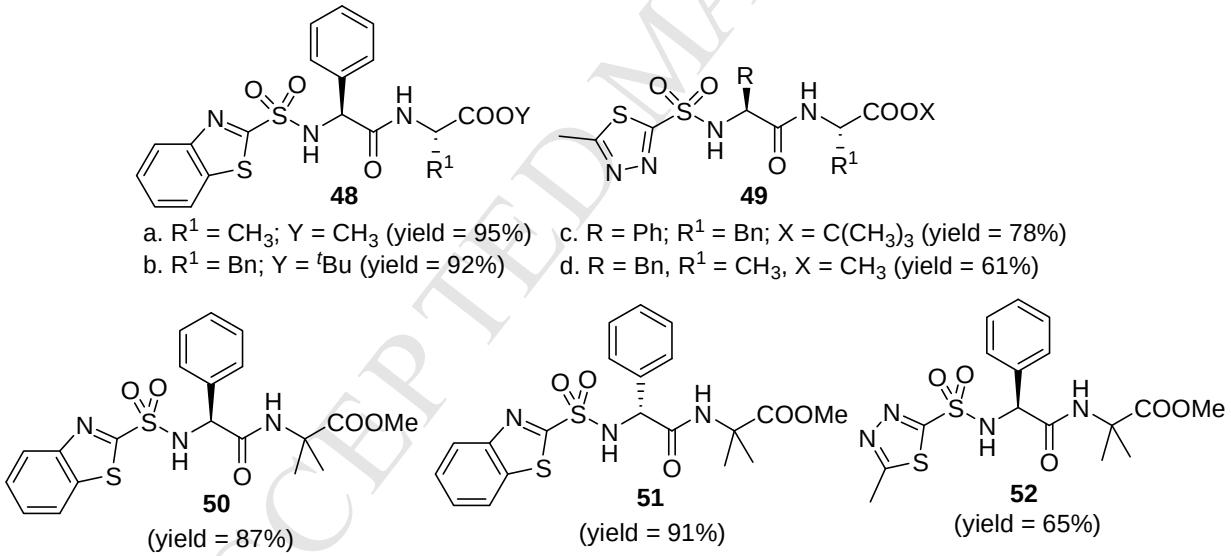


Figure 2. Dipeptides prepared using Bts and Ths amino acid chlorides.

Nosyl amino acid chlorides have been successfully employed in solution phase synthesis of peptides using aqueous $NaHCO_3$/$CHCl_3$ system and found to be compatible with side chain protecting groups used in Fmoc-based strategy (Fig. 3). Nosyl-protected peptides **53** and **54** could be obtained in high yields and purity at room temperature within 1 h.

Racemization study by GC/MS and ^{1}H NMR analyses of diastereomers Ns-L-Phe-L-Ala-OMe and Ns-L-Phe-L-Ala-OMe confirmed the absence of epimerization.[161,162]

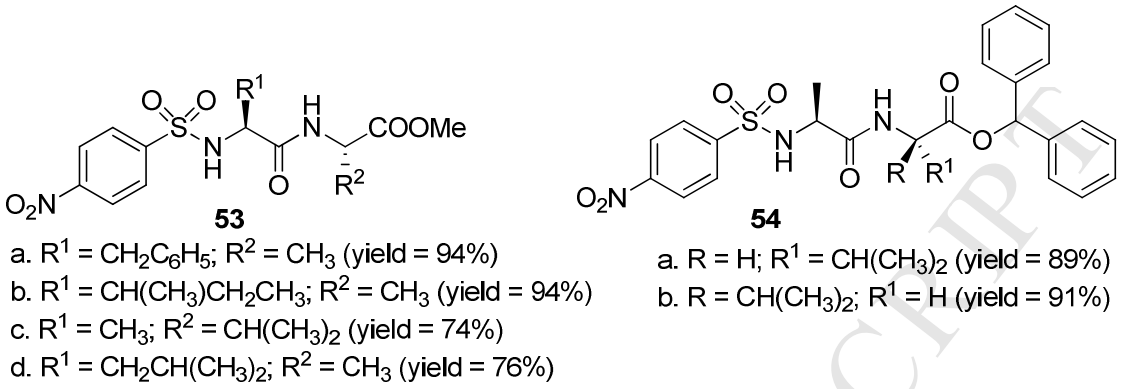
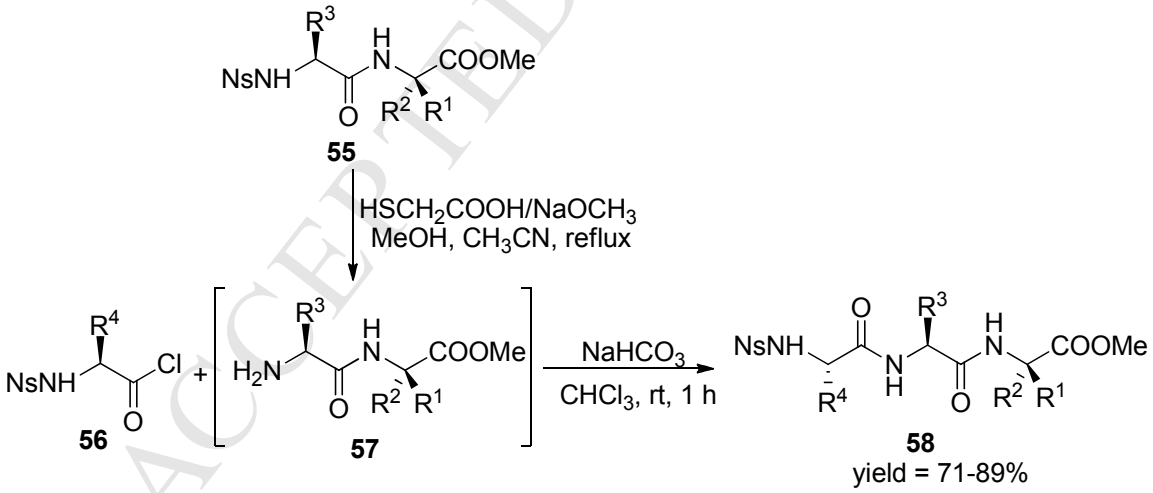


Figure 3. Dipeptides synthesized from Nosyl amino acid chlorides.

Nosyl amino acid chlorides **56** were also coupled with the dipeptide esters **57** and *N*-methylated dipeptide ester to yield tripeptides **58** and few hindered oligopeptides in high yield with no contamination by epimers as established by ^{1}H NMR studies of diastereomeric peptides. The coupling conditions were compatible with acid labile side chain protecting groups which was demonstrated by coupling of Nosyl-amino acid chlorides **56** with dipeptide methyl esters containing acid labile side chain protecting groups to yield corresponding tripeptides in good yields of 71-85% (Scheme 11; Table 8).[106,163]



Scheme 11. Coupling of Nosyl amino acid chlorides **56** with dipeptide esters.

Table 8 List of tripeptides prepared through Ns-protected amino acid chlorides[106,163]

Entry	R^1	R^2	R^3	R^4	Yield (%)
1	$CH(CH_3)_2$	H	CH_3	$CH(CH_3)CH_2CH_3$	89

2	H	$CH(CH_3)_2$	CH_3	$CH(CH_3)CH_2CH_3$	84
3	H	CH_3	$(CH_2)_4NH(Boc)$	$CH(CH_3)_2$	85
4	H	$CH(CH_3)_2$	$CH_2C_6H_4O(^tBu)$	$CH(CH_3)CH_2CH_3$	75
5	H	CH_3	$CH_2S(Trt)$	$CH(CH_3)_2$	71

Ns-*N*-Methyl-β^3-amino acid chlorides were also treated with aqueous 10% $NaHCO_3/CHCl_3$ solution of α-amino acid methyl ester hydrochloride at room temperature and corresponding products **59** and **60** were obtained in 64-75% overall yields in about 25-30 min (Fig. 4).[107]

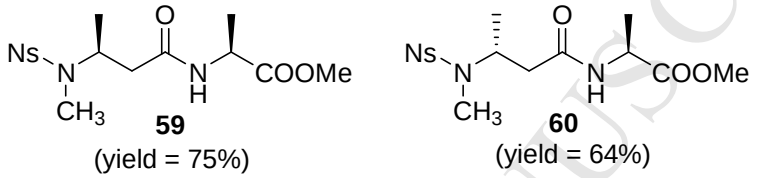


Figure 4. Dipeptides prepared from Ns-*N*-methyl-β^3-amino acid chlorides.

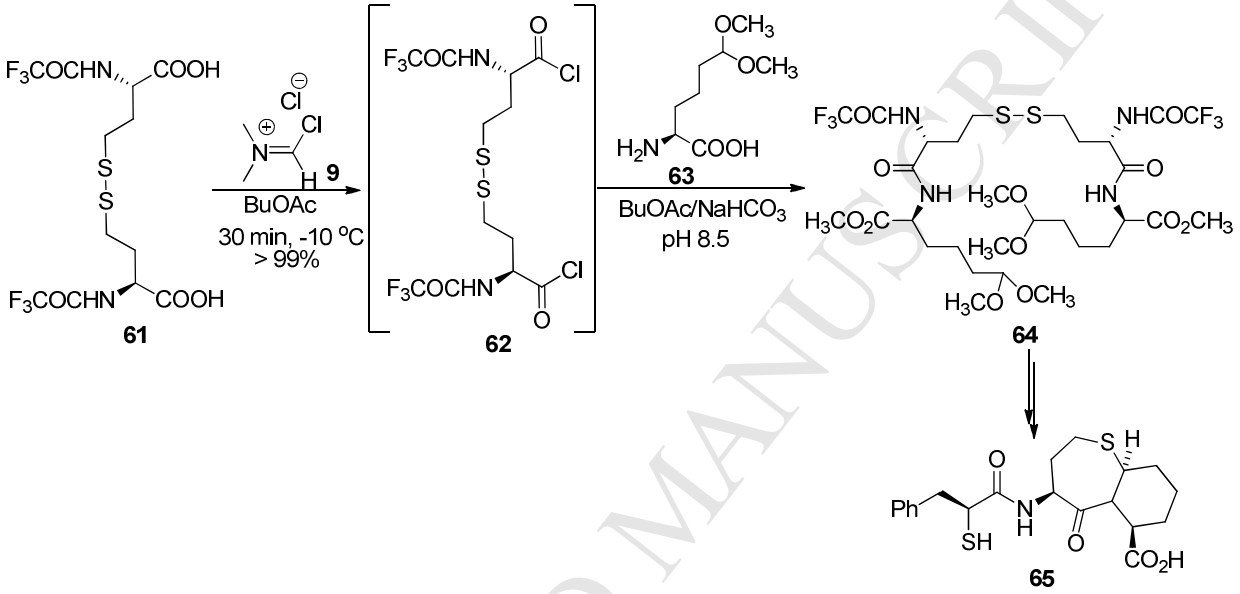
Jass et al. studied in detail the use of trifluoroacetyl (TFA) amino acid chlorides in peptide coupling.[54] Herein the Vilsmeir reagent was employed at temperatures below -10 ^oC and the acid chlorides were directly employed in subsequent coupling reactions under Schotten-Baumann conditions at low temperatures in conjunction with excellent agitation and pH control resulting in peptides with high retention of stereochemistry (Table 9). Various TFA protected amino acid chlorides were coupled to H-Phe-OMe in good yields and the diastereomeric products were found to be < 0.2% by HPLC or GC. An aqueous buffer (K_2HPO_4) was used to maintain the pH in the aqueous layer, and pH was maintained throughout the addition of acid chloride by simultaneous addition of aqueous NaOH. Alternatively large excess of aqueous 10% $NaHCO_3$ could be used as buffer to the aqueous phase. However TFA-Pro-Phe-OMe was obtained in as low as 44% yield which was attributed to side reactions.

Table 9 List of TFA protected peptides prepared[54]

TFA-Protected peptide	Yield (%)
TFA-Met-Phe-OMe	92
TFA-Ile-Phe-OMe	98
TFA-Phe-Phe-OMe	91
TFA-Leu-Phe-OMe	95

N^{α},N^{ϵ}-Bis(TFA)-Lys-Phe-OMe	89
TFA-Tyr-Phe-OMe	98

Extending the protocol, in a synthesis of anti-hypertensive agent vanlev **65**, the key intermediate **64** was prepared in high yield (> 99 %) and purity at > 100 kg input scale by employing acid chloride activation of TFA protected diacid as illustrtated in scheme 12.[54]



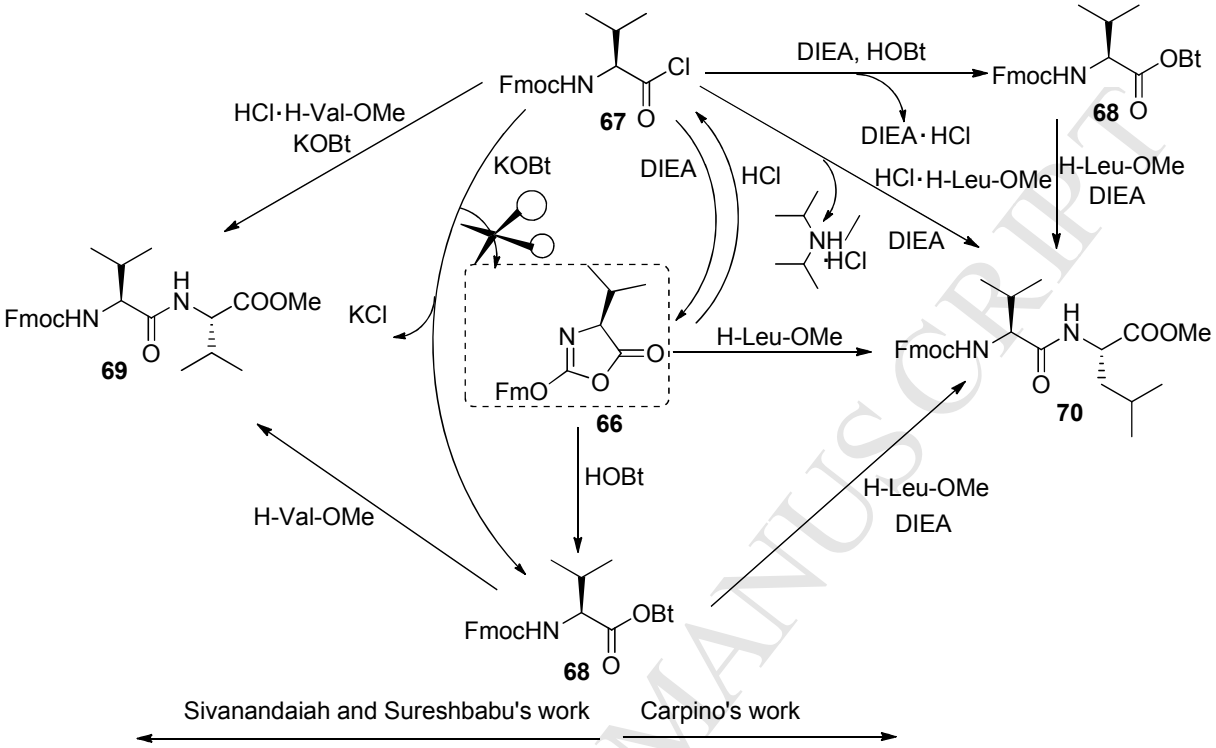
Scheme 12. Synthesis of anti-hypertensive agent vanlev **65**.

4.1.2. Non Schotten-Baumann conditions

4.1.2.1. Use of co-coupling agents

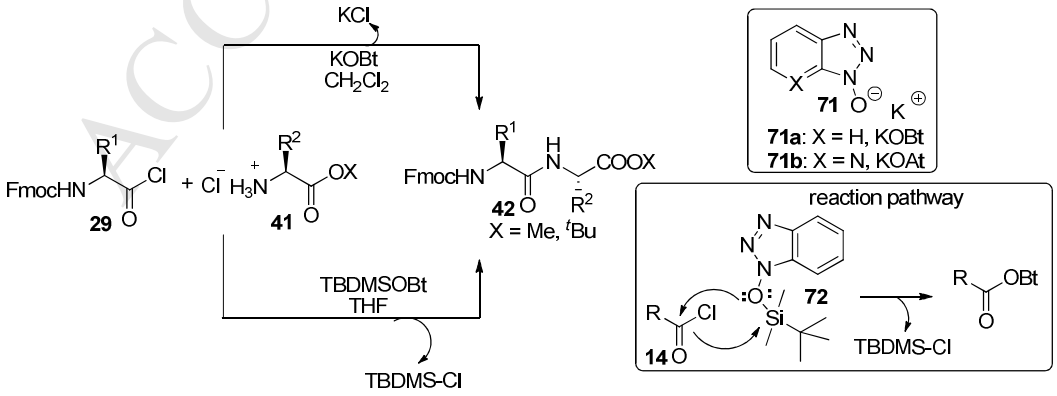
As delineated previously, Fmoc amino acid chlorides **29** act as rapid acylating agents in biphasic system. However the use of organic bases like DIEA, NMM or pyridine in homogeneous solution lead to the formation of corresponding oxazolone **66** with which coupling reaction become sluggish. Another concern is the premature deblocking of Fmoc group.[164] To circumvent these side reactions, the concept of co-coupling reagents was introduced which avoids the use of an organic base. KOBt **71a**, was applied by Sivanandaiah et al. (Scheme 13) in acid chloride chemistry.[165] KOBt reacts with HCl, as well as with hydrochloride salt of the amino component to ensure both rapid and complete coupling.[166] As a base does not mediate the coupling, 5(4*H*)-oxazolone **66** formation is circumvented.[76,149,150,167] The undesired product, KCl is formed out as a solid which is removed by filtration. Similarly, a combination of Fmoc-amino

acid chloride/KOAt **71b** has also been utilized successfully. This protocol, similar to that of KOBt, is also operationally simple and peptides were obtained in good yields.[168]



Scheme 13. Coupling of Fmoc-amino acid chlorides using co-couping agents under non Scotten-Baumann conditions.

Further improvement in no base coupling was demonstrated by the use of TBDMS-OBt **72**.[151] The reagent **72** can be easily prepared by reacting TBDMS-Cl with HOBt and is stable at room temperature for longer periods. Instead of KCl, it results in TBDMS-Cl as other product, which is soluble in organic solvent and thus a solvent wash ensures its separation from the product (Scheme 14).



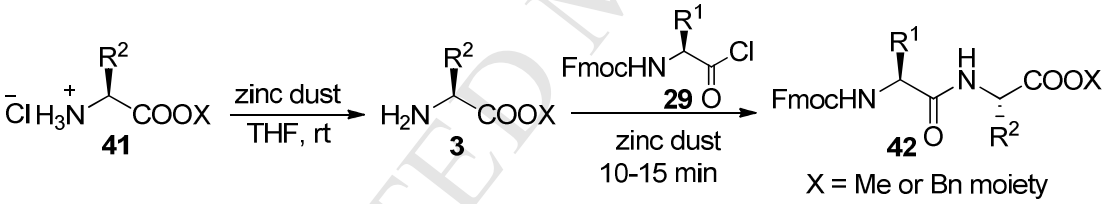
Scheme 14. Coupling of Fmoc-amino acid chlorides using KOBt and TBDMSOBt.

4.1.2.2. Metal/metal salts mediated coupling

Metal mediated acid chloride coupling has been investigated with some encouraging results.[145]

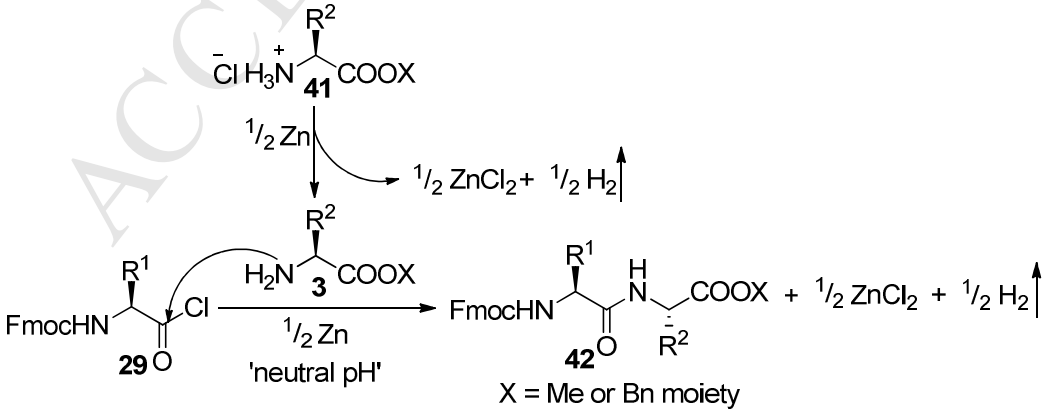
4.1.2.2.1. Coupling mediated by commercial zinc dust

Gopi and Sureshbabu employed activated commercial zinc dust as a simple alternative to KOBt/KOAt route (Scheme 15; thus in absence of any inorganic/organic base).[146] The reaction can be carried out in organic solvent such as THF, toluene and found to be free from racemization and other side reactions. The noteworthy point of this study is that the deprotonation of amino acid methyl ester hydrochloride salts **41** can be concomitantly carried out. Thus the use of 2 eq of zinc leads to deprotonation of amino acid ester hydrochloride salt **41** thereby ensuring the efficient coupling whereas another half acts as HCl acceptor. The $ZnCl_2$ formed can be removed completely through filtration before workup of the reaction mixture (Scheme 16).



Scheme 15. Zinc dust mediated coupling of Fmoc-amino acid chlorides.

The mechanism for the zinc dust mediated acid chloride coupling can be illustrated as detailed in Scheme 16.[169]



Scheme 16. Plausible mechanism for the zinc dust mediated acid chloride coupling.

The use of samarium iodide (SmI_2) in reactions of Fmoc-Pro-Cl with carbonyl compounds was tried but with limited success with respect to stereo control.[170]

4.1.2.2.2. Microwaves enhanced coupling in the presence of zinc dust

Microwave assisted coupling is paramount in peptide chemistry as well.[171-185] Tantry et al. demonstrated microwave assisted peptide coupling in the presence of zinc dust or TBDMS-OBt **69** for rapid and efficient coupling of peptides.[186] Both ^{1}H NMR and HPLC analyses of diastereomers, Fmoc-L-Phe-Ala-OMe and Fmoc-D-Phe-Ala-OMe showed the absence of racemization during the coupling reaction. Employing a rapid deprotection condition using TAEA, assembly of Fmoc-Val-Pro-Gly-Val-Gly-OBn, a repeating pentapeptide fragment of the protein elastin could be achieved in 67% yield.

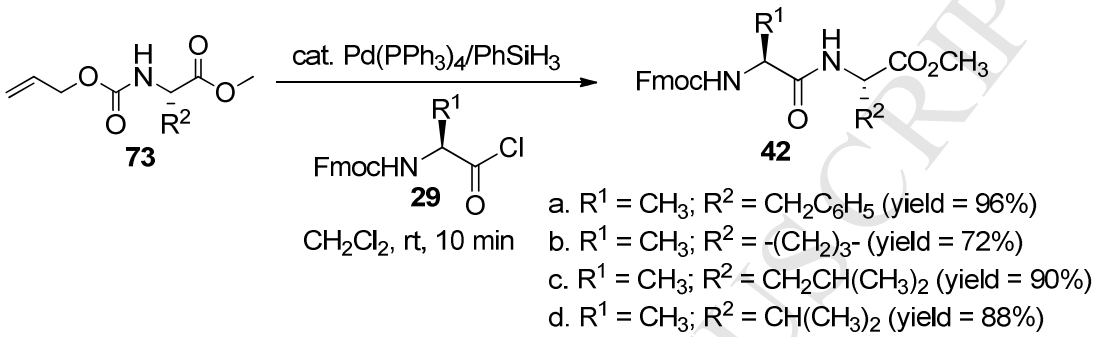
Jang's group reported indium metal mediated efficient synthesis of amides from corresponding acyl chlorides. Indium mediated reaction of Fmoc-amino acid chlorides lead to peptides in good yields of 75-88% in about 6-10 h at room temperature (Table 10).[147] No epimerization or deblocking of Fmoc-group observed based on both ^{1}H NMR and HPLC analysis of reaction mixture. Also Fmoc-amino acid chlorides in presence of catalytic CuO coupled efficiently with amino acid esters in 5-6 h at room temperature.[148] However only two examples were illustrated, *viz.*, Fmoc-Ala-Leu-OMe, Fmoc-Phg-Phe-OMe in 83-85% yields (Table 10). Reaction was aclaimed racemization free by ^{1}H NMR analysis and no premature deblocking of N^{α}-protecting group was reported.

Table 10 List of peptides prepared employing metal catalysts[147,148]

Entry	Peptide	Metal catalyst	Reaction duration	Yield (%)
1	Fmoc-Ala-Leu-OMe	In	6 h	81
		Cuo	5 h	83
2	Fmoc-Phg-Phe-OMe	In	10 h	85
		Cuo	6 h	85
3	Fmoc-D-Phg-Phe-OMe	In	9 h	88
4	Fmoc-Phe-Leu-OMe	In	9 h	85
5	Fmoc-Pro-Pro-OMe	In	12 h	75

Coupling condition: Fmoc-AA-Cl, amino ester, metal catalyst, CH_3CN, room temperature

In another protocol, Alloc amino acid methyl esters **73** were sequentially treated with cat. $Pd(PPh_3)_4/PhSiH_3$ (10 min) and acylating agent Fmoc-amino acid chloride **29**.[153] Thus non Schotten-Baumann condition during acid chloride coupling could be achieved. Although not fully established, the reaction pathway presumed to involve the formation of silyl carbamate (Scheme 17).

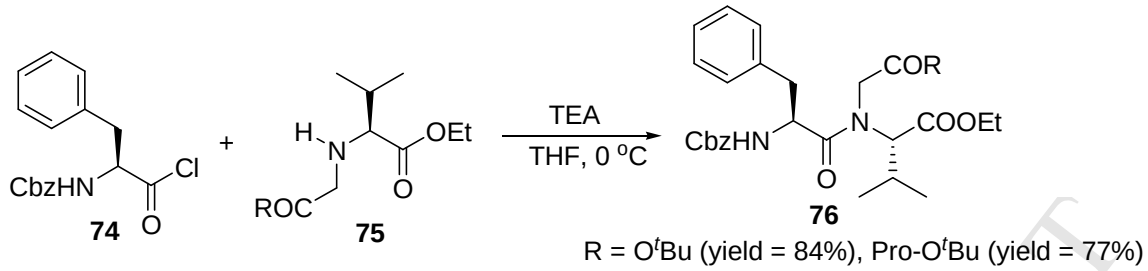


Scheme 17. Coupling of Fmoc-amino acid chlorides with Alloc amino acid methyl esters using cat. $Pd(PPh_3)_4/PhSiH_3$.

4.1.3. Coupling involving Cbz- and Boc-chemistry

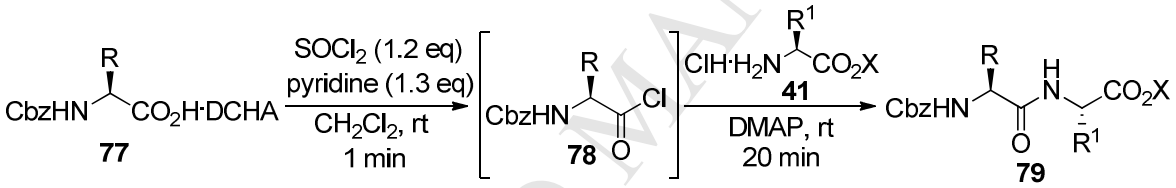
Bergmann et al. employed Cbz-amino acid chlorides in several of their syntheses owing to their compatibility with the amide bond formation.[187] However inherent drawbacks such as limited shelf stability and decomposition to the corresponding NCAs sidelined their utility by 1950s. Thus it is not unreasonable that there are very limited reports describing the use of Cbz-amino acid chlorides. However in the later years, attempts have been made to obtain Cbz-amino acid chlorides in situ at low temperatures and use immediately for coupling without isolation. Thus Cbz-amino acid chlorides, though unstable due to their rapid conversion into oxazolidinones, have been employed occasionally as intermediates in several acylations.

In 1985, Miyazawa et al. reported coupling of Cbz-Phe-Cl **74** to amino group of *N*-carboxymethyl amino acid i.e., to H-Cm(O^{t}Bu)Val-OEt **75** (Cm = carboxymethyl) at 0 ^oC in 84% yield. In the same report, Cbz-Phe-Cl was coupled to H-Cm(Pro-O^{t}Bu)-Val-OEt **76** in 77% yield (Scheme 18).[188]



Scheme 18. Coupling of Cbz-Phe-Cl to amino group of H-Cm(O^{t}Bu)Val-OEt **75**.

Rapid synthesis of thyrotropin releasing hormone (TRH) by Cbz chemistry was demonstrated employing DCHA salts of Cbz-protected amino acids **77** in the presence of $SOCl_2$-pyridine in overall yield of 76% (Scheme 19).[69] Coupling of Cbz-L-Leu·DCHA with Gly-OEt·HCl in $SOCl_2$-pyridine/CH_2Cl_2 was found racemization free by both ^{1}H NMR as well as Young's test. However in the synthesis of TRH, 6% of racemized Cbz-D-His(CH_2Ph)-L-Pro-NH_2 was obtained during coupling of Cbz-L-His(CH_2Ph)-OH·DCHA and L-Pro-NH_2.

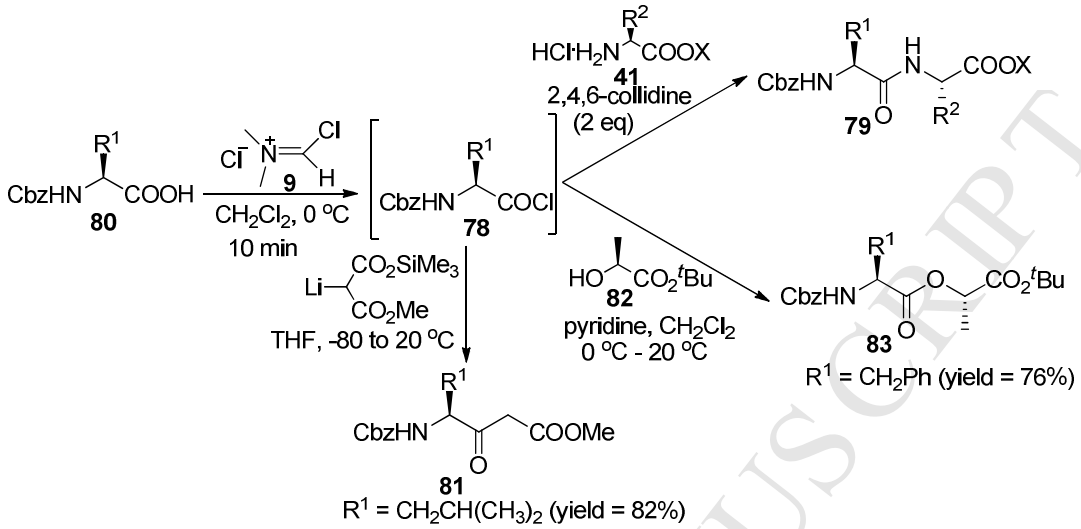


X = Et; R^1 = H; R = CH_3 (yield = 85%), $CH_2C_6H_5$ (yield = 83%), $CH(CH_3)_2$ (yield = 73%), $CH_2CH(CH_3)_2$ (yield = 82%), $(CH_2)_2CO_2Et$ (yield = 85%)
X = Me; R^1 = $CH_2C_6H_5$; R = CH_3 (yield = 80%), $CH_2CH(CH_3)_2$ (yield = 76%)
X = Me; R^1 = CH_3; R = $CH_2C_6H_5$ (yield = 94%)
X = Me; R^1 = $CH(CH_3)_2$; R = $CH(CH_3)_2$ (yield = 85%)

Scheme 19. Coupling via Cbz-amino acid chlorides starting from DCHA salts of Cbz-amino acids.

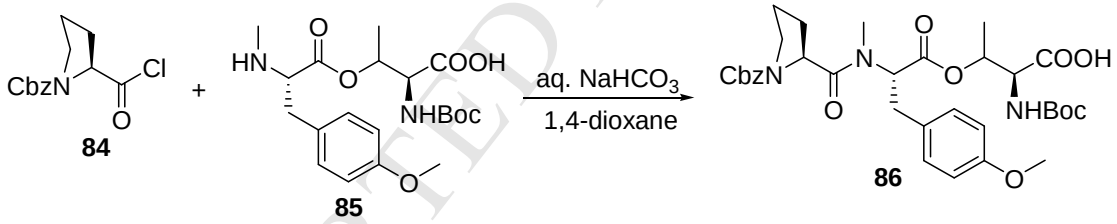
In an improved protocol, Cbz-amino acid chlorides **78** generated in situ using 1-chloro-*N*,*N*-2-trimethyl-1-propen-1-amine **8** were coupled with amino acid esters **41** and α-hydroxy esters **82** in presence of a base using either pyridine or collidine in the same vessel[189] (Scheme 20). The coupling was carried out in organic phase (CH_2Cl_2) or biphasic solution of aqueous $NaHCO_3$ and 1,4-dioxane. The racemization test on Cbz-L-Ala-L or D-Pro-OBn and Cbz-L-Phe-L-Ala-OBn by HPLC analysis revealed absence of diastereomers (Scheme 21).[189] In another report, Cbz-Val-Cl prepared in situ was coupled with *tert*-butoxycarbonylhydrazone **87**, followed

by ring closure in trifluoroacetic acid to furnish the Cbz-Val-tetrahydropyridazine-3-carboxylic acid ester **89** (Scheme 22).

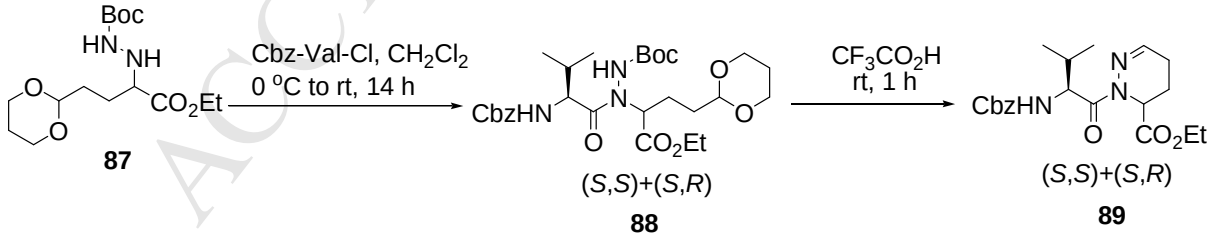


79: a. Cbz-Phe-Pro-OMe (yield = 90%), b. Cbz-Phe-Ala-OBn (yield = 77%), c. Cbz-D-Phe-Leu-Pip(OCH_3) (yield = 88%), d. Cbz-Val-Ala-OBn (yield = 70%), e. Cbz-Ala-Pro-OBn (yield = 75%), f. Cbz-Admpa-Pro-OBn (yield = 75%; Admpa = 3-amino-2,4-dimethylpentanoic acid)

Scheme 20. Coupling via Cbz-amino acid chlorides **78** generated in situ using 1-chloro-*N*,*N*-2-trimethyl-1-propen-1-amine **8**.



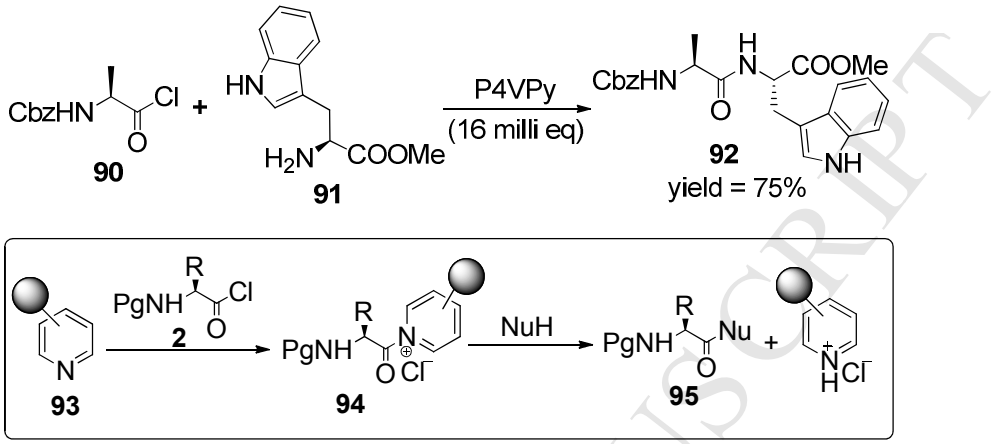
Scheme 21. Coupling of Cbz-Pro-Cl under Schotten-Baumann condition.



Scheme 22. Coupling of Cbz-Val-Cl to *tert*-butoxycarbonylhydrazone **87**.

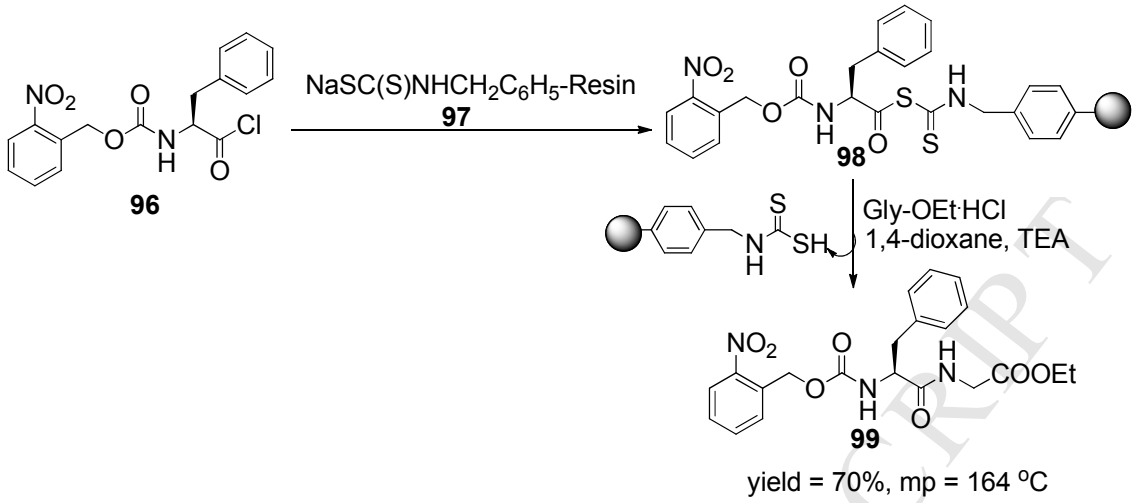
Rodriguez et al.[144] employed linear poly-4-vinylpyridine (P4VPy) **93** as solid phase hydrochloric acid acceptor for the synthesis of benzamides and peptides. Cbz-Ala-Trp-OMe **92** was obtained in 75% yield by pyridinium catalyzed acyl transfer employing Cbz-Ala-Cl **90** in

presence of excess of P4VPy. However, formation of Boc-alanyl chloride and subsequent coupling in the presence of P4VPy was not satisfactory and Boc-Ala-Trp-OMe was obtained as oil in merely 12% yield (Scheme 23).



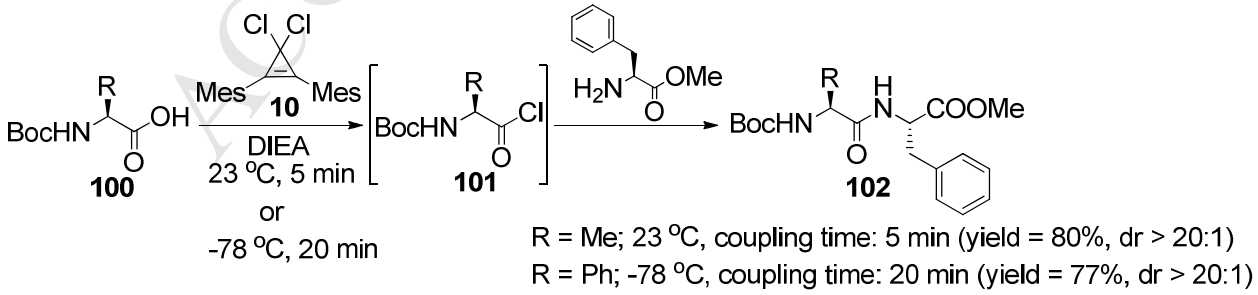
Scheme 23. Synthesis of peptides from Cbz-amino acid chlorides using linear poly-4-vinylpyridine (P4VPy) **93** as solid phase hydrochloric acid acceptor.

Haridasan et al. developed polymer-supported mixed carboxylic dithiocarbamic anhydrides as reusable solid phase acylating agents by reaction of acid chlorides with sodium dithiocarbamate resins (Scheme 24). The resulting resins were prepared from cross linked poly(chloromethylstyrene) (Merrifield resin). Thus, NBOC-Phe-Cl **96** (NBOC = 2-nitrobenzyloxycarbonyl) was reacted with sodium dithiocarbamate resin **97**, to obtain *N*-protected aminoacyl dithiocarbamic anhydride **98**, which was then treated with a solution of ethyl glycinate hydrochloride in presence of TEA, to afford the dipeptide NBOC-Phe-Gly-OEt **99**.[190]



Scheme 24. Polymer-supported mixed carboxylic dithiocarbamic anhydrides as reusable solid phase acylating agents.

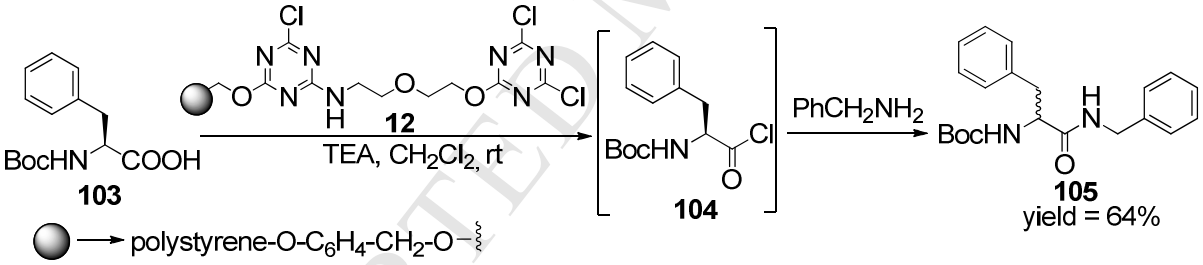
Hardee et al. developed an efficient aromatic cation activation method for rapid generation of acid chlorides in the presence of an amine (Scheme 25).[55] The protocol was mild enough to accommodate substrates with acid-sensitive functionalities such as glycol acetal, silyl ether, etc. and peptide coupling involving Boc amino acids was carried out on a preparatory scale. Boc amino acids **100** were reacted with 3,3-dichloro-1,2-dimesitylcyclopropene **10** (generated in situ from 2,3-dimesitylcyclopropenone and oxalyl chloride or can be used after isolation as well) and DIEA, which was then treated with amino acid ester. Thus two peptides were synthesized on gram scale without loss of any stereochemical integrity. Boc-Ala-Phe-OCH_3 was obtained in 80% yield (1.13 g, > 20:1 dr) at 23 °C in 5 min. For racemization prone Boc-Phg, reaction was carried out at -78 °C and Boc-Phg-Phe-OCH_3 was isolated in 77% yield (1.28 g, > 20:1 dr) in 20 min.



Scheme 25. Coupling of in situ generated Boc-amino acid chlorides using 3,3-dichloro-1,2-dimesitylcyclopropene **10**.

Fuse et al. employed BTC in rapid and efficient activation of carboxylic acids in microflow reactor for the continuous-flow synthesis of amides (44-95% yield) and peptides (74%-quantitative yield) without significant epimerization (≤ 3%).[191a,b] Ley and coworkers developed a machine-assisted flow synthesis of meclinertant (SR48692), a neurotensin receptor antagonist wherein similar strategy was employed for the coupling of an intermediate pyrazole 3-carboxylic acid to *tert*-butyl ester of adamantane amino acid using in situ generated phosgene.[191c] Herein a FlowIR™ inline infrared spectrometer was employed to monitor the formation of acid chloride i.e., disappearance of the phosgene stretch at 803 cm^{-1} allowed an injection of a matching solution of the amino acid ester.

In another report, modified Wang resin supported cyanuric chloride **12** has been developed for conversion of Boc-Phe-OH **103** to Boc-Phe-$NHCH_2Ph$ **105** albeit with complete racemization (Scheme 26).[56]



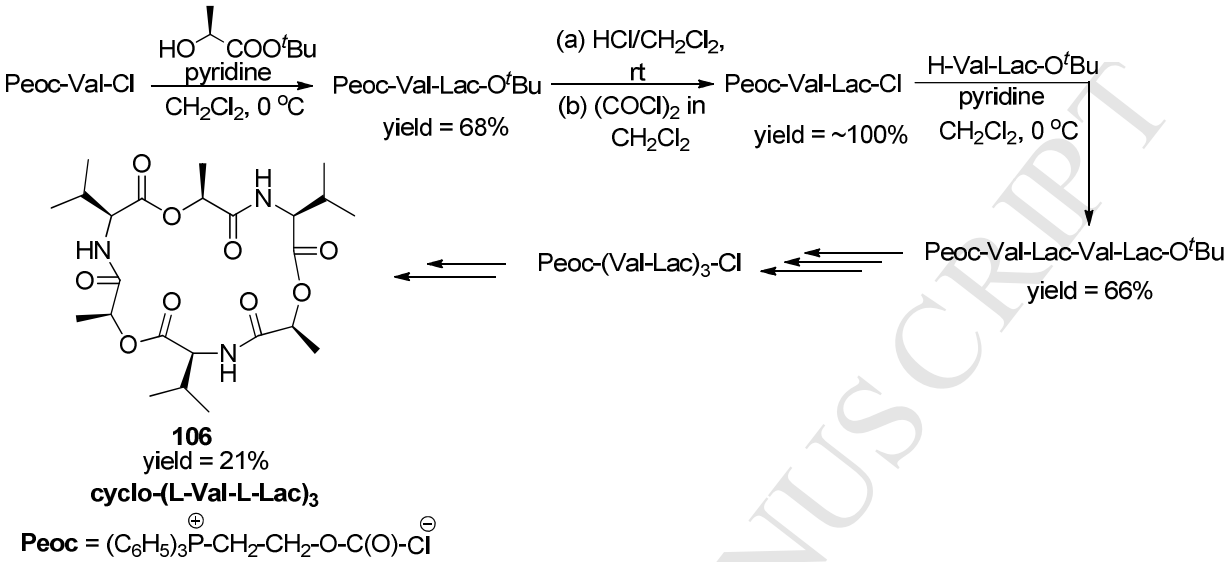
Scheme 26. Coupling of in situ generated Boc-amino acid chloride using modified Wang resin supported cyanuric chloride.

4.1.4. Coupling involving other protecting groups

4.1.4.1. Peoc chemistry

Reactivity of Peoc-amino acid chlorides was explored in racemization free synthesis of sporidesmolic acid B (H-Hyiv-Val-MeLeu-OH, Hyiv = α-hydroxyisovaleric acid) by Kunz's group.[192] Sterically demanding amide couplings were achieved satisfactorily by employing stable Peoc protected acid chlorides of the amino and hydroxy acids in presence of pyridine at room temperature. Herein sporidesmolic acid B was accomplished with no racemization despite two fold activation and condensation involved. In another report, synthesis of all L-configurated

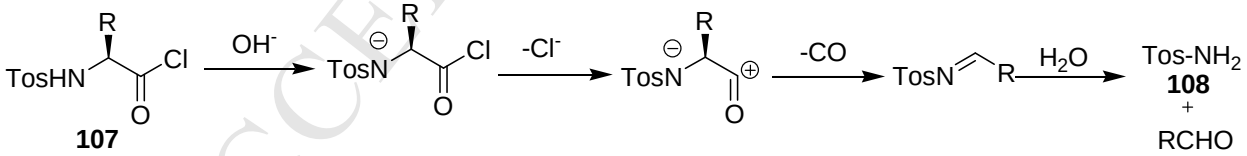
cyclohexadepsipeptide cyclo-[L-Val-L-Lac]$_3$ **106** has been achieved using the Peoc/acid chloride method (Scheme 27).[193]



Scheme 27. Synthesis of cyclohexadepsipeptide cyclo-[L-Val-L-Lac]$_3$ **106** using Peoc-amino acid chlorides.

4.1.4.2. Tosyl chemistry

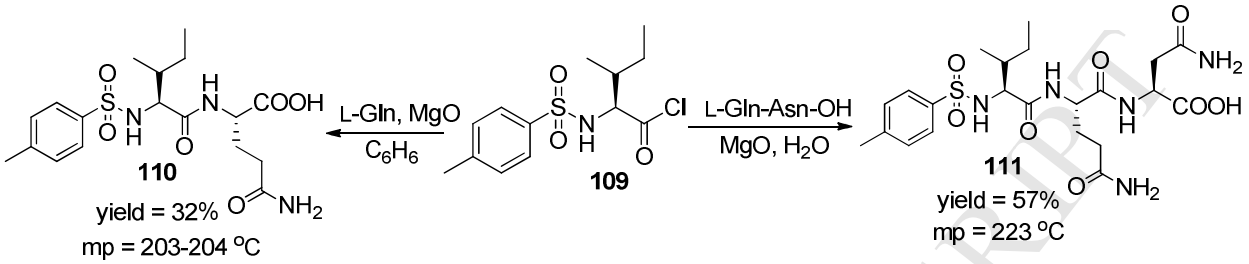
It is known that even under mild alkaline conditions, α-tosylamino acid chlorides **107** undergo decomposition to yield tosylamide **108**, CO, and an aldehyde (Scheme 28). However at the pH of an aqueous MgO suspension[194] successful acylation can be carried out using α-tosylamino acid chlorides, wherein rate of decomposition becomes slow enough to permit acylation.[195,196]



Scheme 28. Decomposition α-tosylamino acid chlorides **107** to tosylamide under mild alkaline condition.

Katsoyannis and Du Vigneaud employed Tos-L-Ile-Cl **109** in presence of aqueous MgO above pH 8.0 in the synthesis of Tos-L-Ile-L-Gln-OH **110** and Tos-L-Ile-L-Gln-L-Asn-OH **111** (Scheme 29).[145] The chemistry was extended to Tos-L-Ile-L-Leu-OH and Tos-L-Ile-L-Gly-OH assembly as well. Similar protocol was employed for the preparation of glutamyl-asparagine by

using l-tosylpyroglutamyl chloride.[105,197] In addition, Tos-L-Phe-L-Gln-L-Asn-OH was obtained by treatment of the magnesium salt of L-Gln-L-Asn-OH in aqueous solution with Tos-L-Phe-Cl in presence of excess MgO.[100]

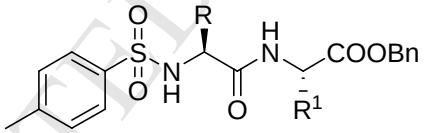


Scheme 29. Coupling of Tos-amino acid chlorides using MgO.

Tos-Phg-Cl and Tos-D-Phg-Cl were utilized in the synthesis of a set of diastereomers Tos-Phg-Ala-OMe and Tos-D-Phg-Ala-OMe.[99]

Berse et al. obtained protected dipeptides **112** containing cysteine, glycine, phenylalanine and tyrosine by employing tosyl amino acid chlorides with amino acid benzyl or ethyl esters.[101] As observed previously, tosyl protected amino acid chlorides were found efficient as the mixed anhydride method failed to result in any coupling product (Table 11).

Table 11 List of dipeptides using Tos-amino acid chlorides



112

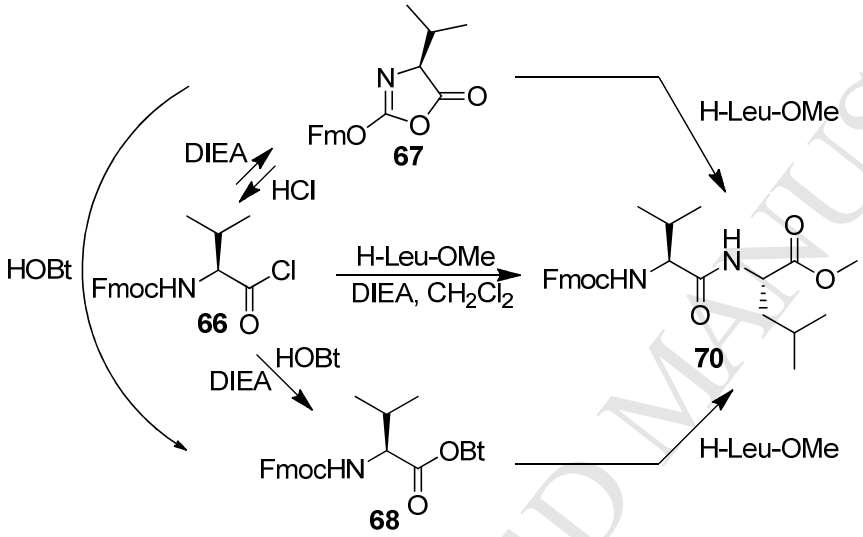
Entry	R	R^1	Yield (%)
1	$CH_2S(Bn)$	H	60
2	$CH_2S(Bn)$	$CH_2C_6H_5$	70

4.1.4.3. Phthaloyl chemistry

Phthaloyl protection was employed by Sheehan et al. in the synthesis of several stereochemically pure peptide derivatives.[198] Pht-Phe-Cl was prepared by reacting Pht-Phe and PCl_5 in dry benzene at 50-55 ^oC for 1 h. Then it was reacted with glycyl anilide hydrochloride to obtain phthaloyl-L-phenylalanylglycyl anilide. Methyl phthaloyl-glycylglycinate (yield = 90%, mp = 203-204 ^oC) and ethyl phthaloyl-L-phenylalanylglycinate (yield = 59%, mp = 160-161.5 ^oC) were also prepared in good yields.[198-200]

4.2. Solid phase peptide synthesis

The acid chlorides as coupling agents failed to come good in case of solid phase peptide synthesis (SPPS) due to their sluggish reactivity. Infrared studies on model acylating reactant Fmoc-Val-Cl **66** upon addition of DIEA or NMM, revealed that a competing oxazolone **67** formation (Scheme 30) accelerated by the tertiary amine has driven this sluggishness.[201-205] It was reasoned that lesser reactivity of the polymer-bound amine compared to its counterpart in solution has lead to the formation of oxazolone.



Scheme 30. Oxazolone formation during coupling of Fmoc-amino acid chlorides and the use of HOBt to avoid in situ oxazolone formation.

In studies carried out by Carpino et al. upon addition of methyl leucinate hydrochloride salt to a solution of Fmoc-valine derived oxazolone in CH_2Cl_2, initial rapid reaction levels to the formation of a mixture comprising 50% Fmoc-Val-Leu-OMe, 50% Fmoc-Val-Cl and 50% H-Leu-OMe·HCl.[206-208] Consequently, a 1 : 1 mixture of organic base-HOBt as promoter for rapid coupling reaction between Fmoc amino acid chlorides and resin bound amino acids was initially tried.[208] Infrared studies confirmed that Fmoc amino acid chlorides get rapidly converted to the corresponding HOBt ester, which mediated the reaction leading to efficient acylation process. Thus under HOBt/DIEA conditions 97.3% coupling occurred within 1 min. The HOBt anion is the active catalytic species, generated by the reaction of the added HOBt and the resin bound amino acid. There was no premature deblocking of Fmoc moiety of Fmoc-Leu-Pepsyn KA (Pepsyn KA, kieselguhr supported polyacrylamide resin) up to 4 h. Racemization studies

in the coupling of Fmoc-Phe-Cl with H-Leu-Pepsyn KA under 1 : 1 HOBt/DIEA conditions, as analysed by RP-HPLC, showed less than 0.1% of the DL diastereomer.

Synthesis of [Leu^5]enkephalin was carried out on a one gram scale of Pepsyn KA resin loaded with 0.1 milli eq/g of Fmoc-Leu using 5 eq of acid chloride (0.1 M in DMF) and the binary mixture of HOBt/DIEA in DMF solution. The acylation duration was 10 min. After completion of the assembly of sequence, the acylated resin was treated with TFA (2 h), to afford the TFA salt of the crude peptide (69%, approximately 93% pure). No significant racemization (< 0.1% of the D-Phe diastereomer) was observed by GC analysis of the hydrolysed pentapeptide on a chiral column. Similarly, acyl carrier protein (ACP) decapeptide 65-74 fragment (H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-OH), prothrombin (1-9), substance P analog (H-Lys-Pro-Lys-Pro-Gly-Gly-Phe-Phe-Gly-leu-Nle-NH_2) and eledoisin were assembled in solid phase successfully while substituting the pentafluoro or other stable esters for amino acids bearing tert-butyl protected side chains.[208]

A combination of HOBt/DIEA proved most efficient as both catalyst and HCl acceptor when compared to others including HOBt/TEA, HOOBt/DIEA (study involved Fmoc-Val-Cl + H-Leu-Pepsyn-KA or Fmoc-Phe-Cl + H-Phe-Gly-OCH_2CO-BHA; BHA = benzhydrylamine resin), other *N*-hydroxy compounds *N*-hydroxysuccinimide (HONSu), *N*-hydroxyphthalimide in combination with DIEA (Fmoc-Phe-Cl + H-Leu-Pepsyn-KA). HOBt/DIEA also catalyzes the aminolysis of Fmoc amino acid pentafluorophenyl esters (OPfp), however Fmoc-Asn-OPfp and Fmoc-Gln-OPfp rapidly decomposed in solutions of HOBt/DIEA in DMF.[208]

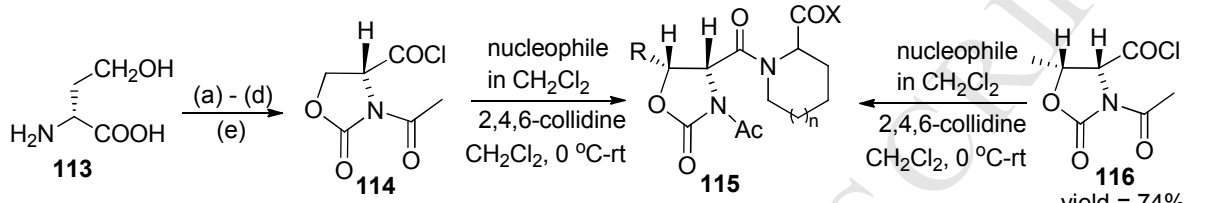
The study also revealed that Fmoc amino acid chlorides and pentafluorophenyl esters compared to benzotriazol-1-yloxytris(dimethyl-amino)-phosphonium hexafluorophosphate (BOP) and *O*-benzotriazol-1-yl-1,1,3,3-tetramethyluroniumtetrafluoroborate (TBTU) mediated couplings, gave the highest Fmoc-Val incorporation. Thus several short and medium sized peptides [Leu^5]enkephalin, substance P analogs, ACP 65-74 fragment, prothrombin (1-9) were assembled using both polystyrene and polyacrylamide resins.[209]

5. Assembly of sterically hindered peptides

High reactivity of acid chlorides has been adopted for introducing sterically hindered amino acids into peptide sequences, which otherwise have shown inferior results by most of the

conventional methods. Several protocols have been developed for the assembly of peptides containing hindered amino acids through acid chloride method in both solution as well as solid phase.[203,204]

N-Acetyl oxazolone derivatives of Ser and Thr have been converted to highly reactive acid chlorides, and the crude acid chlorides **114** and **116** are utilized efficiently with a variety of nucleophiles, particularly notoriously unreactive ones such as pipecolinate esters (Scheme 31).[210]



Scheme 31. Coupling of acid chlorides prepared from *N*-acetyl oxazolone derivatives of Ser and Thr.

5.1. Coupling mediated by AgCN

Takimoto et al. reported preparation of sterically hindered esters from the corresponding acyl chlorides and alcohols mediated by AgCN.[211,212] The reaction seems to proceed with the aid of electrophilic catalysis of Ag^+ ion. Similar protocol was then adopted for peptide bond formation including hindered amino acids, as it was found to accelerate the rate of coupling leading to an increase in the yields.

5.1.1. Cyclic hexapeptides: Oxytocin antagonists

Perlow et al. reported SPPS of cyclic hexapeptide oxytocin antagonists [analogs of L-365,209 (**117**)] cyclo-(D-Phe-Ile-D-Pip-Pip-D-(*N*-Me)Phe-Pro) (**118**), L-366,682 (**119**) and L-366,948 (**120**) (Fig. 5).[213] The antagonist cyclo-(D-Phe-Ile-D-Pip-Pip-D-(*N*-Me)Phe-Pro) (**118**) was synthesized in 70% yield starting from Boc-L-Pro-*O*-PAM-resin [PAM = 4-(hydroxymethyl)phenylacetamidomethyl poly(styrene-codivinylbenzene) resin]. The high reactivity of Fmoc-L-pipecolic acid chloride used in the di- to tripeptide step averted the diketopiperazine formation usually observed with active ester couplings (Scheme 32). Further L-

366,682 (**119**) and L-366,948 (**120**), two potent and selective antagonists were made in 45-48% overall yield on a twenty mmol scale.

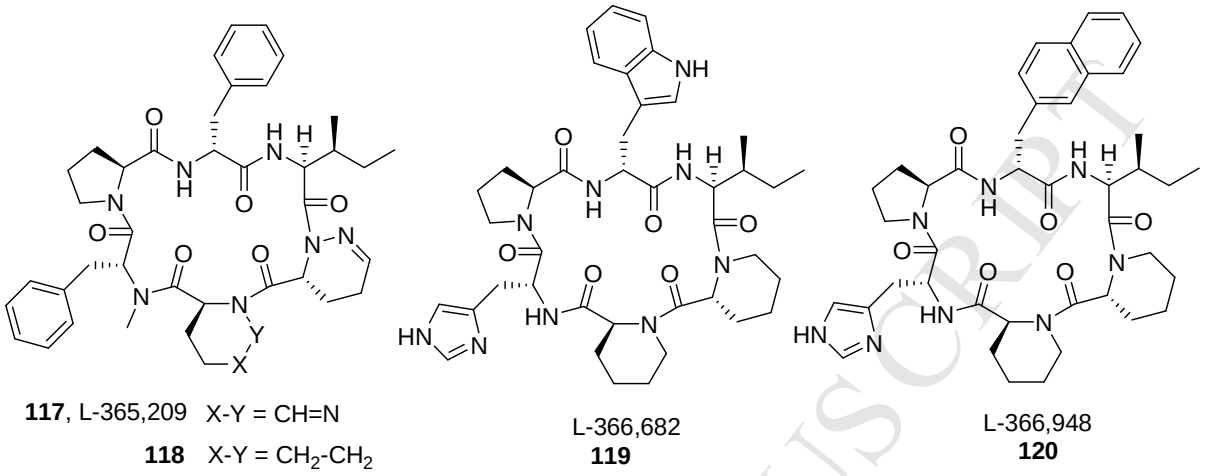
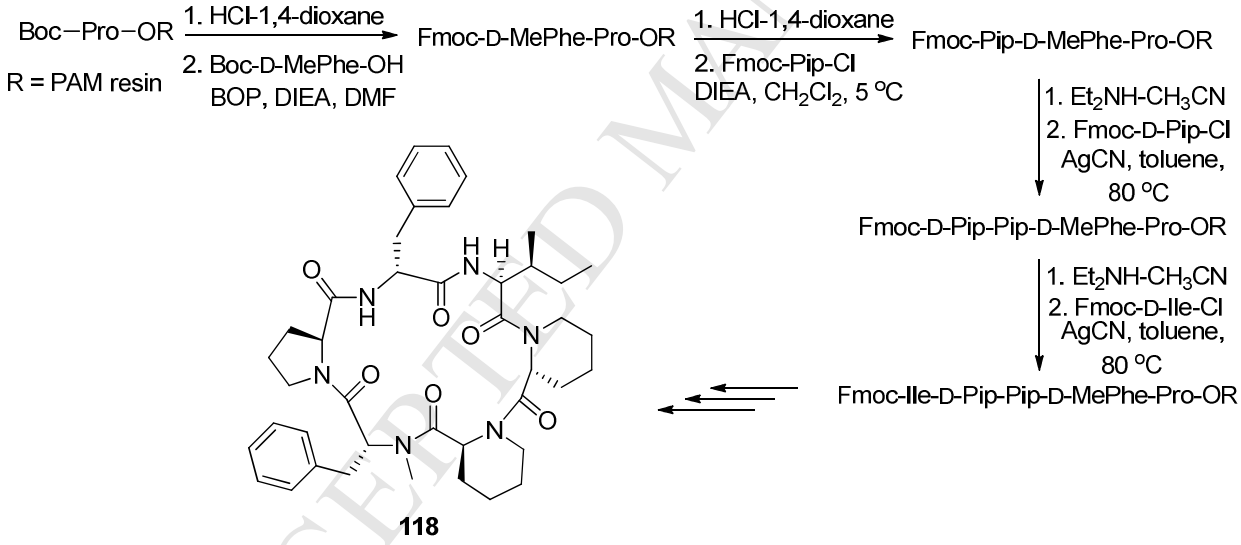


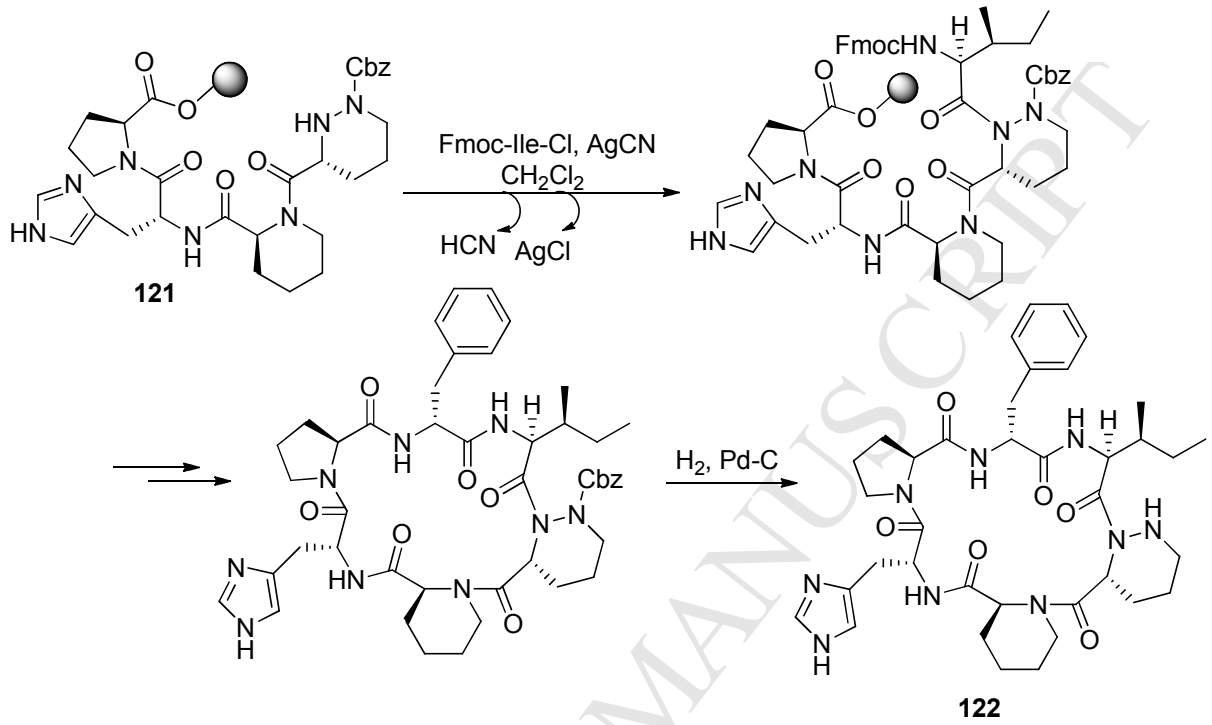
Figure 5. Cyclic hexapeptide oxytocin antagonists [analogs of L-365,209 (**117**)].



Scheme 32. Synthesis of oxytocin antagonist cyclo-(D-Phe-Ile-D-Pip-Pip-D-(*N*-Me)Phe-Pro) **118**.

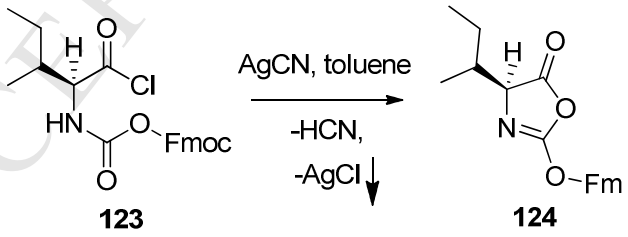
In a synthesis of another analog of oxytocin antagonist cyclo-(D-Phe-Ile-D-Δ-Piz-Pip-D-His-Pro) (**122**, Δ-Piz = dehydropiperazic acid), the acylation of sterically hindered N^{δ}-Cbz-piperazic acid N-terminus with Fmoc-L-isoleucine was found to be cumbersome. Only 30% yield could be obtained even when excess Fmoc-L-Ile-Cl was used in the presence of DIEA.[214] A modification of coupling protocol with 4 eq AgCN in toluene at 80 °C, lead to improved

conversion up to 76% with one treatment and 96% conversion could be achieved with two treatments (Scheme 33).



Scheme 33. Synthesis of oxytocin antagonist cyclo-(D-Phe-Ile-D-Δ-Piz-Pip-D-His-Pro) **122**.

Although the mechanistic aspects of coupling is not completely understood, an activated form of the isoleucine 2-alkoxy-5(4*H*)-oxazolone derivative **124** was proposed as an intermediate under these conditions (Scheme 34).[213]

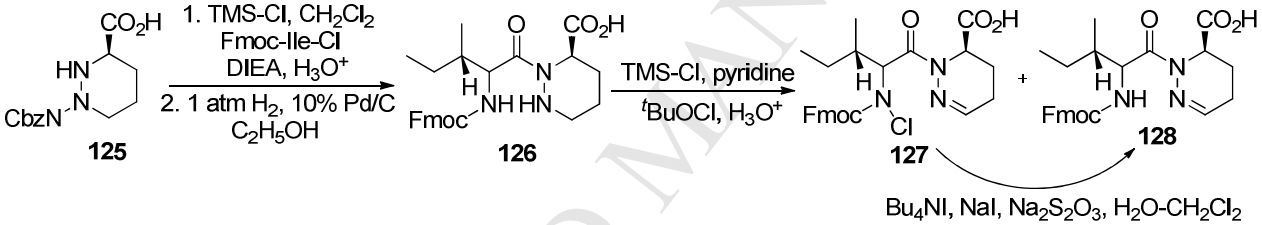


Scheme 34. AgCN mediated formation of 2-alkoxy-5(4*H*)-oxazolone derivative **124** from Fmoc-Ile-Cl.

5.2. Coupling of acid chlorides to *N*-silylated amino esters

N-Silylamines[215-217] have been prominent class of nitrogen nucleophiles, by virtue of increased nucleophilicity of nitrogen on account of silylation.[218,219] The *N*-trimethylsilylamines or lactam derivatives have been synthesized using trimethylchlorosilane (TMS-Cl) and equimolar quantity of a tertiary base to trap HCl.[220,221] Alternatively, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) has been employed for silylation of amines whenever the use of organic base need to be avoided.[222,223] It acts as a non basic acid scavenger and thus avoids premature deprotection.

Williams et al.[224] reported the synthesis of sterically hindered dipeptide fragment Fmoc-Ile-D-Δ-Piz wherein Fmoc-Ile-Cl was coupled to D-(N^{δ}-Cbz)Piz **125** using TMS-Cl in presence of DIEA (Scheme 35). This approach was employed for the incorporation of oxidation sensitive functionality in the cyclic hexapeptide oxytocin antagonists derived from *streptomyces silvensis* (known as L-365,209) using fragment coupling strategy.



Scheme 35. Synthesis of sterically hindered dipeptide fragment Fmoc-Ile-D-Δ-Piz from Fmoc-Ile-Cl.

BSA was employed for the silylation of amino acid esters to demonstrate its utility particularly in the incorporation of sterically hindered amino acids into peptide sequences.[223] The *N*-silylation of amino component during peptide coupling was further fine-tuned by Sureshbabu et al. using TMS-Cl and zinc dust under no base conditions.[225] Amino acid methyl ester hydrochloride salt was initially deprotonated using zinc dust and then converted to its *N*-silylated one by treatment with TMS-Cl in presence of zinc dust. After filtering out salts, *N*-silylated amino ester was treated with Fmoc-amino acid chloride to yield peptides in good yields. Neither oxazol-5-(4H)-one formation nor the premature deblocking of Fmoc group was observed, as so due to the absence of any organic base.[226]

Sureshbabu and Gopi applied acid chloride-KOBt protocol for coupling involving hindered Fmoc amino acid chlorides.[227] Under no base condition, the coupling duration could be extended to ensure efficient as well as complete coupling. Significantly, the danger of premature

deblocking of Fmoc group does not arise at all. Thus the preparation of α-aminoisobutyric acid (Aib) containing fragments of amphipathic peptaibol antibiotics, alamethicin 1-4 fragment Aib-Pro-Aib-Ala, the emerimicin 2-6 fragment Aib-Aib-Aib-Val-Gly and the Aib tetramer Fmoc-$(Aib)_4$-OBn were accomplished in good yields and purity.[227] Fmoc-amino acid chloride/KOBt protocol has also been extended for preparing peptides containing α,α-dialkylamino acids including Ac_5c, Ac_6c, Ac_7c, Dbg, and Dpg.[76] Also, microwaves assisted zinc dust mediated coupling involving highly hindered α,α-dialkylamino acids and cyclic as well as acyclic α,α-dialkylamino acids has lead to their assembly in good yields of 79-90%.[228]

Preparation of hindered peptides possessing up to four successive diphenylglycine or Aib residues was accomplished by using azido acid chloride method.[133] After coupling the azide peptidyl ester was reduced by using dithiothreitol (DTT) and then coupled with another azido acid chloride. A sterically demanding peptide H-Thr-Aib-Aib-Aib-Aib-Lys-Ser-Ser-Tyr-Lys-NH_2 was obtained in good yield of about 71%.[133] H-Dpg-Dpg-Lys-Ser-Ser-Tyr-Lys-NH_2 could also be assembled satisfactorily in 60% yield.[133]

5.3. Assembly of peptides containing *N*-methyl amino acids

N-Alkylation of peptides results in decreased number of possible hydrogen bonds thereby an increased conformational stability. The difficulties encountered during *N*-alkyl amino acid incorporation into peptide sequences were attributed to the severe steric hindrance and cis conformation of peptide bond owing to the bulkier *N*-alkyl group. These features complicate peptide synthesis considerably and coupling reactions involving *N*-methyl amino acids are marked by slow coupling, low yields, accompanied by racemization and diketopiperazine formation. Also, peptides containing *N*-alkyl amino acids are acid labile. The reactivity of resin bound secondary amines sometimes is even lower compared to reactions in solution and hence most of the known coupling protocols are not satisfactory. The target peptides are contaminated by truncated sequences due to unattainable acylation and mismatch sequences, thereby making the isolation of required peptide cumbersome even by preparative RP-HPLC. On the other hand, coupling employing acid chlorides is more than satisfactory. Preformed acid chlorides, with a variety of *N*-protecting groups, have been successfully employed to couple not only amino acid chlorides to *N*-methyl amino acids but also *N*-methyl amino acid chlorides to *N*-methyl amino

acids. Amino acid chlorides generated in situ have been successfully utilized to assemble even four consecutive *N*-methyl amino acids in solid phase method.

In a preparation of *N*-methylated dipeptide methyl esters, Di Gioia et al. employed Fmoc-amino acid chlorides as coupling reagents with *N*-methyl amino acid methyl ester under biphasic $NaHCO_3/CH_2Cl_2$ conditions.[229] In addition, the *N*-methyl di as well as tripeptide could be coupled with *N*-Fmoc-amino acid chlorides in standard Fmoc solution phase peptide synthesis to obtain corresponding *N*-Fmoc-tri and tetrapeptides which are *N*-methylated at the requisite amino acid. Methylated as well as sterically demanding Aib containing dipeptides could well be made using Bspoc amino acid chlorides,[85] Peoc amino acid chlorides[192,193]and Poc amino acid chlorides[86] in satisfactory yields in absence of any additive under Schotten-Baumann conditions. Also Fmoc-amino acid chloride/KOBt protocol has been utilized for the synthesis of peptides containing α,α-dialkyl amino acids as well as *N*-methyl amino acids (tables 12,13).[76] The protocol, as indicated by ^{1}H NMR studies, was reported to be free from racemization.

Table 12 Synthesis of sterically hindered peptides

Entry	Peptide	Method of coupling	Yield (%) [ref]
	Coupling of amino acid chlorides with H-*N*-Me-amino esters		
1	Fmoc-Val-MePhe-OMe		78 [161]
2	Fmoc-Ala-MeVal-OMe	aq. $NaHCO_3/CHCl_3$, rt	72 [161]
3	Fmoc-Ala-MeIle-OMe		98 [161]
4	Bts-Leu-MeVal-O^{t}Bu	Na_2CO_3/CH_2Cl_2, rt	95 [111]
5	Fmoc-Ala-D-MePhe-Ala-OMe		92 [106]
6	Fmoc-Val-D-MeAla-Val-OMe		94 [106]
7	Fmoc-Val-MeLeu-Ala-OMe		93 [106]
8	Ns-Val-MePhe-Ala-OMe	aq. $NaHCO_3/CHCl_3$, rt	86 [106]
9	Ns-Val-D-MePhe-Ala-OMe		88 [106]
10	Ns-Val-MeIle-Ala-OMe		72 [106]
11	Fmoc-Val-MeIle-D-Ala-Val-OMe		83 [106]
12	Bts-Leu-MeLeu-MeVal-O^{t}Bu	Na_2CO_3/CH_2Cl_2, rt	98 [111]
13	Bts-Ala-MeLeu -MeLeu-MeVal-O^{t}Bu		99 [111]
	Coupling of *N*-Me-amino acid chlorides with H-*N*-Me-amino esters		
14	Fmoc-MeVal-Sar-OMe	TMS-Cl, zinc dust, $CHCl_3$, rt	83 [225]
15	Poc-MeAla-MeAla-OMe	$CHCl_3/Na_2CO_3$, -5 to 0 ^{o}C	35 [86]
16	Bts-MeLeu-MeLeu-MeVal-O^{t}Bu	CH_2Cl_2/Na_2CO_3, rt	99 [111]
	Coupling of amino acid chlorides with dialkylamino esters		
17	Bts-Phg-Aib-OMe	Na_2CO_3/CH_2Cl_2, rt	95 [110]
18	Ths-Phg-Aib-OMe		64 [110]

	Coupling of dialkylamino acid chlorides with amino esters		
19	Fmoc-Dbg-Ala-OMe	KOBt, CH_2Cl_2, rt	85 [76]
20	Fmoc-Dbg-Phg-OMe		81 [76]
21	Fmoc-Aib-Ala-OBn		
	Coupling of dialkylamino acid chlorides with dialkylamino esters		
22	Fmoc-Ac_7c-Dbg-OMe	KOBt, CH_2Cl_2, rt	75 [76]
23	Fmoc-Ac_7c-Ac_5c-OMe		70 [76]
24	Fmoc-Ac_6c-Ac_6c-OMe	KOBt, CH_2Cl_2, rt	70 [76]
		zinc dust, CH_2Cl_2, MW	89 [186]
		TMS-Cl, zinc dust, $CHCl_3$, rt	86 [225]
25	Fmoc-Deg-Deg-OMe	zinc dust, CH_2Cl_2, MW	81 [228]
		TMS-Cl, zinc dust, $CHCl_3$, rt	82 [225]
26	Fmoc-Ac_7c-Ac_7c-OMe	zinc dust, CH_2Cl_2, MW	80 [228]
27	Fmoc- Ac_6c-Ac_6c-Ac_6c-OMe		79 [228]

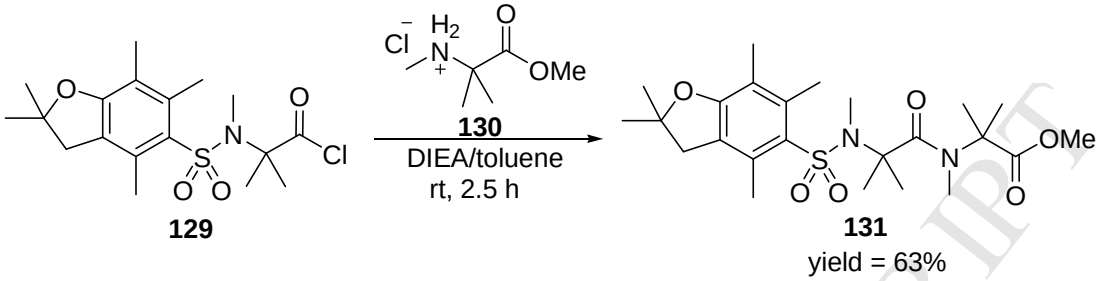
Table 13 Synthesis of sterically hindered Aib peptides

Entry	Peptide	Method of coupling	Yield (%)
1	Fmoc-Aib-Aib-OBn	zinc dust, CH_2Cl_2, MW, 90 sec	84 [186]
		KOBt, CH_2Cl_2, rt, 20-30 min	83 [227]
2	Poc-Aib-Aib-OMe	CH_2Cl_2/Na_2CO_3, -5 to 0 ^oC, 15 min	45 [86]
3	Fmoc-Aib-Aib-OMe	KOBt, CH_2Cl_2, rt, 20-30 min	85 [227]
		TMS-Cl, zinc dust, $CHCl_3$, rt, 15-20 min	88 [225]
4	Fmoc-Aib-Aib-OEt	KOBt, CH_2Cl_2, rt, 20-30 min	81 [227]
5	Fmoc-$(Aib)_3$-OBn	KOBt, CH_2Cl_2, rt	-- [227]
6	Fmoc-$(Aib)_4$-OBn		69 [227]
7	Poc-$(Aib)_3$-OMe	CH_2Cl_2/Na_2CO_3, -5 to 0 ^oC	42 [86]

5.4. Coupling involving N^{α}-benzyl/alkyl-$C^{\alpha,\alpha}$-dimethylamino acid ethyl esters

Neither simple amino acids (Ala, Phe) nor Aib were known to couple to H-MeAib. Thus, the coupling of Cbz-Aib to H-MeAib-NHMe mediated by bromotri(pyrrolidino)phosphonium hexafluorophosphate (PyBroP) in presence of DIEA for two weeks at room temperature gave the methyl amide in 3% yield.[230] The efficacy of the Tos-Aib-Cl due to greater inductive effect of sulfonyl residue was demonstrated by its coupling to obtain Tos-Aib-Aib-OMe in non-aqueous conditions to avoid degradation of acid chloride. On a similar strategy Tos-MeAib-Cl **129** reacted with NMeAib-OMe **130** as well.[107] Tos-Aib-Cl and Tos-MeAib-Cl were reported to couple with Alloc-MeAib-OMe in 4-8 h under Pd cat./$PhSiH_3$ conditions in 60-65% yield. Carpino demonstrated coupling of Pbf-NMeAib-Cl to H-NMeAib-OMe·HCl in toluene in the presence of DIEA to afford the extremely hindered dipeptide **131** in 63% yield (Scheme 36).[107] Unlike tosyl group, Pbf group can be deblocked completely using TFA/Me_2S, thus opening the

avenue for chain extension. However the preparation of Pbf-amino acids is not only multistep but also cumbersome.



Scheme 36. Coupling of Pbf-NMeAib-Cl to H-NMeAib-OMe·HCl in the presence of DIEA.

Zinc mediated microwave assisted peptide coupling protocol was extended to the coupling of *N*-benzyl-α,α-disubstituted amino acids by Harvey and coworkers.[228] The BSA/DIEA method resulted in inferior yields for coupling of extremely hindered H-*N*-Bn-Aib-OEt to Fmoc-Phe-Cl or Fmoc-Phe-F. Thus Cianci et al. developed an optimized protocol for coupling under microwave conditions involving the use of 5 eq of zinc for 2 h at 90 ^{o}C in CH_2Cl_2.[228] Fmoc-Phe-(*N*-Bn)-Aib-OEt was obtained by reacting a mixture of H-*N*-Bn-Aib-OEt·HCl, Fmoc-Phe-Cl and zinc dust in dry CH_2Cl_2 at 90 ^{o}C for 2 h at 60-70 psi in a CEM Discover microwave reactor (Table 14). The peptide was obtained in 61% yield, twice the best yield achieved with benchtop conditions (under reflux).

Table 14 Synthesis of sterically hindered *N*-Me- and *N*-Bn-Aib peptides[228]

Entry	Peptide	Method of coupling	Yield (%)
1	Fmoc-Phe-MeAib-OEt	zinc, CH_2Cl_2, 90 ^{o}C,	80
2	Fmoc-Phe-BnAib-OEt	2 h at 60-70 psi in a	61
3	Fmoc-Ile-BnAib-OEt	microwave reactor	40
4	Fmoc-Val-BnAib-OEt		54
5	Fmoc-Pro-BnAib-OEt		46

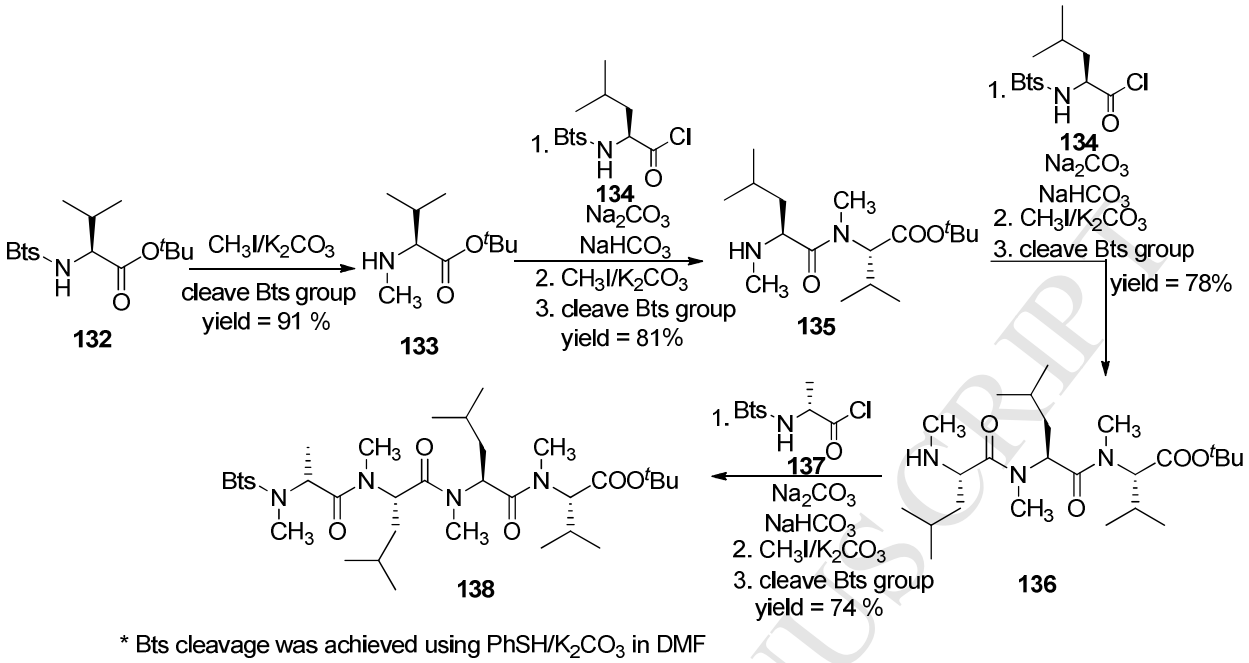
5.5. Cyclosporins and omphalotin A

Cyclosporins are a family of about 25 peptides and produced by the fungus *Beauveria nivea*. Cyclosporin O and cyclosporine A are sequence-homologous cyclic undecapeptides with seven *N*-methyl amino acid units and known for their antifungal, anti-inflammatory, and immunosuppressive activity.[231] Omphalotin A, a dodecapeptide containing nine *N*-methyl amino

acid residues formed by *Basidiomycete Omphalotus olearius*, is structurally related to the cyclosporins and shows selective activity against phytopathogenic nematodes such as meloidogyne incognita and outweighs other known nematicides such as ivermectin in potency and selectivity. Several methods including a combination of *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and 1-hydroxy-7-azabenzotriazole (HOAt)/*N*,*N*'-diisopropylcarbodiimide (DIC), symmetric anhydride coupling using DIC have been employed on solid phase with multiple couplings to obtain adequate coupling yields and site directed methylation protocol at higher expenses of reagents.

Rich group reported the synthesis of D-lysine[8]-cyclosporine A wherein the Fmoc–protected tetrapeptide FmocMeLeu-Val-MeLeu-Ala-OBn was prepared using Fmoc-MeLeu-Cl as acylating reagent in 86% yield (AgCN, CH_2Cl_2, room temperature).[232] Also Fmoc-Val-Cl was employed to obtain the tripeptide Fmoc-Val-MeLeu-Ala-OBn in 61% yield comparable to that obtained with *N*,*N*'-bis(2-oxo-3-oxazolidinyl)-phosphinicchloride (BOP-Cl) mediated coupling.[233]

Vedejs and Kongkittingam reported the synthesis of cyclosporine 8-11 tetrapeptide subunit (D-Ala-MeLeu-MeLeu-MeVal-O^{t}Bu) using Bts-protected amino acid chlorides (Scheme 37).[111] *N*-Methylamino ester could be efficiently coupled to Bts-*N*-methyl amino acid chloride under Schotten-Bauman conditions in excellent yield. However for reasons of step economy, subsequently *N*-methyl amino esters were coupled to Bts-protected amino acid chlorides **134** and the Bts-dipeptide **135** was then *N*-methylated and finally deprotected using PhSH/K_2CO_3. Both RP-HPLC and NMR studies showed no incomplete coupling or incomplete *N*-methylation and that coupling, *N*-methylation and deprotection survived epimerization and > 99.5% ee and ds could be obtained. Thus the tetrapeptide subunit has been assembled in 74-80% overall yield in solution including three repeated cycles of *N*-methylation, deprotection, and peptide coupling. The final product was obtained in high purity without chromatographic purification or crystallization by simple acid/base extraction itself.



Scheme 37. Synthesis of cyclosporine 8-11 tetrapeptide subunit (D-Ala-MeLeu-MeLeu-MeVal-O^{t}Bu) using Bts-amino acid chlorides.

Jung et al. reported solid phase synthesis of cyclosporine O employing BTC and a combination of collidine (for preactivation of carboxy component) and DIEA (for pretreatment of the resin) at room temperature (Scheme 38).[234] The highly acid labile trityl chloride polystyrene resin was chosen due to the acid lability of *N*-methylated peptides. A comparative study involving coupling of amino acids Fmoc-Trp(Boc)-OH, Fmoc-Val-OH, Fmoc-Sar-OH and Fmoc-MeVal-OH onto resin bound MeVal-Phe showed superiority of the BTC method over that of HOAt/DIC, symmetrical anhydride coupling using dicylcohexylcarbodiimide (DCC), acid fluoride activation by tetramethylfluoroformamidinium hexafluorophosphate (TFFH). However original BTC method which involves heating at 50 ^{o}C, was unsuccessfull at the stage of pentapetide, without any cleavage product (Fig. 6). Thus coupling condition was modified using a combination of bases for the preactivation and the coupling of amino acids, collidine and DIEA respectively and the coupling was carried out at room temperature in THF. The permethylated tetrapeptide H-MeLeu-MeLeu-MeVal-MeLeu-OH was obtained in over 99% yield, with coupling for 3 h or less at room temperature. Finally, the deprotected linear undecapeptide of cyclosporin O was obtained in a purity of 90%. However coupling of unmethylated amino acids proved problematic which was overcome by additional coupling cycle using HOAt/DIC for 16 h, except for BTC mediated coupling of norvaline (Nva).

Quantitative comparison of the methods for the coupling of different amino acids onto MeVal-Phe-TCP-resin is as follows,

Coupling method	Fmoc-Ile-OH	Fmoc-Sar-OH	Fmoc-MeVal-OH	Fmoc-Trp(Boc)-OH
BTC	+	+	+	+
HOAt	XX	+	XX	X
TFFH	XX	X	X	XX
DCC	XX	+	XX	XX

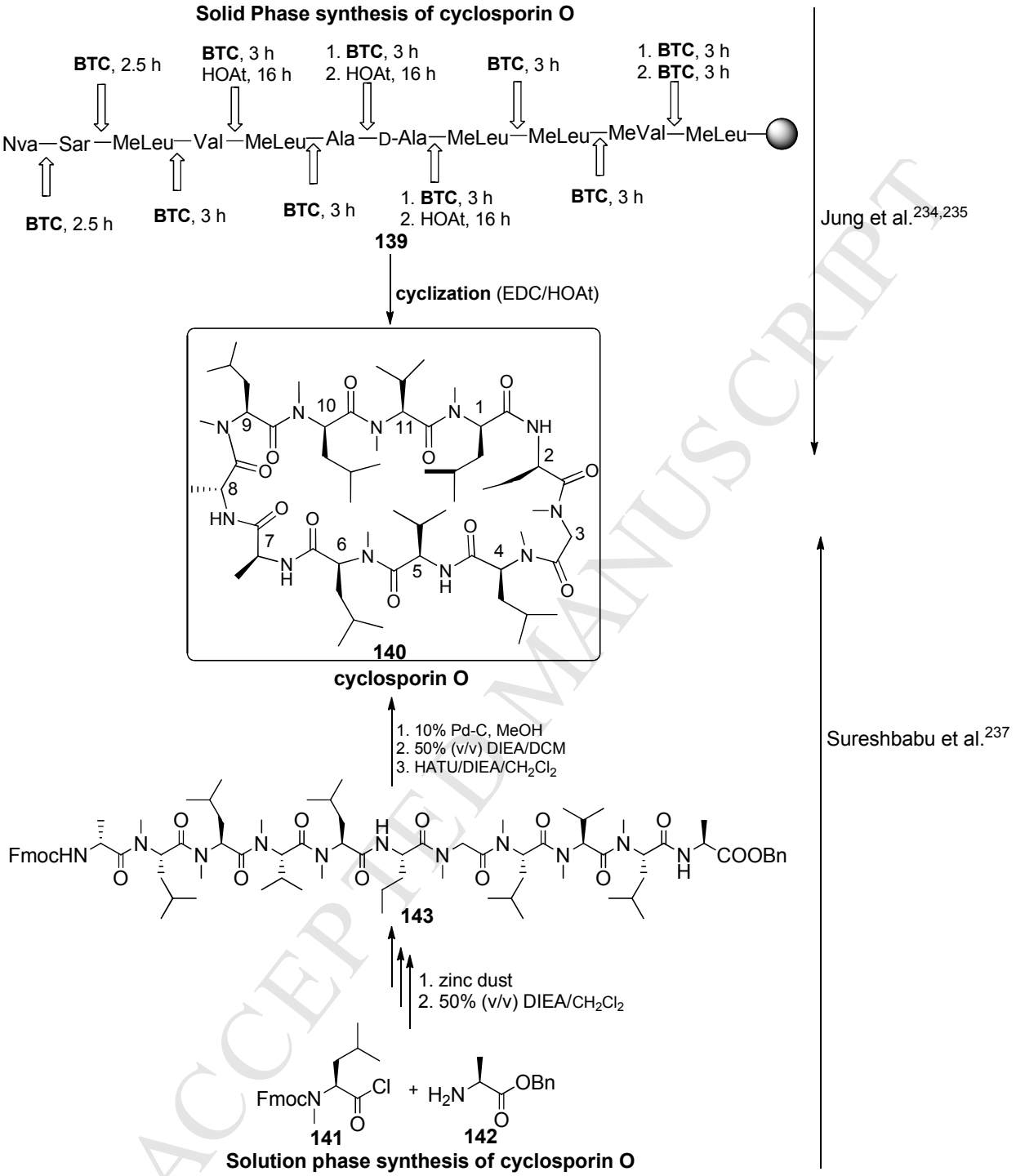
+: chloranil test is negative, indicating complete reaction.
X: chloranil test slightly positive
XX: chloranil test positive
(Sar = sarcosine)

Figure 6. Comparison of the methods for the coupling of different amino acids onto MeVal-Phe-TCP-resin.

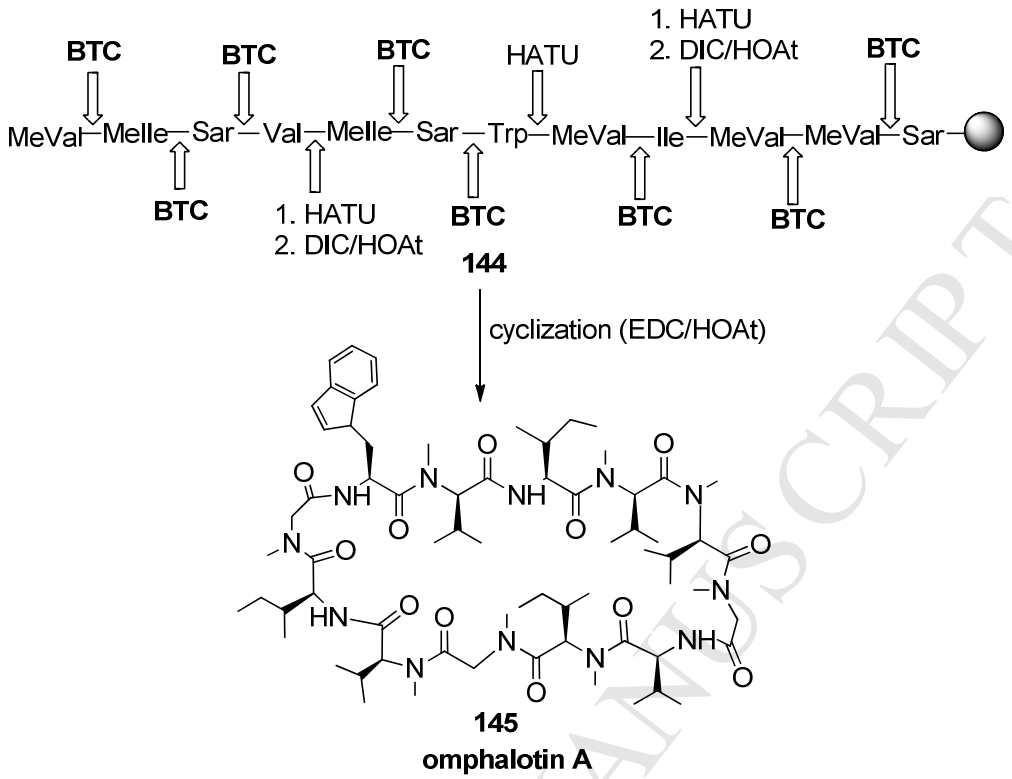
The modified BTC coupling was also utilized in the total synthesis of omphalotin A using TCP resin preloaded with sarcosine, a combination of BTC protocol and DIC/HOAt, HATU (for insertion of unmethylated amino acids) couplings. The linear dodecapeptide with C-terminal Sar^6 was obtained in 84% yield and 90% purity. Diastereomerically pure omphalotin A (**145**) was obtained in 37% yield after cyclization and an overall yield of 31% with respect to the first loading of the resin with Fmoc-sarcosine (Scheme 39).[235]

Sewald has highlighted the efficient solid phase assembly of cyclosporin O and omphalotin A *via* BTC activation.[236] Peptide macrocyclization by activation of C-terminal resin bound sarcosine residue was found superior than from resin bound MeIle due to considerable racemization in the latter case.

An elegant synthesis of cyclosporin O (**140**) was carried out by step-by-step linear condensation approach by employing Fmoc-amino acid chlorides under neutral conditions in the presence of zinc in solution (Scheme 38).[237] The amino free peptide benzyl esters were coupled directly to the next amino acid without isolation. All the ten intermediate Fmoc-protected peptide fragments were isolated in good yields (above 90%). Coupling of consecutive *N*-methyl amino acids could result in upto 73-79% yield. The cyclization of free undecapeptide was achieved in 85% yield with HATU in CH_2Cl_2. Starting from dipeptide, cyclosporine O (**140**) was obtained in an overall yield of 15-18%.



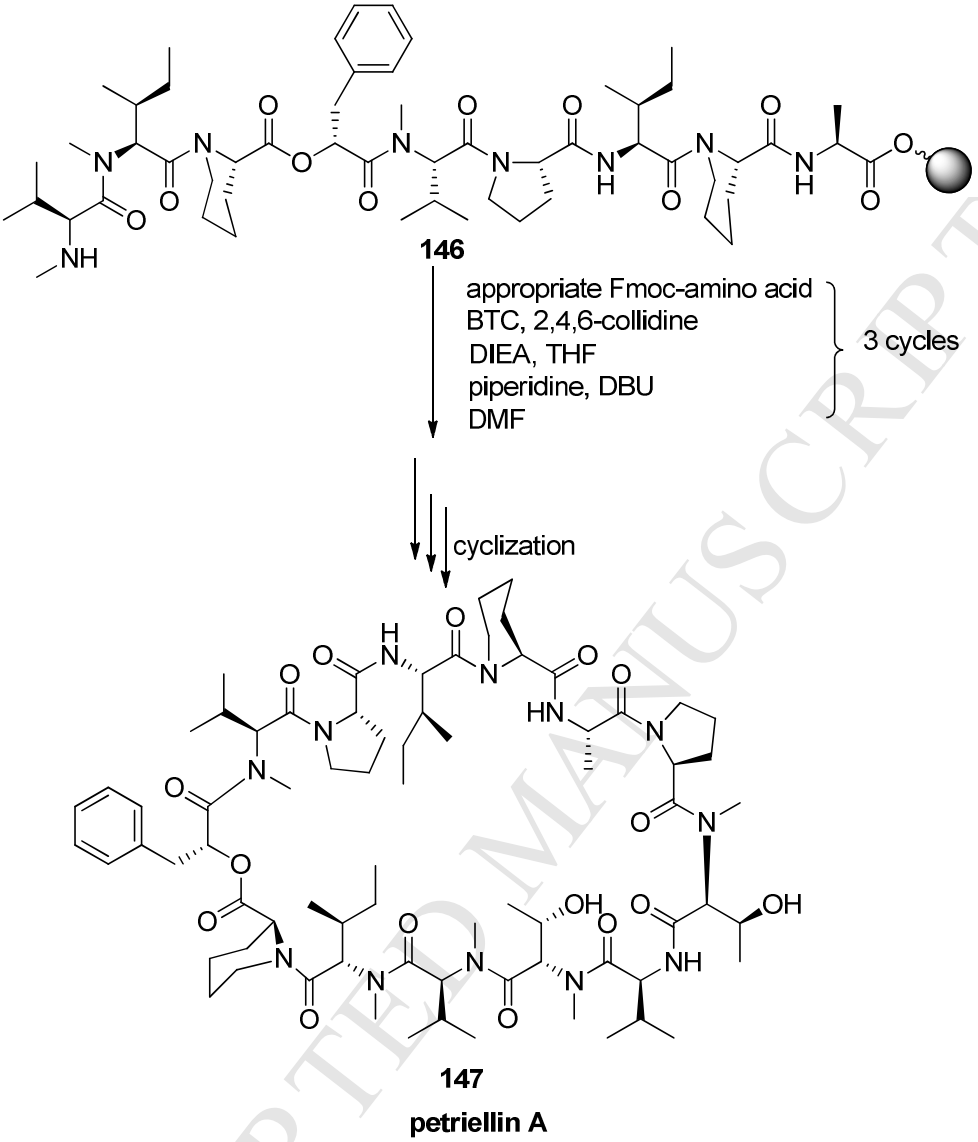
Scheme 38. Synthesis of cyclosporine O using BTC and zinc dust methods.



Scheme 39. Synthesis of omphalotin A using BTC method.

5.6. Petriellin A

Hughes and coworkers reported solid phase synthesis of the antifungal highly modified cyclic depsipeptide petriellin A (**147**) in an overall 5% yield using 2-chlorotritylchloride (ClTrt) resin and Fmoc amino acid derivatives (Scheme 40).[238] Solution phase synthesis was employed for the preparation of depsipeptide fragment by Mitsunobu esterification between Fmoc-L-pipecolic acid and the L-phenyllactate derivative. The depsipeptide fragment and other *N*-alkyl amino acid residues were coupled to growing resin bound peptide by modified BTC method developed by Jung et al. whereas coupling involving unalkylated residues were brought about by *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate/1-hydroxybenzotriazole (HBTU/HOBt). After resin cleavage, the crude linear precursor was isolated in 58% yield, as calculated from the loading of the first residue. The cyclization at the Ala-Pro junction was conducted in high dilution to obtain the cyclized target molecule.

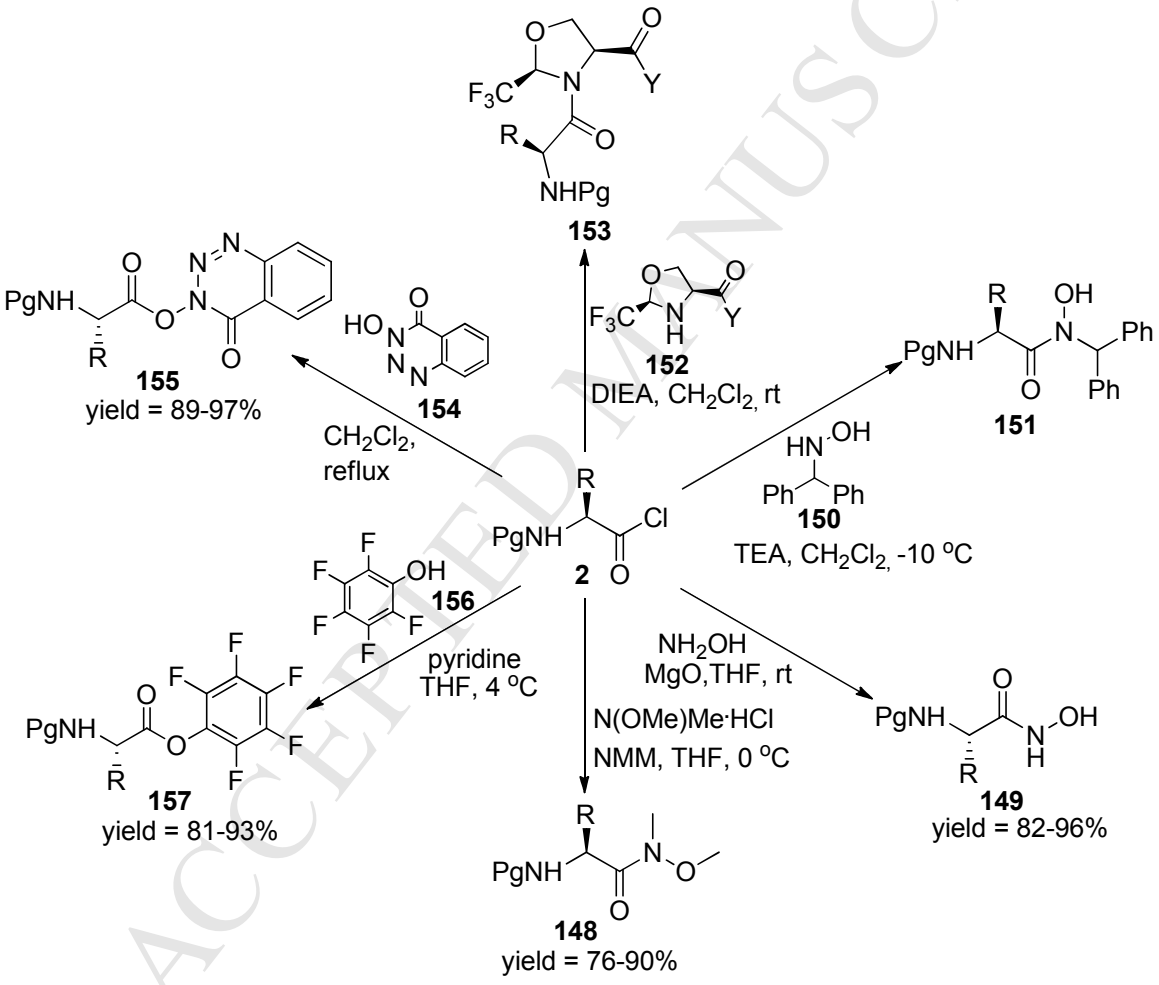


Scheme 40. Synthesis of petriellin A using BTC method.

6. Applications

6.1. Amino acid derivatives

A large number of amino acid derivatives have been prepared by acylation of nitrogen and oxygen nucleophiles with protected amino acid chlorides. These include, Fmoc-protected amino/peptidyl Weinreb amides **148**, hydroxamic acids **149**, pseudoproline analogs **153**, Pfp and 3,4-dihydro-4-oxo-1,2,3-benzotriazine-3-yl (Dhbt) esters **155** of Fmoc amino acids and α-amino-α'-ketols **151** (Scheme 41).



Scheme 41. Synthesis of various amino acid derivatives using protected amino acid chlorides.

6.1.1. Weinreb amides

Fmoc-protected amino/peptide acid chlorides generated using $SOCl_2$ under ultrasonication were treated with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of NMM to obtain corresponding Weinreb amides **148** in two steps in good yields and purity (Scheme 41).[239]

6.1.2. Hydroxamic acids

Two derivatives of hydroxyl amine, *N*-Boc-O-(THP) (THP = tetrahydropyran) and *N*-Boc-O-TBDMS were employed for the synthesis of *N*,*O*-bisprotected hydroxamic acids by reaction with various carboxylic acid chlorides.[240] A deprotection step is necessary after the acylation of hydroxyl amine derivative. Sureshbabu and Hemantha reported a simplified synthesis of Fmoc-amino acid hydroxamates by direct acylation of hydroxylamine using Fmoc-amino acid chlorides in presence of excess of MgO in one step.[241] Hydroxyl amine hydrochloride was deprotonated using an equivalent of MgO in methanol/water, and treated with Fmoc-amino acid chloride using 2 eq of MgO.

Malkov and coworkers[242] employed amino acid-derived hydroxamic acids **149** as chiral ligands in the vanadium catalysed epoxidation of various allylic alcohols (Scheme 41). The *N*-benzenesulfonyl or mesyl protected amino acid chlorides were reacted with benzhydryl hydroxylamine at low temperature to obtain required hydroxamic acids. Under these conditions, the competing *O*-acylation of the hydroxylamine was reduced to less than 5% and chiral HPLC analysis showed that reaction proceeded with > 99% ee.

6.1.3. 2-CF_3-1,3-Oxazolidine (Tfm-pseudoproline) containing dipeptides

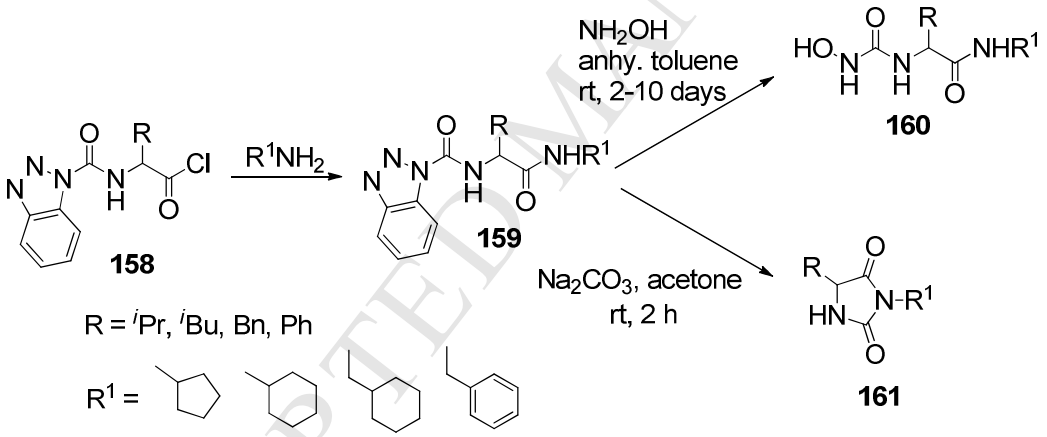
Chaume et al.[243] employed acid chloride strategy to overcome low nucleophilicity of amino group of CF_3-oxazolidine pseudoproline **152** in synthesis of dipeptides **153** incorporating one CF_3-ψPro and studied their conformational features. Methyl-(2*R*,4*S*)-CF_3-pseudoprolinate was coupled with *o*-Nbs-Ala-Cl (generated *in situ* using 1-chloro-*N*,*N*-2-trimethyl-1-propenylamine) and Fmoc-Ala-Cl to obtain diastereomeric peptides (Scheme 41) in good yields (> 70%), which were then purified by flash chromatography.

6.1.4. 3,4-Dihydro-4-oxo-1,2,3-benzotriazine-3-yl (Dhbt) and pentafluorophenyl (Pfp) esters

A one pot preparation of 3,4-dihydro-4-oxo-1,2,3-benzotriazine-3-yl (Dhbt) **155** and two step preparation of Pfp esters **157** involving Fmoc amino acid chlorides as intermediates were reported by Jacobsen et al.[244,245] The method avoids the side reaction of formation of azido benzoyl derivative that prevail when conventional DCC method was employed (Scheme 41).

6.1.5. Hydroxyurea and hydantoin derivatives

Several L- and D-amino acid derivatives of hydroxyurea **160** were prepared by aminolysis of *N*-(1-benzotriazolecarbonyl)amino acid amides **159** with hydroxylamine.[122] These amides were obtained from corresponding Btc-amino acid chlorides **158**. Similarly, hydantoin derivatives **161** are accessed by base catalyzed cyclization of these intermediate amides **159** (Scheme 42).

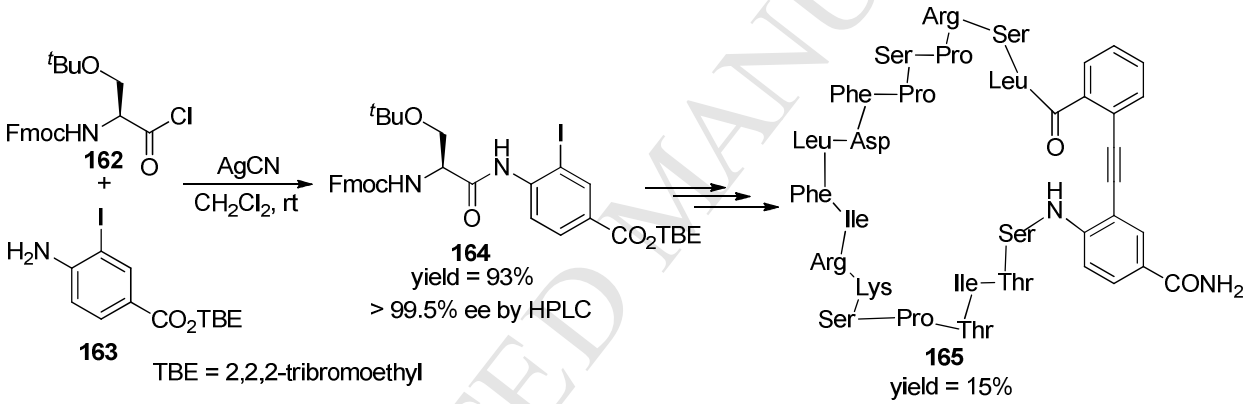


Scheme 42. Synthesis of hydroxyurea and hydantoin derivatives.

6.1.6. Aryl amides

The very first application of Fmoc-amino acid chlorides involved coupling of in situ generated Fmoc-amino acid chlorides with 5-bromo-7-nitroindoline for the preparation of corresponding 5-bromo-7-nitroindolinyl derivatives.[75b] The reaction was carried out by heating a mixture of Fmoc-protected amino acid, $SOCl_2$ and 5-bromo-7-nitroindoline in toluene, at 40-70 ^{o}C for several hours to yield the desired amides in high optical purity (99.5 ± 0.5% ee). 5-Bromo-7-nitroindolinyl derivatives were then employed in photochemical coupling of peptide segments.

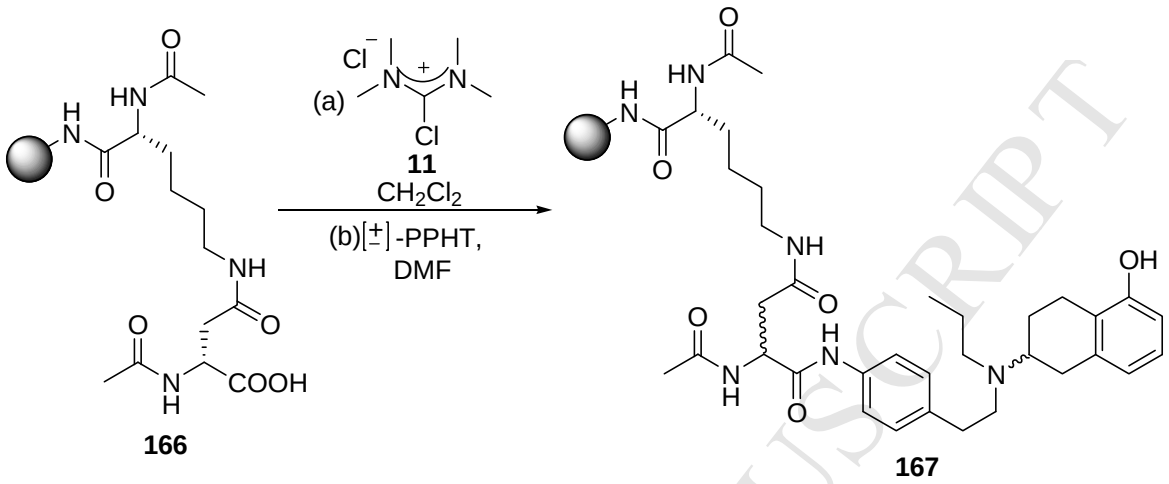
Spivey et al.[246] reported solid phase synthesis of cyclic diphenylacetylene (tolan) amino acid constrained peptidomimetic containing the 21-residue epitope present in the A-B loop of the Cε3 domain of the human immunoglobulin E (hIgE). The serine amide building block **164** was synthesized by coupling Fmoc–Ser(^{t}Bu)-Cl **162** with 2,2,2-tribromoethyl-4-amino-3-iodobenzoate **163** in presence of AgCN in 93% yield (Scheme 43). Initial attempts to form amide bond by employing standard coupling agents and additives failed to afford the desired product. The synthesis of linear peptide having the IgE Cε3 sequence 358-340 fragment was then carried out using Rink amide functionalized polystyrene resin. Finally the peptide macrocyclization was effected by Sonogashira cross coupling of 2-ethynylbenzoic acid and 4-amino-3-iodobenzamide on solid phase in presence of $Pd(PPh_3)_2Cl_2$, CuI, and TEA. The resulting cyclized product **165** was purified by RP-HPLC (~15% yield).



Scheme 43. Synthesis of cyclic diphenylacetylene (tolan) amino acid constrained peptidomimetic.

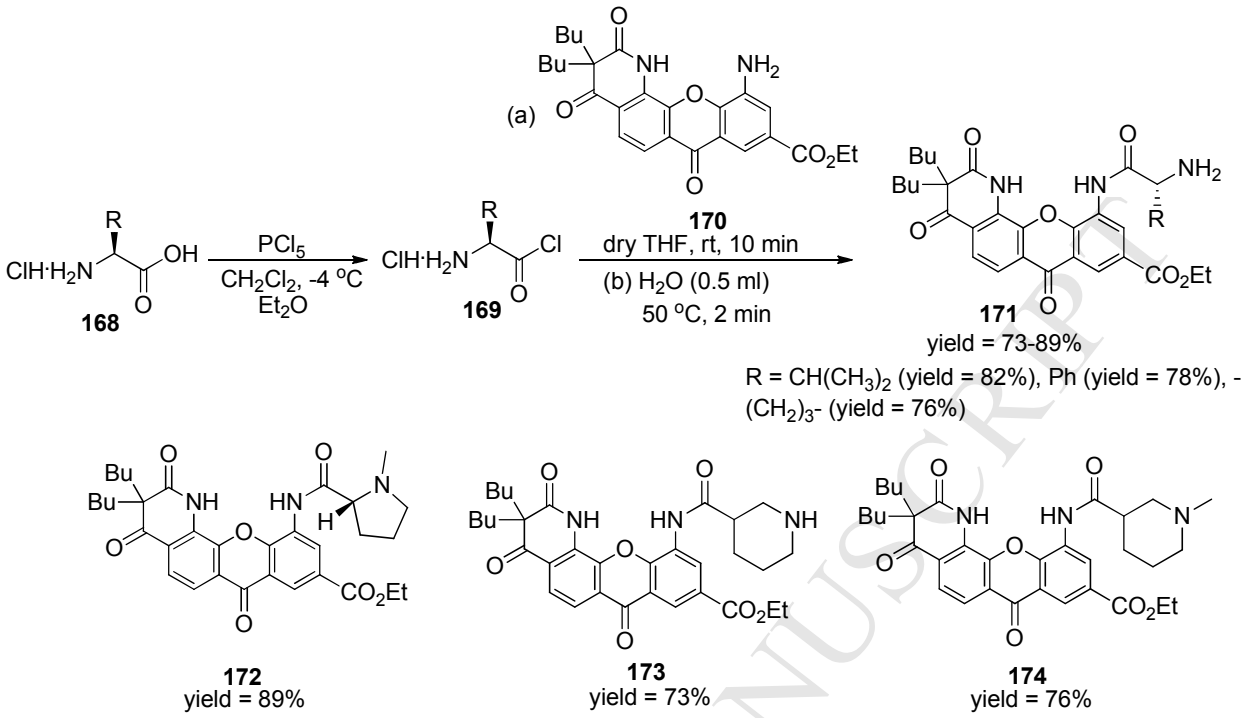
N-[Chloro(dimethylamino)methylene]-*N*-methylmethanaminium chloride (TMUCl Cl) **11** has been employed for the solid-phase organic synthesis of anilides from supported carboxylic acids through corresponding acid chloride activation.[23] The method was found efficient when compared to the *N*,*N*'-carbonyldiimidazole (CDI) activation. Thus three different aromatic amines (benzidine, 4,4'-tiodianiline and 4-nitroaniline) were incorporated to side chain carboxylic acid of Glu anchored onto Rink-PS-resin in high yields (Scheme 44). Also the study involved condensation of [±]-2-[*N*-phenylethyl-*N*-propyl]amino-5-hydroxytetralin {[±]-PPHT}, a selective and potent agonist of D_2 dopamine receptor with Glu residue supported onto polystyrene (PS) resin **166**. In a comparative study, TMUCl Cl was found to yield highest conversion of 62% when compared to CDI and 2,4,6-trichloro[1,3,5]-triazine (TCT) (46% and

40% respectively). The HPLC analysis of diastereomers indicated 15% racemization for this demanding condensation.



Scheme 44. Solid-phase synthesis of anilide using TMUCl Cl.

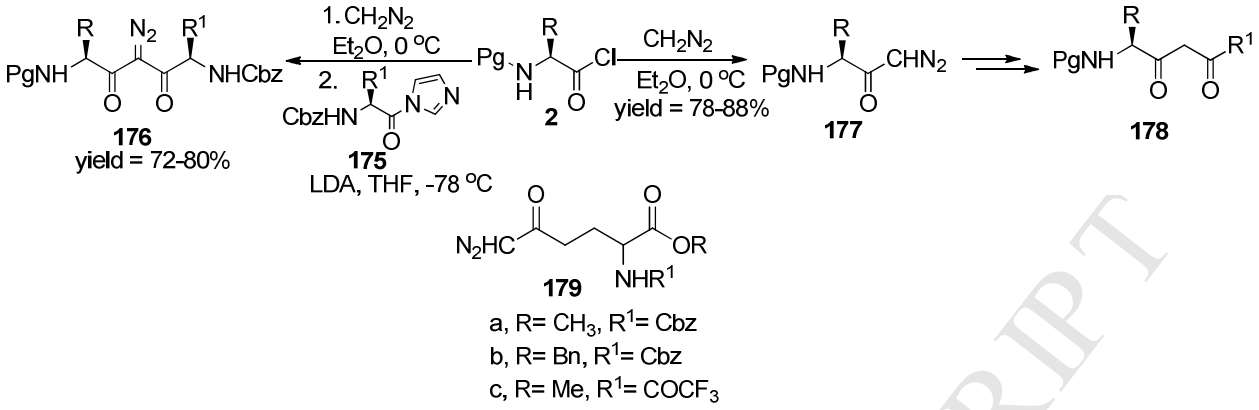
Xanthone amine derivatives **170** were reacted with excess amino acid chlorides **169** in dry THF at room temperature for 10 min to obtain various artificial xanthone based nucleophiles with oxyanion hole structure combined with amino groups (Scheme 45).[247] Excess acid chloride was hydrolyzed by heating with water at 50 ^{o}C. The aqueous work up followed by recrystallization of crude material from methanol/water lead to the isolation of nucleophiles in good yields. Catalytic activity of xanthone based nucleophiles for enantioselective Michael type addition of ethanethiol to the 5,6-dihydro-2-(H)-pyridinone was studied. Relative position of the basic catalytic group in the nucleophile was varied by using various amino acid derivatives with different side chains. The proline derived nucleophile showed good catalytic activity as well as high asymmetric induction.



Scheme 45. Coupling of amino acid chlorides with xanthone amine derivatives.

6.1.7. Diazoketones and homologation to β-amino acids

N$^{\alpha}$-Protected aminodiazoketones **177** are useful intermediates for synthesis of β-amino acids and their derivatives.[248] Ye and Mckervy [249] treated EtOCO-α-amino acid chlorides with ethereal solution of CH_2N_2 and the resulting α-diazo ketones were lithiated and then condensed with aldehydes or ketones (Scheme 46). Thus obtained α-diazoketols were rearranged to homochiral α-amino-β-diketones on treatment with rhodium(II) acetate. In another report, *N*-Cbz protected amino acid chlorides were converted to corresponding diazoketones (only three examples illustrated) which were used as one of the components in synthesis of di(*N*-protected-α-amino)diazo-β-diketones **176**.[250]



Scheme 46. Synthesis of N^{α}-protected aminodiazoketones and di(*N*-protected-α-amino)diazo-β-diketones.

Liguori et al. reported the stereospecific homologation of the Fmoc-α-amino acids to their β-homologues via acid chlorides.[251] *N*-Fmoc-amino acid chlorides were treated with 0.66 M solution of CH_2N_2 in CH_2Cl_2, to obtain α-aminoacyldiazomethanes in 92-97% yield, without any detectable racemization as confirmed by ^{1}H NMR study of (2*S*,3*S*)-isoleucine as a test case. Similarly *N*-nosyl-*α*-aminoacyl chlorides were also converted to corresponding *N*-methyl-*N*-nosyl-*α*-aminoacyldiazomethanes and then subjected to Wolff rearrangement in presence of silver benzoate to obtain *N*-methyl-Nosyl-β^3-amino acids.[107]

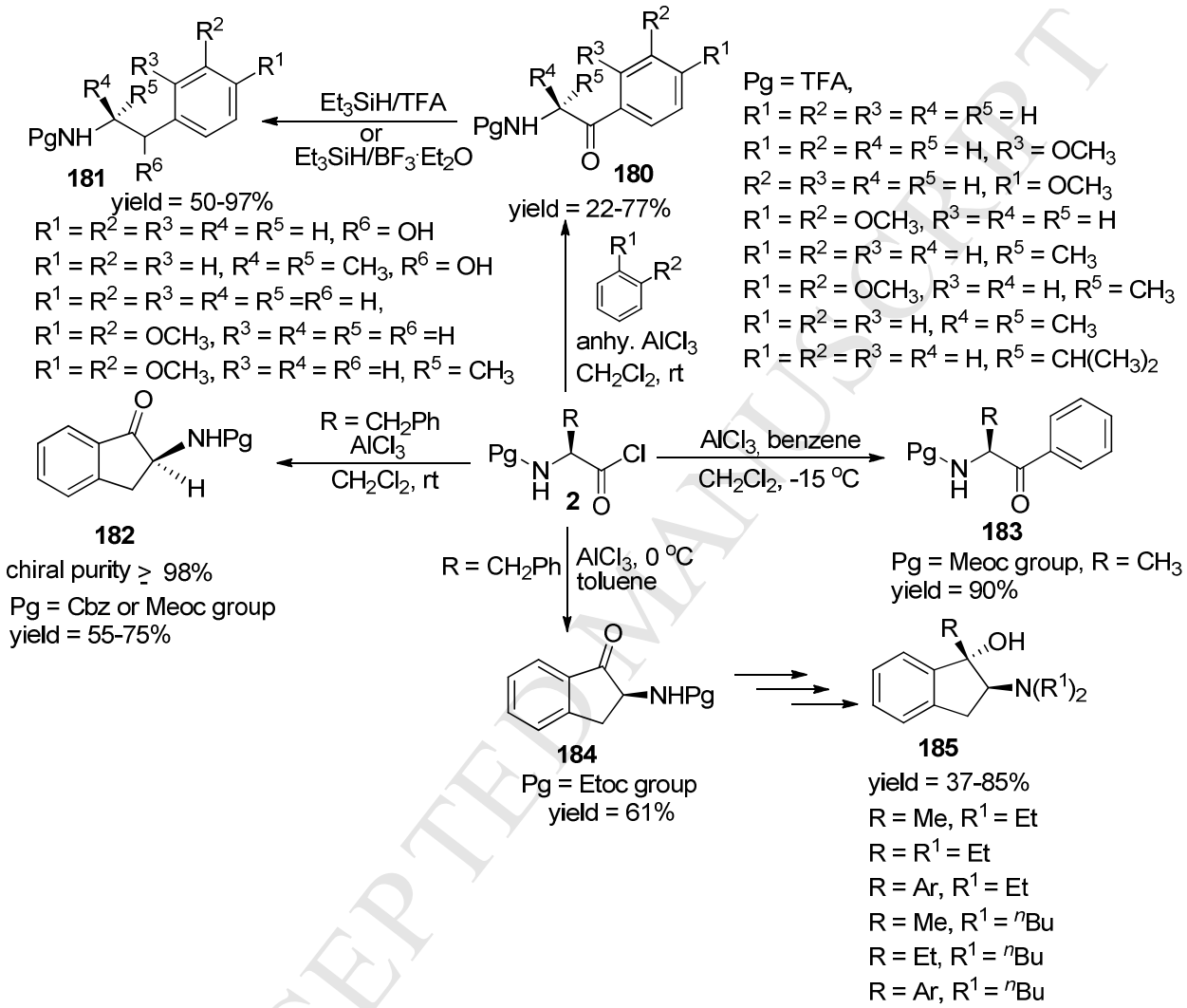
Pettit et al. converted γ-carboxyl group of L-glutamic acid derivatives by using oxalyl chloride in THF and catalytic DMF followed by treatment with diazomethane at -23 °C.[252,253]

6.1.8. Friedel-Crafts reaction: Chiral aryl-α-amino ketones

The utilization of *N*-protected amino acid chlorides in Friedel-Crafts reaction to obtain dissymmetric aromatic amino ketones **183** has been explored since long time. Chiral aryl-α-amino ketones have been used as drugs in the treatment of nicotine dependence, as late life antidepressants. Though phthaloyl, tosyl, acetyl, benzoyl, methyloxy, ethyloxy, TFA protecting groups were compatible with the Friedel-Crafts acylation conditions, difficulties during the deprotection step and partial racemization hampered their general utility.

The use of *N*-methoxycarbonyl-Phe-Cl/Ala-Cl in Friedel-Crafts acylation affords about 60% yield with chiral purity of 96-98% as determined by chiral shift ^{1}H NMR analysis.[95] *N*-Cbz-Phe-Cl found to yield only intractable tars when reacted with $AlCl_3$. However the

corresponding methoxycarbonyl derivative underwent Friedel-Crafts cyclization in 55-75% yield with chiral purity of > 98%. *N*-Methoxycarbonyl alanyl chloride provided acyclic *N*-protected α-amino ketone in 50-60% yield but found to contain 3-4% of epimer (Scheme 47).

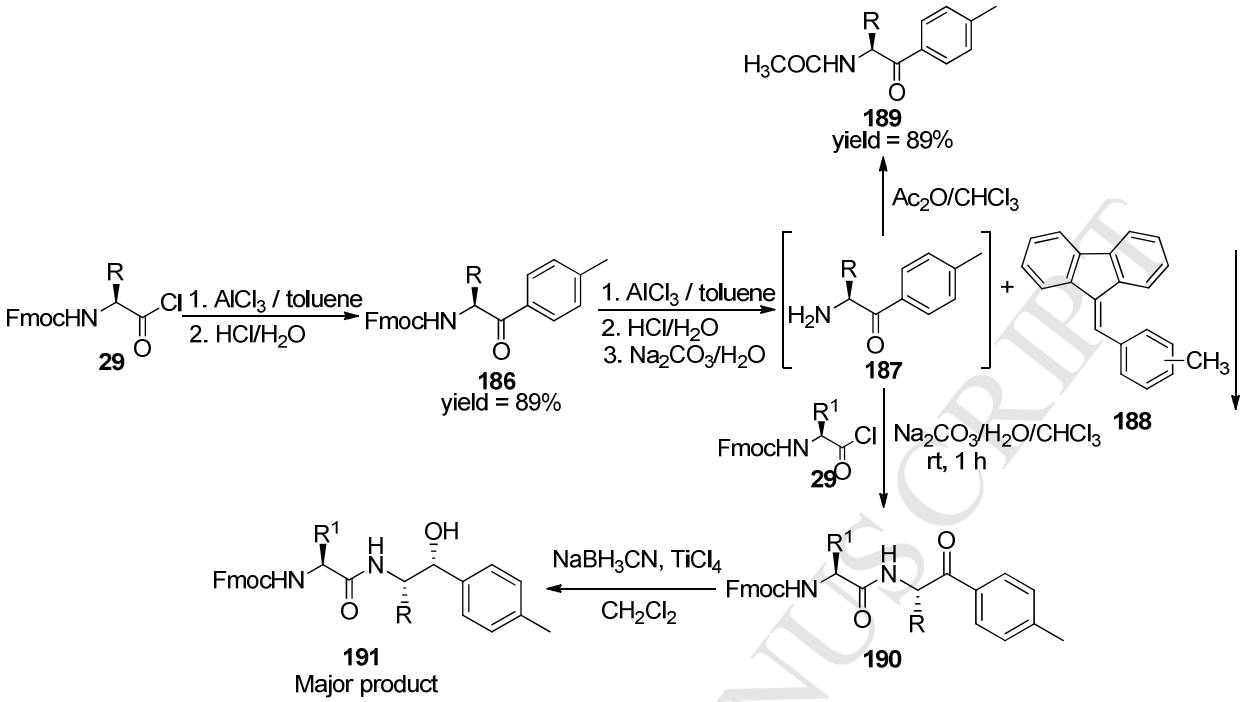


Scheme 47. Use of *N*-protected amino acid chlorides in Friedel-Crafts reaction.

Buckley and Rapoport[91] employed similar chemistry using Etoc-alanyl chlorides as a chiral educt for the synthesis of α-aminoalkyl aryl ketone. Xu et al. utilized ethoxycarbonyl-Phe-Cl in Freidel-Crafts cyclization and the resulting product was employed to prepare optically active trans-(1*S*,2*S*)-1-substitued-2-(*N*,*N*-dialkylamino)-1-indanol derivatives.[94] Nordlander et al.[115,254,255] demonstrated similar chemistry using TFA-α-amino acid chlorides as chiral reagents for Friedel-Crafts reactions. Herein benzene, anisole, and veratrole underwent reaction in

presence of anhydrous $AlCl_3$ or $SnCl_4$ with > 99% preservation of chiral integrity. The ketones were reduced under neutral conditions using Et_3SiH or H_2/Pd-C to the corresponding TFA-β-hydroxy-β-arylalkylamines or TFA-β-arylalkylamines without loss of enantiomeric purity. The latter were then employed to obtain 3-substituted 1,2,3,4-tetrahydroisoquinolines.

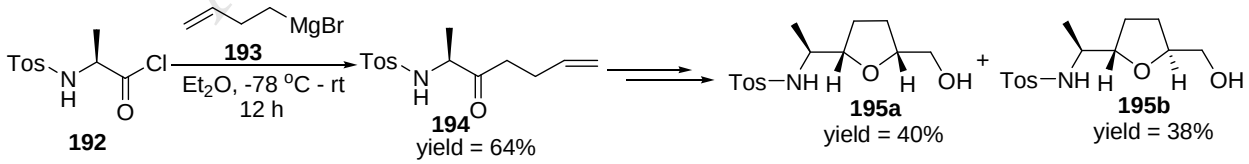
Di Gioia et al.[256a] developed an elegant one pot process for Friedel-Crafts type reaction/deblocking of Fmoc-amino acid chlorides with toluene in presence of $AlCl_3$ controlling both stoichiometry and reaction duration. Herein a solution of Fmoc-amino acid chloride in toluene was treated with three fold excess of $AlCl_3$, at room temperature for 2 h. The desired free base aryl-α-amino ketone was separated by simple hydrolytic work up under basic conditions, followed by solvent extraction (Scheme 48). The treatment of organic layer with acetic anhydride afforded the *N*-acetylated ketone in 89% yield. The protocol could be extended for the preparation of modified dipeptides and a tripeptide as well. The peptide analogs could be obtained in high yields and without the need for any chromatographic purification. The ^{1}H NMR analysis of reaction crudes of diaseteromeric modified dipeptides obtained by coupling of Fmoc-L-valine chloride with epimers of 2-amino-1-*p*-methylphenyl-propanone confirmed total retention of chiral integrity of either precursor or product. The GC-MS and ^{1}H NMR analysis of *N*-acetylated derivatives also confirmed presence of single diasteriomer. The free base chiral aryl-α-amino ketones **187** underwent coupling with Fmoc-amino acid chloride to obtain dipeptidyl ketones **190** as well. Aryl peptidyl ketones could be reduced in presence of titanium tetrachloride as the chelating agent to the corresponding amino alcohols **191**.[256b]



Scheme 48. Synthesis of chiral aryl-α-amino ketones and dipeptidyl ketones.

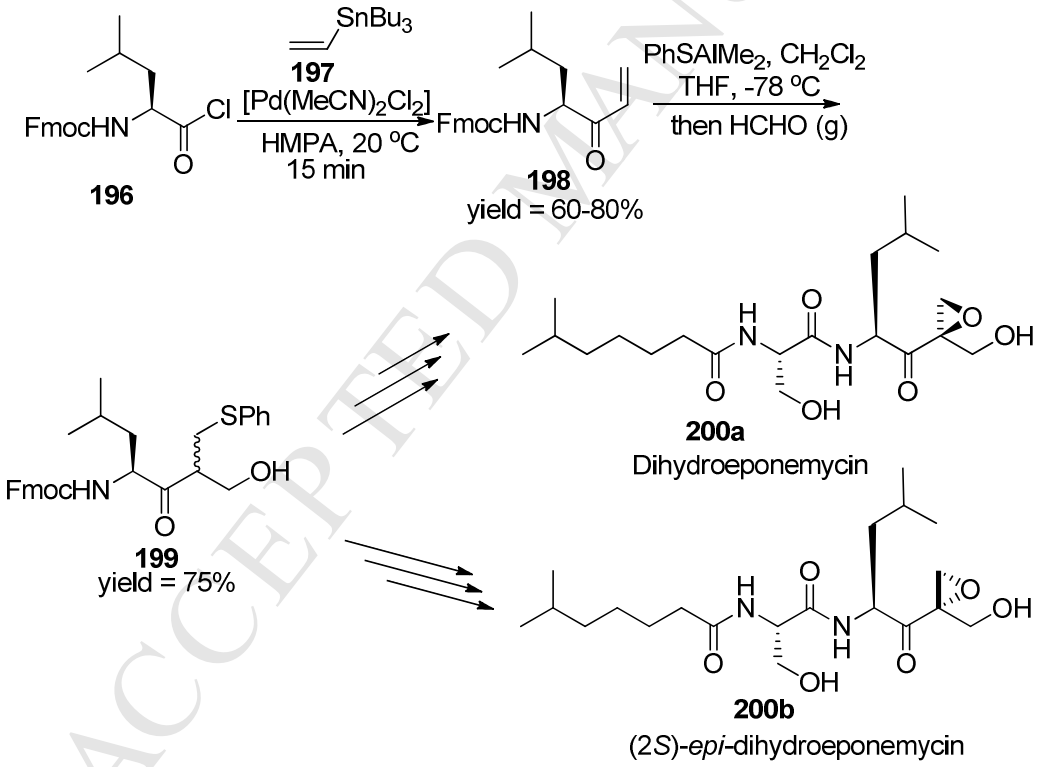
6.1.9. Reaction with Grignard reagent and other organometallic reagents

Schrey et al.[257] reported synthesis of enantiopure cis- and trans-2,5-disubstituted tetrahydrofuran amino acids starting from tosyl-amino acid chlorides. Reaction of butenylmagnesium chloride **193** with *N*-tosyl alanyl chloride **192** resulted in 64% yield of the ketone **194** (Scheme 49). The yield was improved to 94% by conversion of Grignard reagent to organocopper species prior to reaction with the acid chloride. The ketone was subjected to L-selectride reduction and subsequently transformed into enantimerically pure trans- and cis-tetrahydrofuran (THF) amino alcohols **195a** and **195b**, which were eventually converted to the corresponding Boc and Fmoc protected THF amino acids. The acid chloride was found to be a superior starting material than the lithium *N*-tosylalaninate, which affords the corresponding ketone in 40% yield only.



Scheme 49. Synthesis of cis- and trans-2,5-disubstituted tetrahydrofuran amino acids by reaction of Tos-amino acid chloride with Grignard reagent.

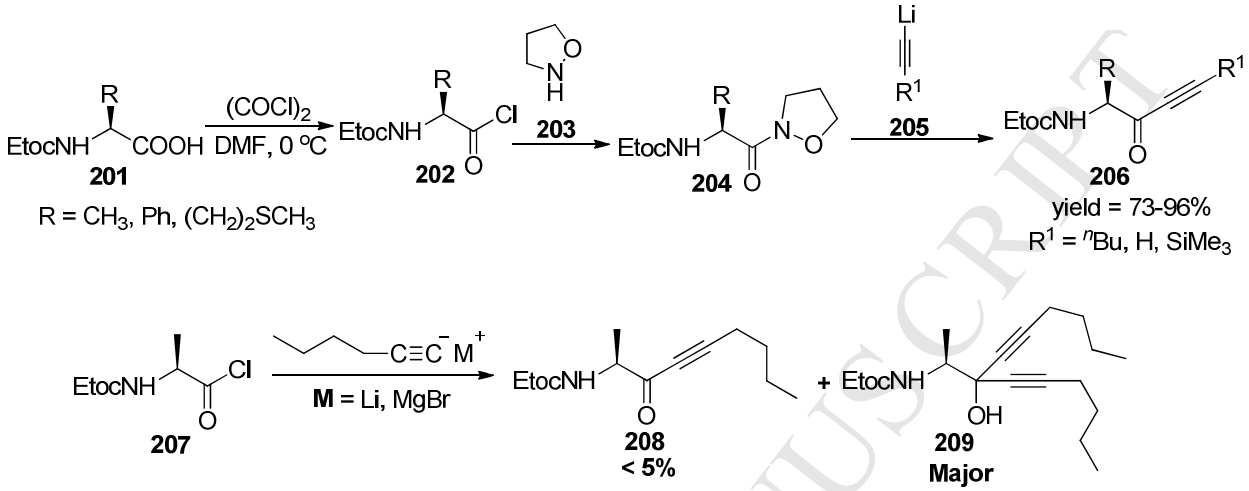
In a synthesis of 6,7-dihydroeponemycin (**200a**), a peptide epoxide with potent cytotoxic and antiangeogenesis activity, Bennacer et al.[258] employed Pd(0) catalysed Stille couping of Fmoc-Ile-Cl **196** with tributylvinyltin **197** in 4-(hydroxylmethyl)phenoxyacetic acid (HMPA) at 20 ^{o}C in 60-80% yield with 98% ee (Scheme 50). The Stille product was then subjected to conjugate addition with $PhSAlMe_2$, S-oxidation, and heat induced syn elimination to obtain an enone intermediate, which was converted to 1 : 1 diastereomeric mixture of epoxides, which could be separated through silica gel chromatography. Finally individual diastereomers are converted into dihydroeponemycin (**200a**) and (2*S*)-*epi*-dihydroeponemycin (**200b**) in a four step one pot protocol.



Scheme 50. Pd(0) catalysed Stille couping of Fmoc-Ile-Cl with tributylvinyltin and synthesis of dihydroeponemycin (**200a**) and (2*S*)-*epi*-dihydroeponemycin (**200b**).

Etoc-amino acid chlorides **202** were used for the synthesis of α-amino acid isoxazolidides **204** derived from Ala, Phe, and Met and subsequently employed for the preparation of optically

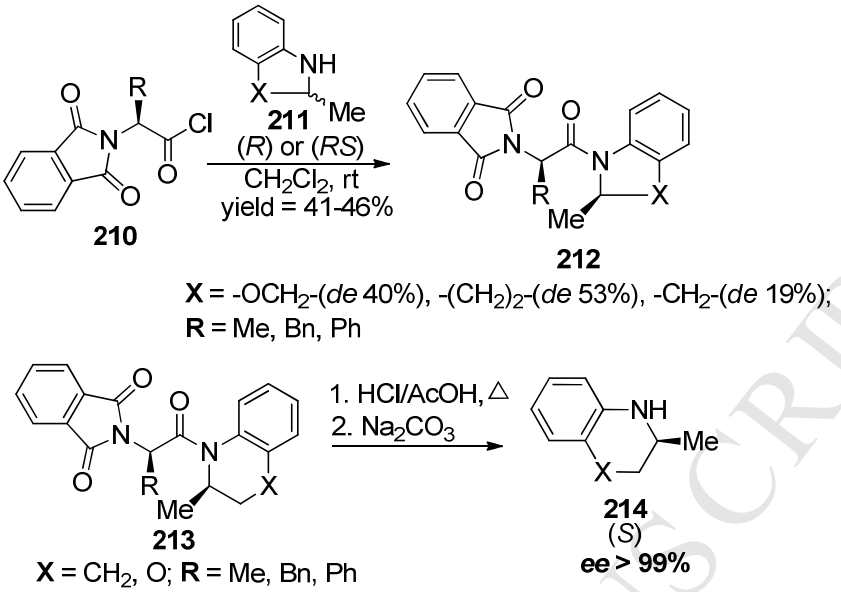
pure α'-amino-α,β-ynones **206** by reaction with lithium acetylides **205** (Scheme 51). However direct reaction of acid chloride with lithium acetylide lead to < 5% yield of respective ynone **208**, producing largely the corresponding tertiary alcohol **209**.[93,249,259]



Scheme 51. Synthesis of α-amino acid isoxazolidides and α'-amino-α,β-ynones.

6.1.10. Kinetic resolution of heterocyclic amines

Levit's group studied kinetic resolution of heterocyclic amines using phthaloyl protected amino acid chlorides **210** as enantiopure acylating agents.[126,260] Acylation of racemic heterocyclic amines, 2-methyl-1,2,3,4-tetrahydroquinoline, 2,3-dihydro-3-methyl-4H-1,4-benzoxazine and 2-methyl indoline with *N*-phthaloyl-(*S*)-alanyl chloride under kinetic resolution conditions lead to diastereomeric amides **212** enriched with (*S*,*S*) amides with de 40%, 53% and 19% respectively. Recrystallization of the (*S*,*S*) amides from hexane-EtOAc resulted in high diastereomeric excess (de > 99.5%) of individual diastereomer. However amide from 2-methylindoline could only be obtained as 1 : 1 ratio of (*S*,*S*)- and (*R*,*S*)-amide (Scheme 52). (*S*,*S*)-Amides are then hydrolyzed in a mixture of conc. HCl and glacial CH_3CO_2H at reflux, to obtain individual (*S*)-isomers of amines **214** in 95% yield.



Scheme 52. Kinetic resolution of heterocyclic amines using phthaloyl protected amino acid chlorides.

Resolution of racemic 2-methyl-1,2,3,4-tetrahydroquinoline and 2,3-dihydro-3-methyl-4H-1,4-benzoxazine, which are biologically important structural fragments, was studied using *N*-phthaloyl-(*S*)-alanyl chloride, *N*-phthaloyl-(*S*)-phenylalanyl chloride as well as *N*-phthaloyl-(*S*)-phenylglycyl chloride. Kinetic resolution of racemic amines with acyl chlorides followed by recrystallization lead to isolation of major (*S*,*S*)-diastereomeric amides in enantiomerically pure form (de > 97%).[261] Solvents CH_2Cl_2, CH_3CN and low temperature has been found to improve the selectivity of acylation of amines. The acyl chlorides with aromatic substituents close to the stereogenic centre proved to be more stereoselective and *N*-phthaloyl-(*S*)-phenylalanyl chloride has been found appropriate chiral acylating agent.

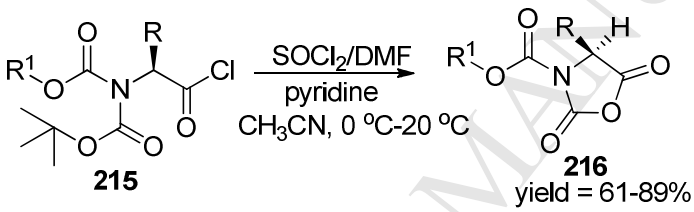
Electronic effects of para substituents (NO_2, H, OCH_3) of phenyl ring of *N*-phthaloyl-(*S*)-phenylalanyl chloride was also studied.[262] An increase in the electron donating property of the phenyl fragment in acyl chloride lead to an increased effectiveness of acylative kinetic resolution of 2-methyl-1,2,3,4-tetrahydroquinoline and 2,3-dihydro-3-methyl-4H-1,4-benzoxazine.

6.2. Heterocycles

6.2.1. *N*-Carboxyanhydrides (NCA) and urethane protected *N*-carboxyanhydrides (UNCAs)

α-Amino acid *N*-carboxyanhydrides were discovered by Leuchs[64-66] from *N*-ethoxycarbonyl or *N*-methoxycarbonyl amino acid chlorides. Also, Cbz-amino acid chlorides undergo spontaneous decomposition to NCA's at high temperatures.

In practice, *N*-bis-Boc-amino acid and *N*-Boc,Cbz-amino acid chlorides **215** can be used to obtain N^{α}-Boc-NCAs and N^{α}-Cbz-NCAs **216** respectively by $SOCl_2$ method.[263] Synthesis of Boc- and Cbz- amino acid *N*-carboxyanhydrides was demonstrated by the action of Vilsmeir reagent $SOCl_2$/DMF on the pyridinium salts of bic(Boc)amino acids.[264,265] Thus, when at least one of the alkoxy groups is Boc, the cyclization involving the participation of *tert*-butyl carbamate occurred under mild conditions (0 ^{o}C) with high yields of UNCA (Scheme 53). This method avoids the use of phosgene and other unstable reagents such as *tert*-butyl chloroformate and NCAs. It is obvious that the method cannot be extended to Fmoc-NCAs.



R^1 = ^{t}Bu; R = H (yield = 72%), CH_3 (yield = 80%), $CH(CH_3)_2$ (yield = 86%)
R = Bn (yield = 92%), CH_2COOBn (yield = 82%)
R = CH_2OBn (yield = 89%), $(CH_2)_4$(Cbz,Boc) (yield = 61%)
R^1 = Bn; R = H (yield = 87%), Bn (yield = 75%)

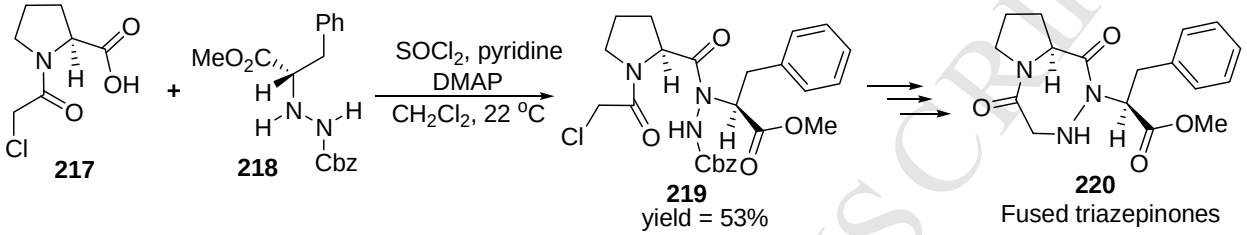
Scheme 53. Synthesis of N^{α}-Boc-NCAs and N^{α}-Cbz-NCAs from *N*-bis-Boc-amino acid and *N*-Boc,Cbz-amino acid chlorides.

Smeets et al. reported leucine-NCA synthesis using corresponding acid chloride hydrochloride salt which has been successfully scaled up, maintaining high product purity on a 1.0 dm^3 scale.[266]

6.2.2. Fused 1,2,5-triazepine-1,5-diones

In a synthesis of fused 1,2,5-triazepine-1,5-diones **219** which mimic cis-peptidyl prolinamides, Lenman et al.[267] employed acid chloride activation using $SOCl_2$ in pyridine for the difficult coupling reaction between *N*-chloroacetyl-(2*S*)-proline (**217**) with the sterically hindered secondary amino group of the hydrazide (Scheme 54). Due to the steric bulkiness on the

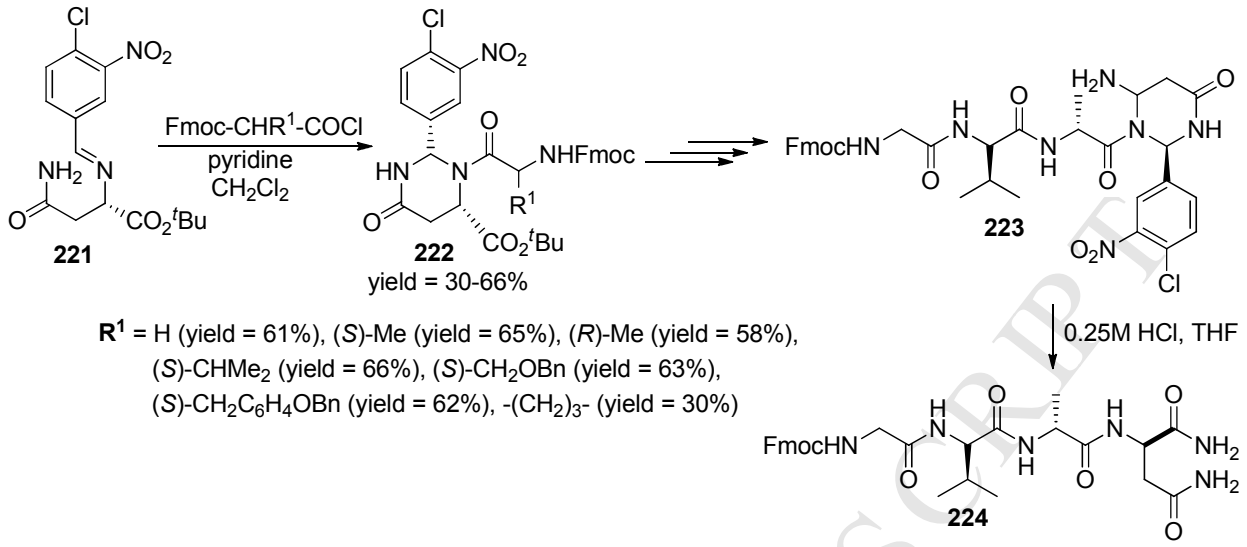
coupling nitrogen of the hydrazide, activation of the carboxylic acid by reagents including isobutyl chloroformate, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), TBTU, benzotriazol-1-yloxytri(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP) and diphenylphosphoryl azide (DPPA) failed to deliver the desired compound. However, activation by preformed acyl pyridinium salt could yield the required peptidic ester in 53% yield.



Scheme 54. Synthesis of fused 1,2,5-triazepine-1,5-diones.

6.2.3. Asparagine derived tetrahydropyrimidinones

Konopelski et al. developed dipeptide surrogates **224** containing asparagine derived tetrahydropyrimidinones by treating the imine **221** derived from 4-chloro-3-nitrobenzaldehyde and *tert*-butyl-L-asparaginate with Fmoc-amino acid chloride in anhydrous benzene in the presence of pyridine (Scheme 55).[268,269] The acid chloride reacted efficiently with weak nucleophile such as an imine. However other coupling methods including active ester, anhydride, acyl fluoride and acyl imidazole gave inferior results. The yields varied from 58-66% for a range of amino acid side chains including Pro. These tetrahydropyrimidines have known absolute configuration and conformation, thus their incorporation into oligopeptides by SPPS could result in stereochemically defined peptidomimetics. As a demonstration, the tetrapeptide as the Fmoc-protected primary amide was synthesized by SPPS in good yield.

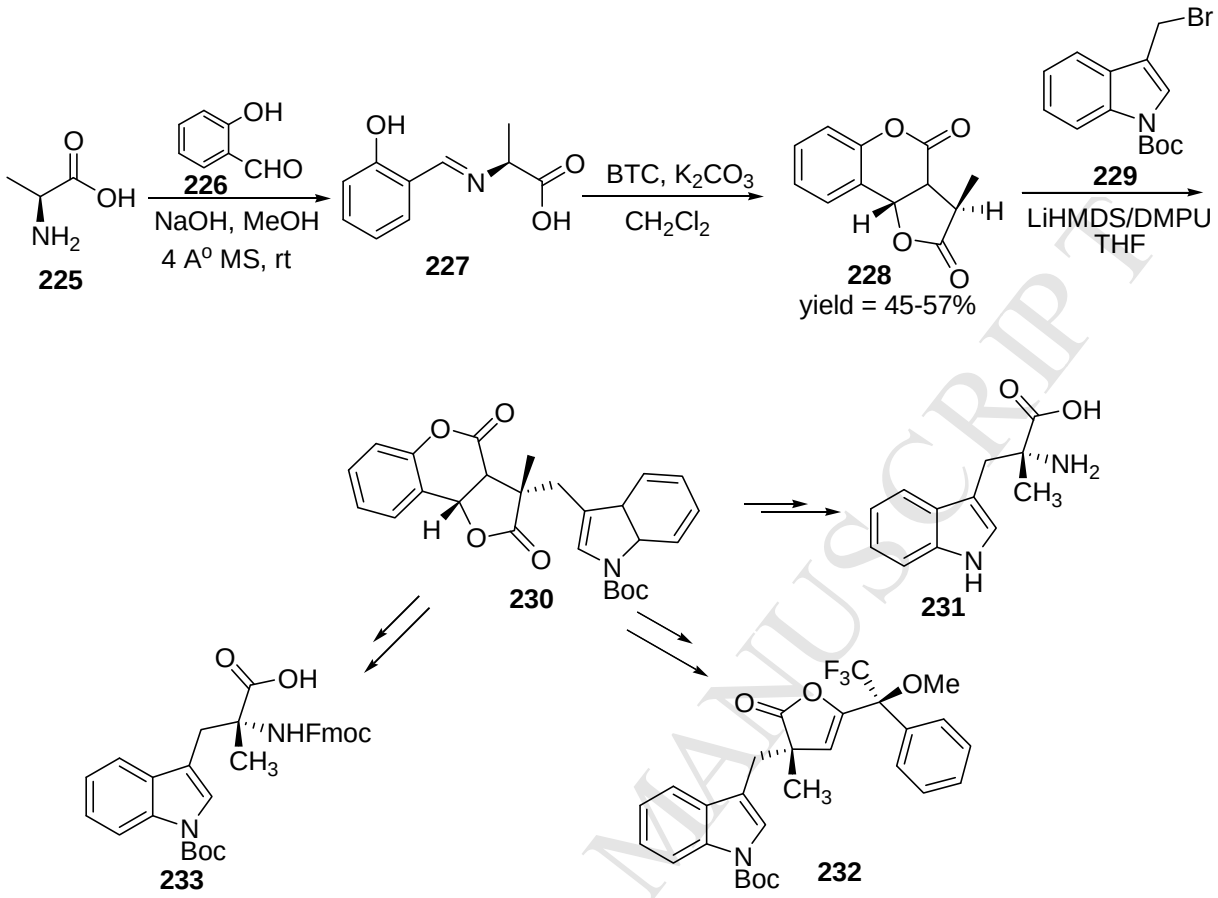


R^{1} = H (yield = 61%), (*S*)-Me (yield = 65%), (*R*)-Me (yield = 58%), (*S*)-$CHMe_2$ (yield = 66%), (*S*)-CH_2OBn (yield = 63%), (*S*)-$CH_2C_6H_4OBn$ (yield = 62%), -$(CH_2)_3$- (yield = 30%)

Scheme 55. Synthesis of asparagine derived tetrahydropyrimidinones.

6.2.4. α-Methyltryptophan analogs

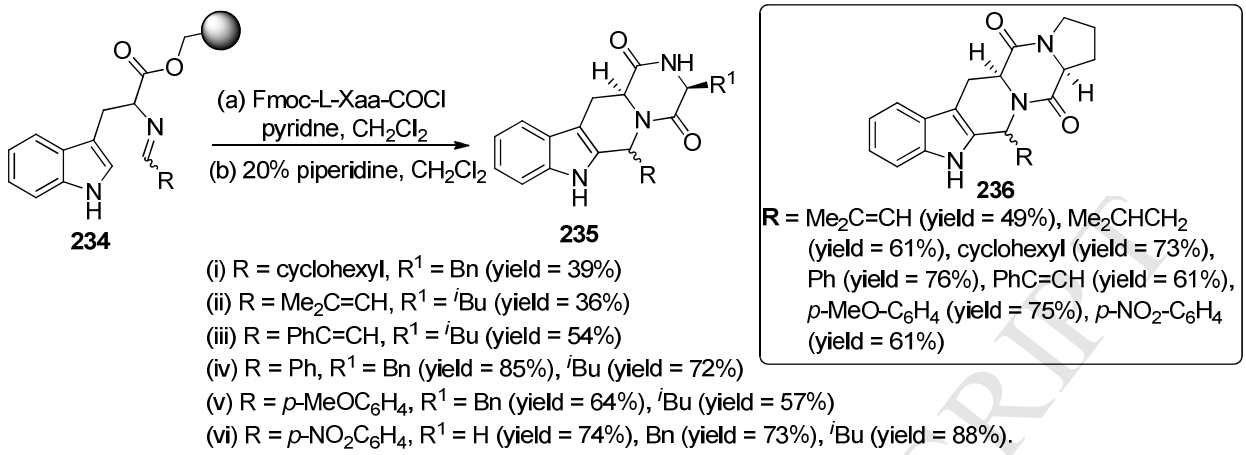
A highly stereocontrolled synthesis of (*R*)-α-methyltryptophan **230** and its orthogonally protected analogs **231**, **232** and **233** has been carried out by Goodmann in a four step conversion from Ala (Scheme 56).[270] The method involved the stereoselective alkylation of salicylaldehyde derived oxazolidinone by *N*-protected 3-bromomethyl indole, a strategy initially developed by Zydowsky and coworkers.[271] The Schiff base intermediate **227** was treated with BTC to generate the required oxazolidinone **228** at moderate yields of 45-57%. The method is particularly attractive for amino acids with acid labile side chains, as the alkylated intermediates could be removed under basic conditions.



Scheme 56. Synthesis of (*R*)-α-methyltryptophan **230** and its orthogonally protected analogs.

6.2.5. Demethoxyfumitremorgin C analogs

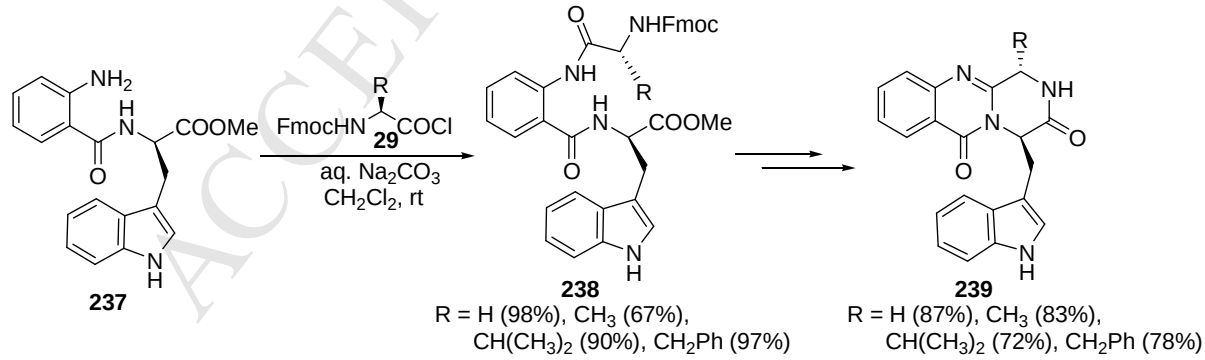
Demethoxyfumitremorgin C, most active fungal natural product that causes eukaryotic cell cycle arrest at the G_2/M transition possesses tetrahydro-β-carboline and diketopiperazine rings. Demethoxyfumitremorgin C and its analogs were synthesized using solid phase *N*-acyliminium Pictet-Spengler condensation followed by cyclative cleavage forming the piperazine ring.[272] Thus Fmoc-L-tryptophan immobilized on the polystyrene-Wang resin **234** was deprotected and reacted with senecialdehyde (Scheme 57). The key step involved the reaction of imine with *N*-Fmoc-proline chloride inducing *N*-acyliminium Pictet-Spengler condensation. The Fmoc deprotection lead to cyclative resin cleavage by piperazine ring closure giving demethoxyfumitremorgin C **235** and its trans epimer. Various analogs **236** were also synthesized by varying the aldehyde and amino acid chloride components to obtain target compounds in good yields.



Scheme 57. Synthesis of demethoxyfumitremorgin C and its analogs using solid phase *N*-acyliminium Pictet-Spengler condensation.

6.2.6. Fumiquinazoline alkaloids

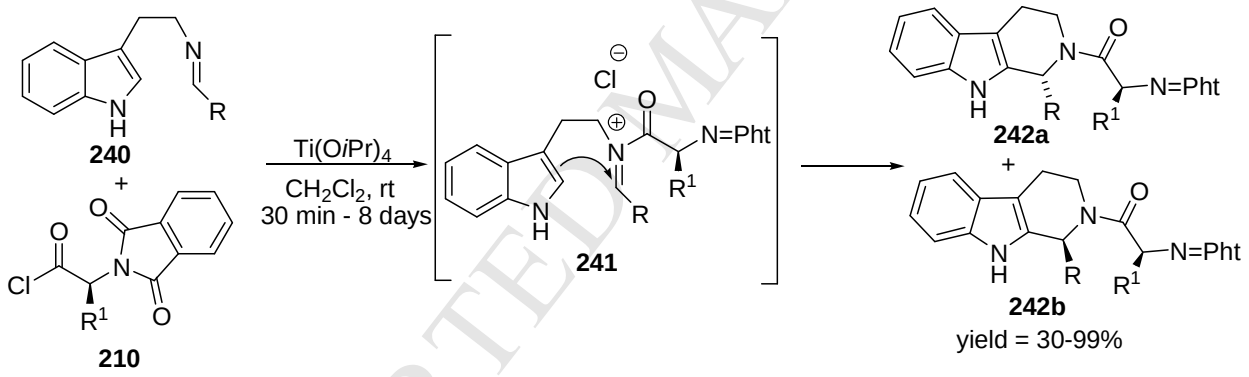
Biomimetic total syntheses of fumiquinazoline alkaloids **239** namely glyantrypine, fumiquinazoline F, fumiquinazoline G, and fiscalin B were achieved in four steps starting from methyl tryptophanate.[273] Condensation of the dipeptide ester (obtained from coupling of anthranilic acid with methyl-D-tryptoyphanate) with Fmoc amino acid using PyBroP led to lower yields (35%) of the product (Scheme 58). On the other hand, corresponding acid chloride employed under Schotten-Baumann conditions resulted in linear tripeptides **238** in high yields of 97-98% in 2 h. The resulting products were then dehydrated to benzoxazines and then subsequently rearranged to natural products.



Scheme 58. Syntheses of fumiquinazoline alkaloids.

6.2.7. Pictet-Spengler reaction: β-Carbolines

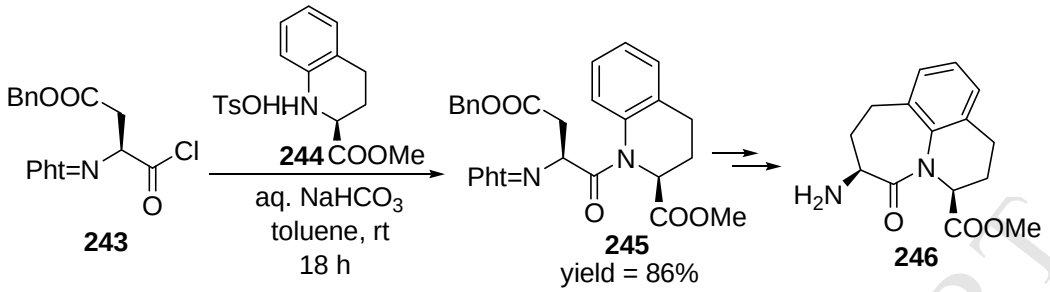
Phthaloyl amino acid chlorides were employed as removable chiral auxiliaries in the asymmetric Pictet-Spengler reaction for synthesis of β-carbolines **242** with very high levels of stereoselectivity (> 99 : 1; Scheme 59).[129,274,275] The Schiff bases derived from tryptamine were treated with 2 eq of acid halide in presence of 2 eq of titanium alkoxide in CH_2Cl_2 at room temperature within 5 min to 1 h. In case of aromatic Schiff bases, longer reaction periods (several days) are required and the diastereomeric ratio found to increase with increasing steric demand of amino acid side chain. The proposed pathway of reaction involved attack of acid chloride on nitrogen of imine resulting in *N*-acyl iminium intermediate **241**, which undergoes Pictet-Spengler cyclization by the attack of electron rich nucleophilic indole C-2 carbon on the iminium ion. The stereoselectivity observed found to depend on amino acid side chains, nature of imine substituent, and the alcohol incorporated in the titanium lewis acid. Other protecting groups namely Fmoc and Cbz, lead to lower stereoselectivity. The use of phthaloyl group lead not only to high diastereoselectvity but also highly crystalline compounds could be obtained.



Scheme 59. Phthaloyl amino acid chlorides as chiral auxiliaries in the asymmetric Pictet-Spengler synthesis of β-carbolines.

6.2.8. Benzofused bicyclic azepinones

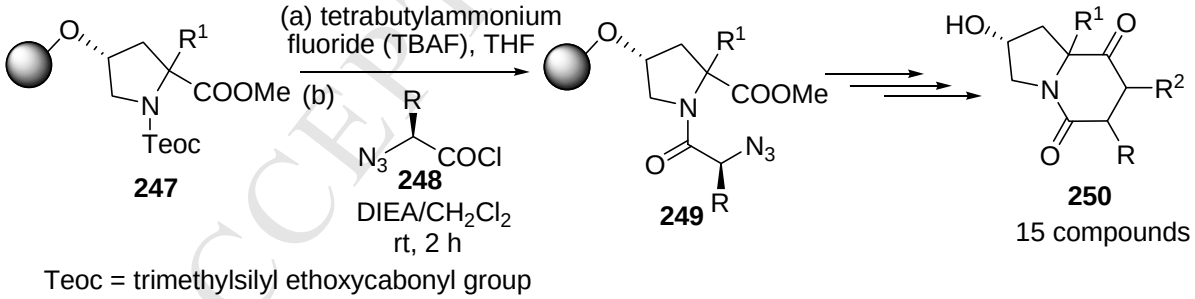
Robl et al. reported synthesis of benzofused bicyclic azepinones **246**, 7,5- and 7,6-fused compounds, wherein *N*-phthalimido-γ-benzyl-L-aspartic acid was coupled to methyl (*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylate through acid chloride activation (Scheme 60).[276] The coupling of acid chloride with the desired amine under Schotten-Baumann type conditions at room temperature for 18 h lead to the product in 86% yield with high diastereomeric purity (de 99.4% by HPLC). However the acylation using acid fluoride was unsuccessful.



Scheme 60. Synthesis of benzofused bicyclic azepinones.

6.2.9. Substituted hydroxyproline based 2,5-diketopiperazines

Bianco et al. reported solid phase synthesis of highly substituted hydroxyproline-based 2,5-diketopiperazines containing the trans-L-Pro residue (Hpp) (Scheme 61).[277] The key step involved the difficult acylation of pyrrolidine nitrogen which was carried out using two approaches. In the first, Fmoc-amino acid fluoride was coupled to hindered amino function of pyrrolidine by silylation using BSA. Coupling was repeated two to three times and the formation of 2,5-diketopiperazine initiated immediately during the cleavage of Fmoc-group. In a second approach, azido acid chloride was employed to acylate the nitrogen of hydroxyproline, which required shorter reaction time and without multiple coupling. The azide moiety was reduced using suspension of $SnCl_2$, TEA, thiophenol in THF. The resin was then heated in DMF in the presence of KCN as catalyst to complete cyclization to 2,5-diketopiperazine **250**.

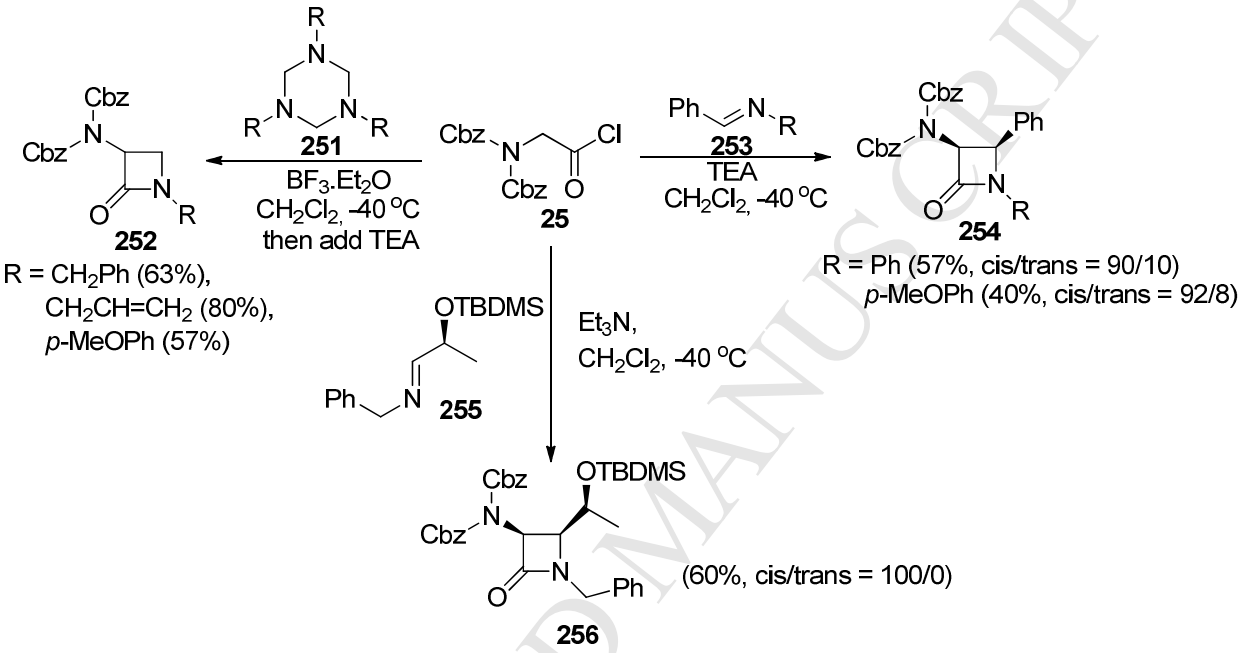


Scheme 61. Solid phase synthesis of highly substituted hydroxyproline-based 2,5-diketopiperazines.

6.2.10. Azetidine-2-ones

N,*N*-Dibenzyloxycarbonylglycyl chloride **25** has been employed as ketene equivalent in the synthesis of *N*,*N*-dibenzyloxycarbonylaminoazetidin-2-ones **252** as well as C-4 substituted

azetidinones **254** (Scheme 62). Reaction of *N*-allyl, *N*-benzyl, and *N*-*p*-methoxyphenylhexahydrotriazines with *N*,*N*-bis-Cbz-glycyl chloride in presence of TEA at -40 ^{o}C afforded corresponding lactams in 57-80% yield. Also *N*,*N*-bis-Cbz-glycyl chloride can be reacted with imines under similar conditions, to obtain C-4 substituted azetidinones with cis isomer as major product **256**.[70]



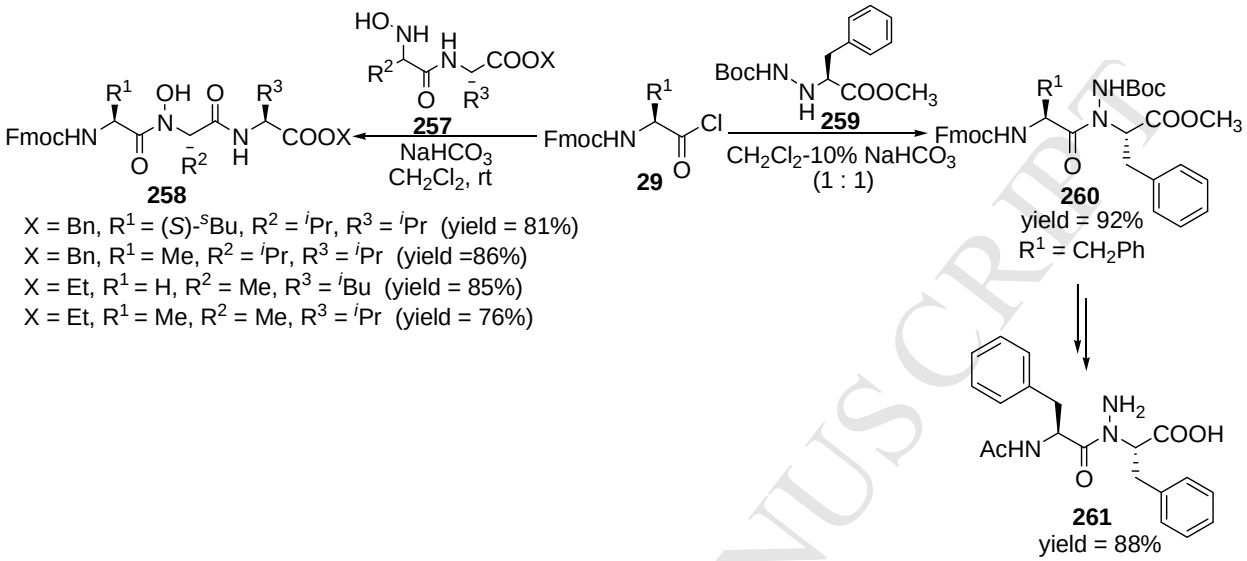
Scheme 62. Synthesis of azetidin-2-ones using *N*,*N*-dibenzyloxycarbonylglycyl chloride as a ketene equivalent.

6.3. Peptidomimetics

6.3.1. Hydrazino-tethered dipeptides, *N*-hydroxy tethered tripeptidomimetics

Killian et al.[278] studied the ribosome mediated incorporation of the (*S*)-α-hydrazinophenylalanine into modified peptide and protein analogs using (*S*)-α-hydrazinophenylalanyl-tRNA as the A-site tRNA (Scheme 63). Thus synthesized dipeptide product mixtures were analyzed by HPLC in comparison with peptides prepared through chemical means using acid chloride strategy. Herein *N*-Fmoc-(*S*)-Phe-Cl was coupled with methyl-*N*-Boc-(*S*)-α-hydrazinophenylalaninate using 10% $NaHCO_3/CH_2Cl_2$ to yield dipeptide acylated regioselectively at the nitrogen attached to C^{α} of hydrazinophenylalanine in high yield

of 92%. The peptide was then converted to the required *N*-acetylphenylalanyl-α-hydrazinophenylalanine **261**.

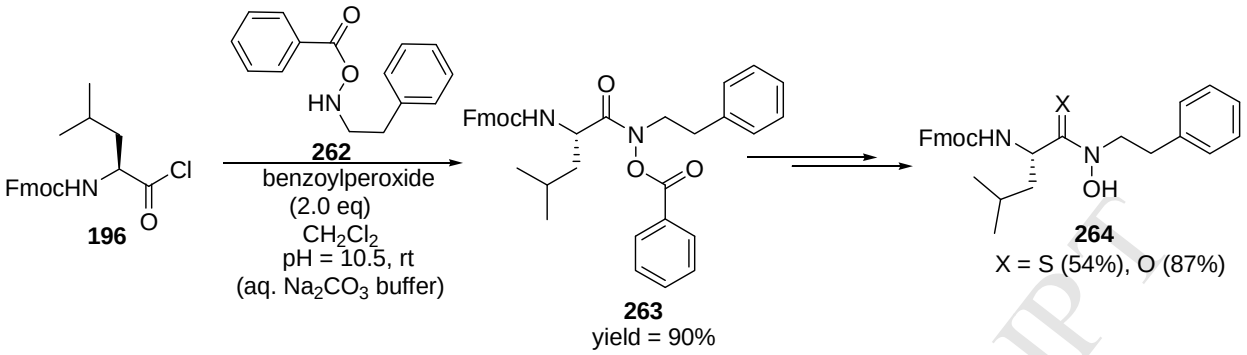


Scheme 63. Synthesis of hydrazino-tethered dipeptides and *N*-hydroxy tethered tripeptidomimetics.

Lawrence et al. synthesized Fmoc-protected inner *N*-hydroxy tripeptides **258** by selective *N*-acylation of hydroxyl amines with Fmoc-amino acid chlorides under $NaHCO_3/CH_2Cl_2$ conditions in 76-86% yields.[279] The nature of the base was found to be important, for instance, the use of pyridine lead to *O*-acylated hydroxylamine as the major product.

6.3.2. *N*-(Hydroxy)amide and *N*-(hydroxy)thioamide containing pseudopeptides

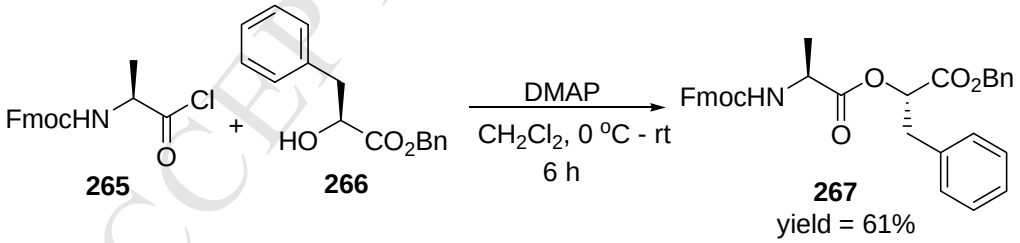
Acid chloride method was explored for the synthesis of *N*-(hydroxy)amide- and *N*-(hydroxy)thioamide containing pseudopeptides **264** without any racemization.[280] Acylation of *N*-(benzoyloxy)phenethylamine **262** with Fmoc-Leu-Cl **196** resulted in the corresponding amide **263** in 90% yield. Deprotection of benzoyl group using 10 vol% of NH_4OH/MeOH lead to *N*-Fmoc-*N*-(hydroxy)-L-leucine amide in 87% yield (Scheme 64). Further, the thionation of *N*-Fmoc-*N*-(benzoyloxy)-L-leucine amide followed by deprotection of benzoyl group gave the *N*-hydroxy thioamide **264**. Deprotection of Fmoc group and then extension of chain through coupling with another amino acid results in *N*-hydroxyamide or *N*-hydroxy thioamide linkages into the pseudopeptide oligomers.



Scheme 64. Synthesis of *N*-(hydroxy)amide- and *N*-(hydroxy)thioamide containing pseudopeptides.

6.3.3. Depsipeptides

Davies et al.[281] carried out a comparative study of various coupling reagents and their chiral efficacy during the formation of a depside bond in case of Fmoc-L-Ala-L-Phlac-OBn (**267**) (Phlac = phenyllactic acid; Scheme 65). The HPLC analysis of products obtained through different coupling conditions revealed that CDI, DCC/DMAP and mixed anhydride methods gave nearly 50% yields, whereas TBTU, 2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU) and 2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU) resulted in low yields. Interestingly, using acid chloride method in the presence of DMAP, 61% of coupling product could be obtained in 6 h without racemization. But, best yields of 83% were obtained using PyBroP coupling at ambient temperature for 3 h.

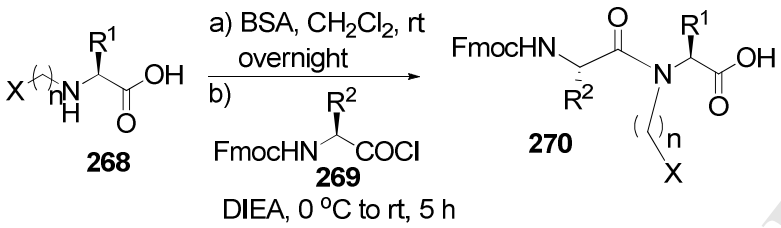


Scheme 65. Synthesis of depsipeptides using Fmoc-amino acid chlorides.

6.3.4. *N*-Carboxylalkyl and *N*-amino alkyl functionalized dipeptides

Muller et al. reported the synthesis of *N*-carboxylalkyl and *N*-aminoalkyl functionalized dipeptide units **270** for the assembly of cyclic peptides, in particular, bradykinin and somatostatin analogs in solid-phase synthesis.[282] *N*-Alkyl amino acids were initially silylated using BSA to the corresponding tetramethylsilane esters (Scheme 66). The coupling with Fmoc-

amino acid chlorides in presence of DIEA resulted in the required dipeptide building blocks in good yields (37-47%) and purity. The resulting Fmoc-protected *N*-functionalized dipeptide units could be employed directly in standard solid phase synthesis.

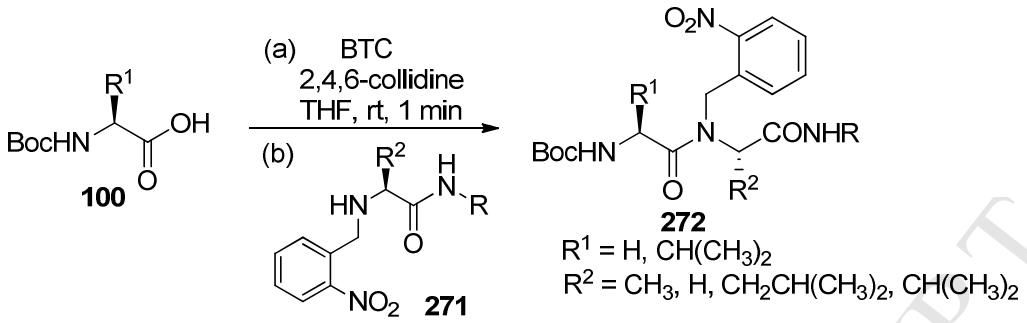


270: a. n = 1; X = $CO_2{}^tBu$; $R^1 = CH_2C_6H_5$; $R^2 = (R)\text{-}CH_2C_6H_5$ (yield = 47%)
b. n = 2; X = $CO_2{}^tBu$; $R^1 = CH_2C_6H_5$; $R^2 = (R)\text{-}CH_2C_6H_5$ (yield = 46%)
c. n = 1; X = $CO_2{}^tBu$; $R^1 = CH_2C_6H_5$; $R^2 = CH(CH_3)_2$ (yield = 39%)
d. n = 2; X = $CO_2{}^tBu$; $R^1 = CH_2C_6H_5$; $R^2 = CH(CH_3)_2$ (yield = 37%)
d. n = 2; X = NHBoc; $R^1 = CH_2C_6H_5$; $R^2 = (R)\text{-}CH_2C_6H_5$ (yield = 43%)
e. n = 3; X = NHBoc; $R^1 = CH_2C_6H_5$; $R^2 = (R)\text{-}CH_2C_6H_5$ (yield = 41%)
f. n = 2; X = NHBoc; $R^1 = CH_2C_6H_5$; $R^2 = CH(CH_3)_2$ (yield = 40%)
g. n = 3; X = NHBoc; $R^1 = CH_2C_6H_5$; $R^2 = CH(CH_3)_2$ (yield = 43%)

Scheme 66. Synthesis of *N*-carboxylalkyl and *N*-aminoalkyl functionalized dipeptide units.

6.3.5. 2-Nitrobenzyl backbone modified peptides

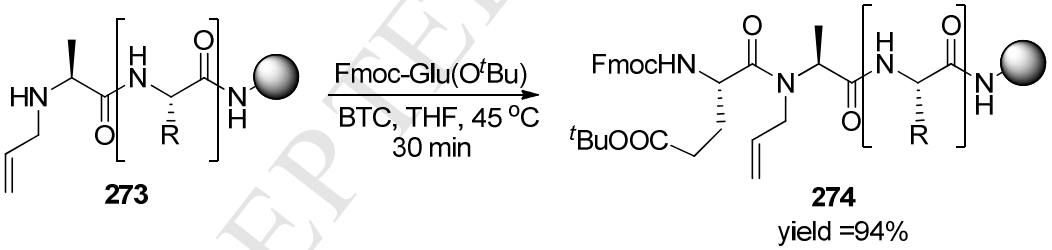
Johnson and Kent[283] reported synthesis and photolytic cleavage of 2-nitrobenzyl, 4-methoxy-2-nitrobenzyl and 4,5-dimethoxy-2-nitrobenzyl backbone modified peptides. Acylation of N(2-nitrobenzyl)-glycine-, N(2-nitrobenzyl)-alanine-, N(2-nitrobenzyl)-leucine-, N(2-nitrobenzyl)-valine-, peptides was studied with increasing bulk of the side chain on the α-carbon. Acylation of *N*-(2-nitrobenzyl)-aminoacyl peptide becomes difficult with increasing bulk of the side chain on the α-carbon, with β-branched *N*-(2-nitrobenzyl)-valyl peptide to be the most difficult. Thus, incoming Boc-amino acid (Gly or Val) was coupled to sterically hindered *N*-(2-nitrobenzyl)-aminoacyl peptides [test peptide MD(G/V)(X)VK, where X is N(2-Nb)-amino acid; test peptide for the N(2-nb)Gly was MG(X)FL] using HOAt active ester (HOAt/DIC and HATU), symmetric anhydride (DIC), or acid chloride (BTC). It was reported that only BTC method gave quantitative yield for coupling of Boc-Val to *N*-(2-nitrobenzyl)-alanine (Scheme 67). Acylation of *N*-(2-nitrobenzyl)-Leu **271** with Boc-Gly could be achieved in 66% yield, whereas other methods lead to unsatisfactory yields. However acylation of *N*-(2-nitrobenzyl)-valine by Boc-Gly or Boc-Val was not successful.



Scheme 67. Synthesis of 2-nitrobenzyl backbone modified peptides.

6.3.6. *N*-Allyl amino peptides

Patgiri et al.[284] reported the solid phase synthesis of hydrogen bond surrogate derived helices which involved Fukuyama-Mitsunobu reaction for the synthesis of *N*-allyl amino peptides **274** under microwave irradiation and subsequent difficult coupling to the next Fmoc amino acid using BTC method. Coupling of the *tert*-butyl protected Glu to an allyl amine is difficult because of the bulky side chain. Only the BTC activation lead to efficient coupling of *N*-allyl alanine residue on Rink amide resin (in XFEA*IYRLELLKAEEAN-NH_2; X = pentenoic acid residue; A* = *N*-allyl alanine residue) with Fmoc-Glu(O^tBu)-OH in 94% yield without racemization, as found by HPLC (Scheme 68). In this case, the reagents including HATU/HOAt, TFFH, HOAt and PyBroP/DMAP provided low yields for the difficult coupling.

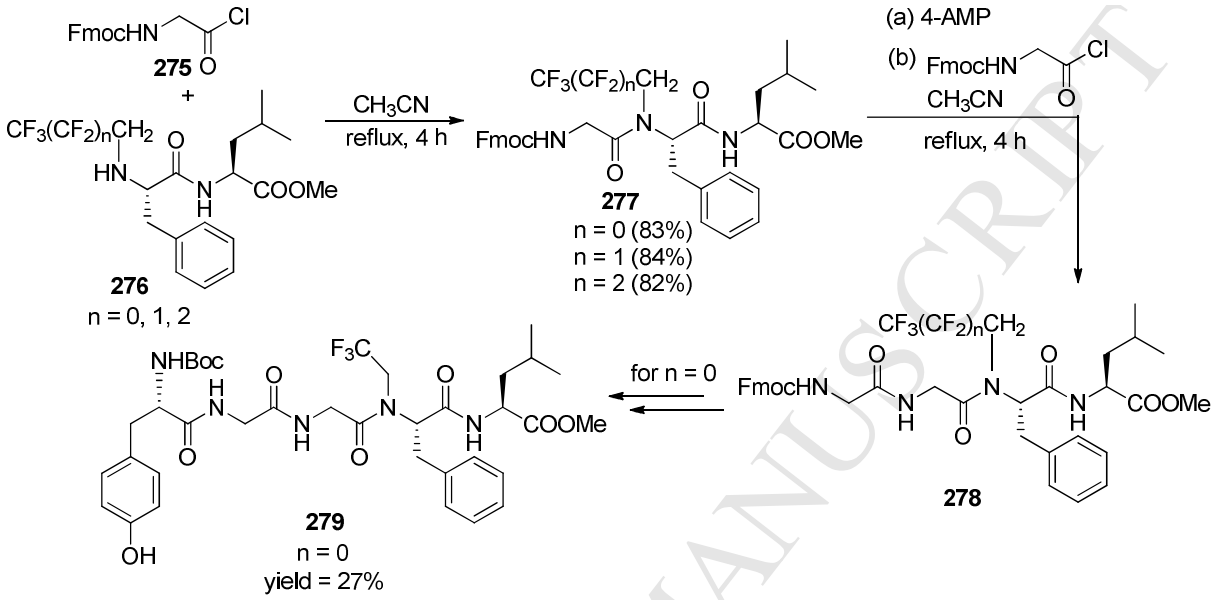


Scheme 68. Solid phase synthesis of *N*-allyl amino peptides.

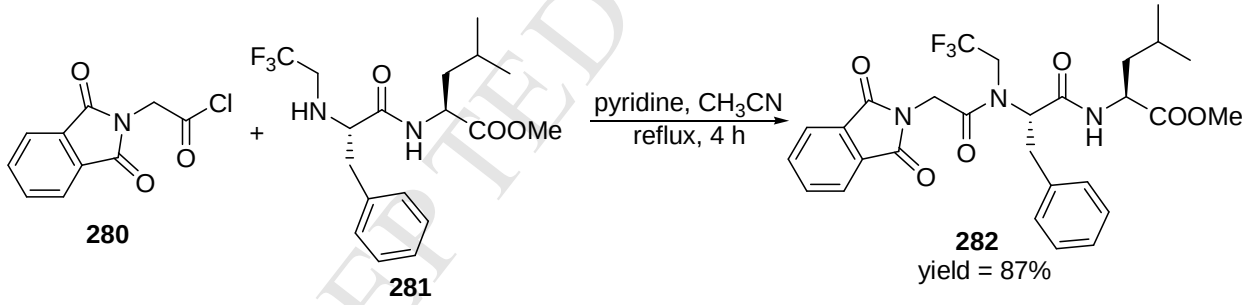
6.3.7. Peptoids: *N*-1*H*,1*H*-Perfluoroalkylated peptides

Optically pure peptide building blocks with *N*-1*H*,1*H*-perfluoroalkyl label on a selected backbone amide bond could be synthesized efficiently using Fmoc amino acid chlorides with excess of N-terminus 1*H*,1*H*-perfluoroalkylated peptide ester **277** as a base (Schemes 69 and 70).[285] Excess (2 eq) trifluroalkylated peptide ester **278** was condensed with Fmoc-Gly-Cl **275** in CH_3CN at reflux for 4 h, to obtain peptide building block. After deprotection of Fmoc group at the N-terminus, the chain elongation lead to [Leu^5]enkephalin **279** possessing *N*-1*H*,1*H*-

perfluoroalkylated moiety at the desired position. The labeled peptide ester has also been coupled to N^{α}-phthaloyl glycyl chloride **275** in the presence of pyridine, however difficult deprotection condition is rather unattractive for the preparation of oligomers.



Scheme 69. Coupling of Fmoc amino acid chloride with N-terminus 1*H*,1*H*-perfluoroalkylated peptide ester.



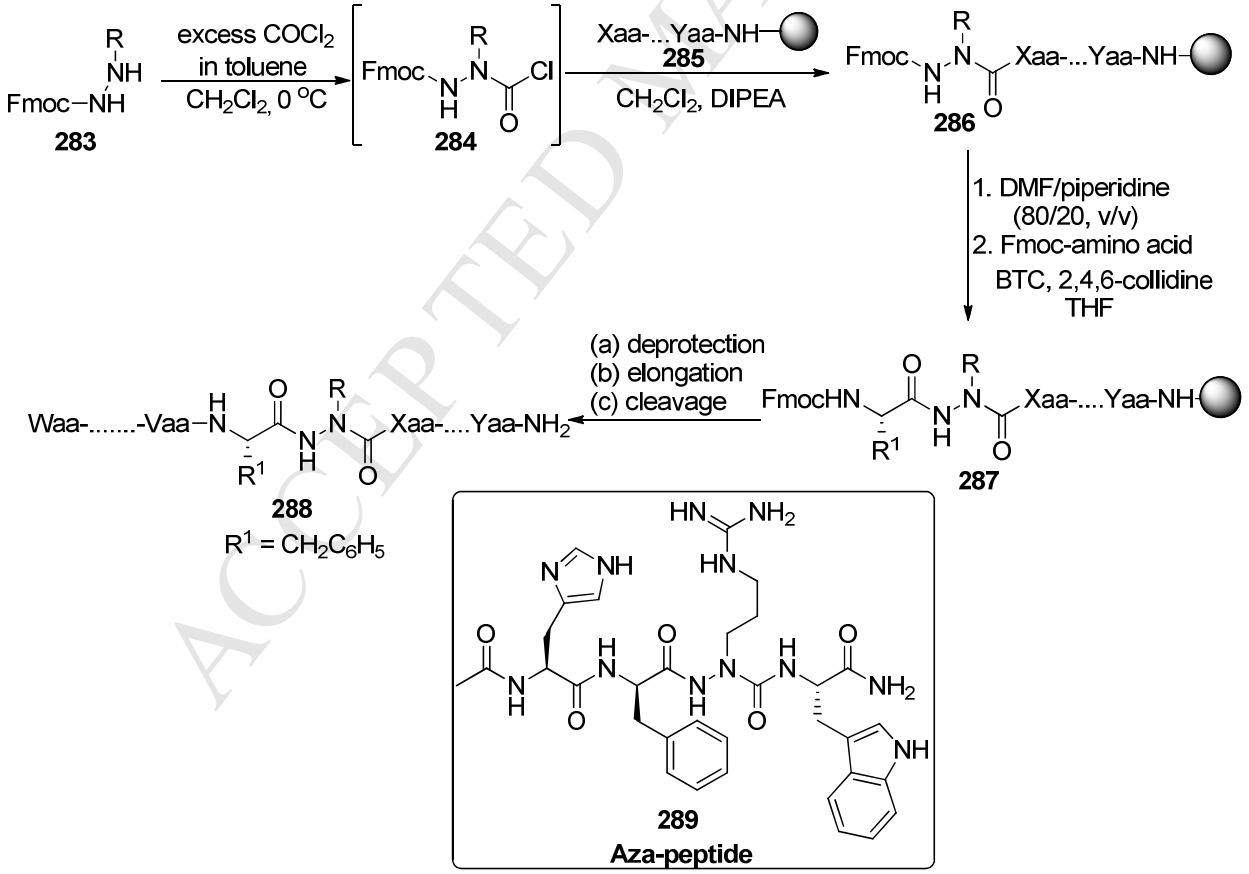
Scheme 70. Coupling of phthaloyl amino acid chloride with N-terminus trifluroalkylated peptide ester.

6.3.8. Aza-peptides

Aza-peptides in which one or more of the carbons, bearing side-chain residues, being replaced by nitrogen, are one of the important classes of peptidomimetics.[286] Systematic replacement of amino acid residues in a desired peptide sequence with aza counterparts, namely aza-scan has lead to the generation of drug leads and structure-activity relationship studies of biologically active peptides. Boeglin and Lubell demonstrated both solution as well as solid

phase synthesis of aza-peptides and developed a methodology for the systematic replacement of amino acid residues in a peptide with their aza counterparts using Fmoc-aza amino acid chlorides as building blocks.[287]

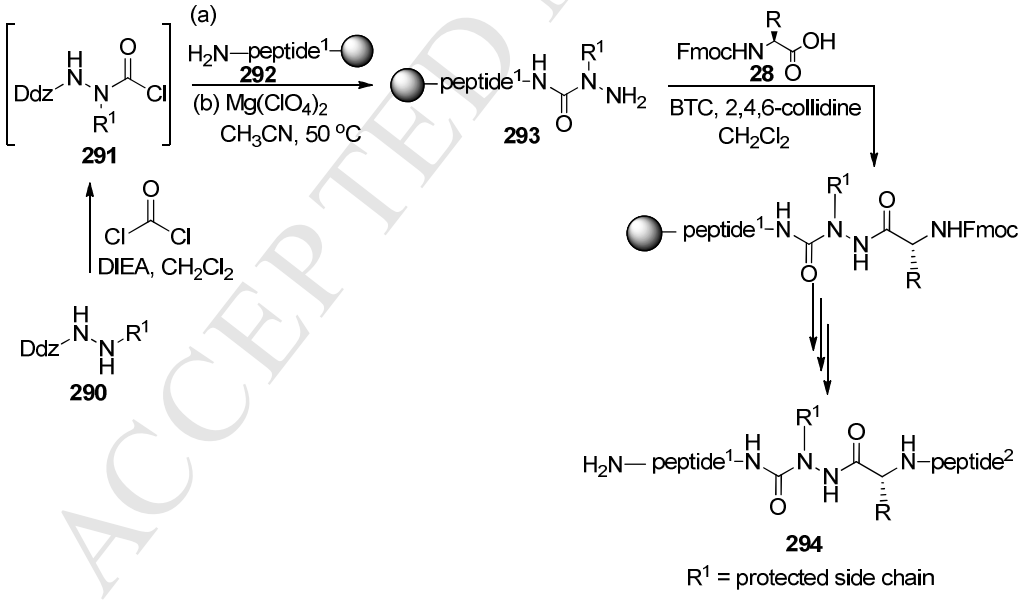
Appropriate *N'*-substituted fluorenylmethyl carbazates **283** were activated with phosgene and employed in coupling reactions on Rink resin to obtain aza-peptides with aliphatic, aromatic, and heteroaromatic side chains. In SPPS, free amine of growing resin bound peptide was treated with three fold excess of requisite Fmoc-aza amino acid chloride **284** and DIEA in CH_2Cl_2 for 6 h. After Fmoc deprotection, free aza-amino acid residue was acylated with in situ generated Fmoc-amino acid chloride of next amino acid using BTC and 2,4,6-collidine (Scheme 71). Acylation using HBTU method failed due to less reactivity of aza-amino acid residue. Using this protocol, SPPS of aza-peptide analogs of MCR agonist, a growth harmone secretagogue hexapeptide (GHRP-6) and a human calcitonin gene related peptide **289** (hCGRP antagonist) were accomplished.



Scheme 71. Solid phase ynthesis of azapeptides using *N'*-substituted fluorenylmethyl carbazates.

Freeman et al. followed similar procedure with due modifications for a microwave assisted solid-phase aza-peptide synthesis.[288] The application of microwaves reduced the standard reaction time and lead to efficient coupling of the aza-amino acid to the growing peptide and next amino acid coupling to the aza residue. The protocol was then employed for the aza-scan of potent persistently activated protein kinase B (PKB/Akt) inhibitor, PTR6154.

Freeman et al. also prepared *N′*-substituted 2-(3,5-dimethoxyphenyl)propan-2-yl-carbazates (*N′*-substituted Ddz protected hydrazines) and employed them in the solid-phase aza-peptide synthesis using acid labile Rink amide methylbenzhydrylamine (MBHA) resin with mild Lewis acid [$Mg(ClO_4)_2$] mediated Ddz deprotection (Scheme 72).[289] Thus, Fmoc-Lys-azaVal-Ala-Ala-Phe-NH_2 was synthesized in an overall yield of 50%. *N′*-Substituted Ddz protected hydrazines **290** were treated with excess phosgene in toluene, thus activated aza amino acid chlorides **291** were reacted with the free N-terminal amine of the peptidyl resin **292**. Deprotection of Ddz was carried out using $Mg(ClO_4)_2$ in CH_3CN at 50 ^oC. Difficult coupling of next Fmoc amino acid to the aza amino acid **293** has been carried out with BTC and 2,4,6-collidine in CH_2Cl_2.

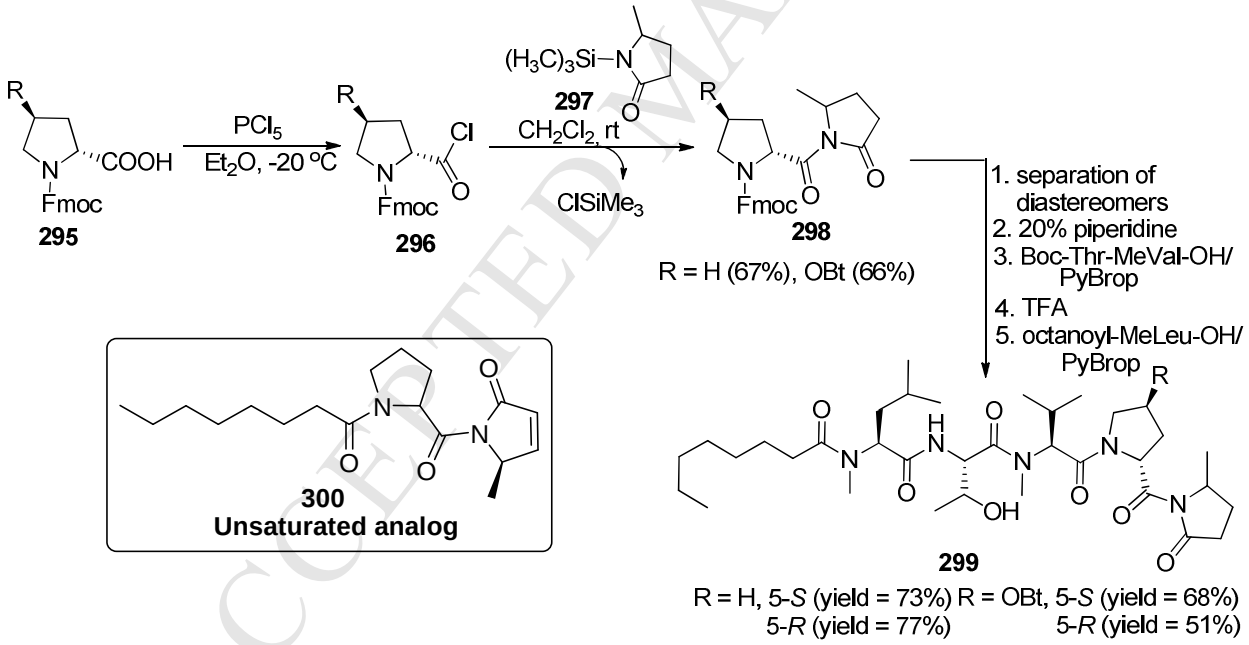


Scheme 72. Solid phase synthesis of azapeptides using *N′*-substituted 2-(3,5-dimethoxyphenyl)propan-2-yl-carbazates.

6.4. Biologically important molecules

6.4.1. Microlin analogs

Acid chloride strategy was successfully utilized in the synthesis of microlin analogs and the strategy allowed insertion of the desired Xaa-pyrrolin-2-one unit which could be explored for biological screening.[290] Methodology involved silylation of the 5-methyl-pyrrolidin-2-one using TMS-Cl/TEA. The purified lactam was reacted with Fmoc-Pro-Cl and Fmoc-Hyp(OBt)-Cl (prepared using PCl_5 in diethyl ether at -20 ^oC). The diastereomers 5-*R*- and 5-*S*-Fmoc-Xaa-5-methylpyrrolidin-2-one were separated by RP-HPLC. Following Fmoc deprotection, they were reacted with Boc-Thr-MeVal-OH in presence of PyBroP. The TFA deprotection followed by coupling with octanoyl-*N*-methylleucine has lead to the final products. Similar methodology was then extended for unsaturated analogs of microlin B **300** as demonstrated by the synthesis of *N*-(octanoylprolyl)-5-methyl-pyrrolin-2-one **299** (Scheme 73).

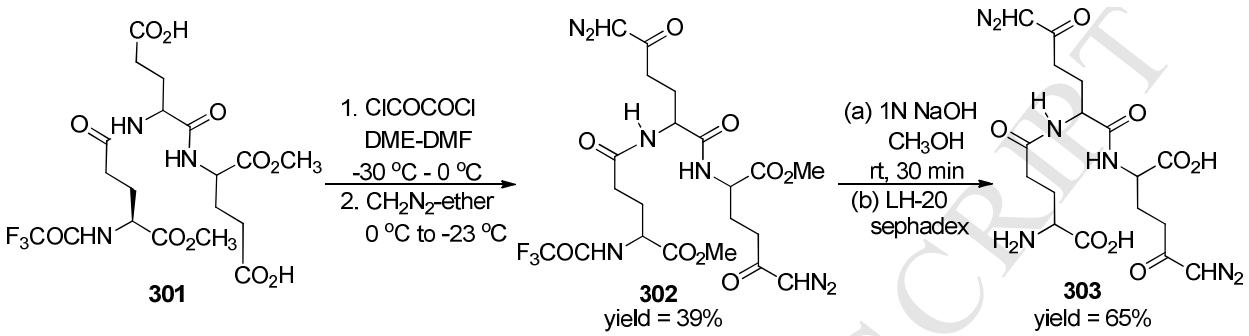


Scheme 73. Synthesis of microlin analogs.

6.4.2. Azotomycin

In a nine step total synthesis of (-)-azotomycin, a *streptomyces ambofaciens* anticancer constituent, the key intermediate bis diazoketones **302** from dicarboxylic acid **301** was obtained

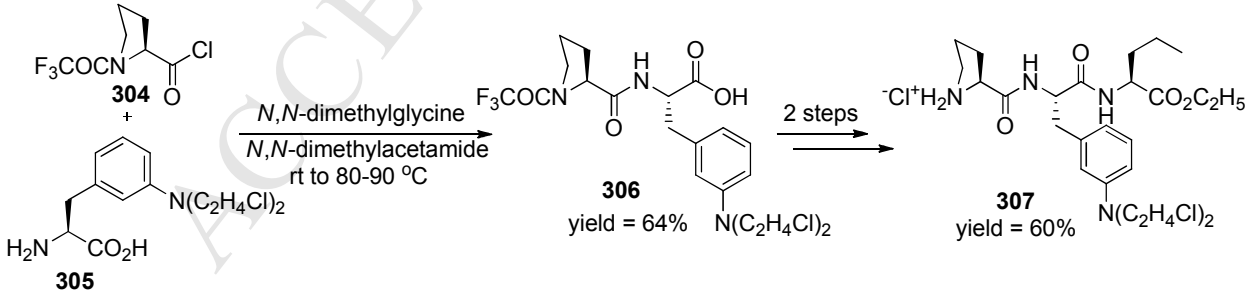
by the treatment of diacid chloride with CH_2N_2 in 39% yield.[251,252] Herein the diacid chloride was formed by treatment of *N*-(γ-*N*-Tfa-Glu-α-OMe)-Glu-Glu-α-OMe **301** with oxalyl chloride in dimethylether (DME)-DMF at -30 °C to 0 °C with 50% yield (Scheme 74).



Scheme 74. Synthesis of (-)-azotomycin via diacid chloride intermediate.

6.4.3. L-m-Sarcolysin containing tripeptide esters

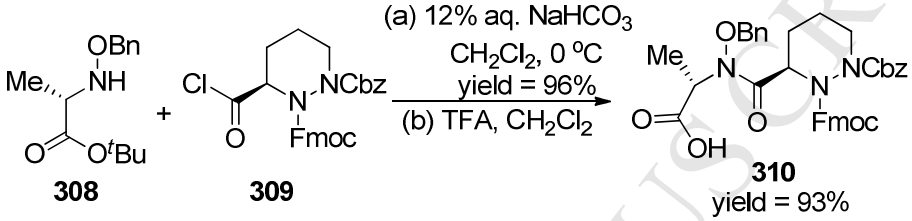
Weisz et al. employed acid chloride coupling and aminolytic TFA cleavage in synthesis of tripeptide ester which possesses antitumor properties.[291] The L-m-Sarcolysin, L-m-[bis(2-chloroethyl)amino]-L-phenylalanine (**305**) was acylated with *N*-TFA-L-prolyl chloride (**304**) in an acidic medium in the presence of *N*,*N*-dimethylglycine (DMG) in *N*,*N*-dimethylacetamide (DMA) at 80-90 °C to afford the corresponding dipeptide **306** in 64% yield (Scheme 75). The reaction in acidic medium without any added basic reagent, reduces the risk of racemization and eliminates the need for deprotection of carboxyl group. The quantity of epimer was found to be less than 5%. DMG served as the HCl scavenger. TFA-Pro-Phe[*m*-(bis(2-chloroethyl)amino)] was eventually transformed to the desired final tripeptide ester **307**.



Scheme 75. Synthesis of L-m-Sarcolysin containing tripeptide esters.

6.4.4. Hexapeptide precursor of antitumor antibiotic A83586C

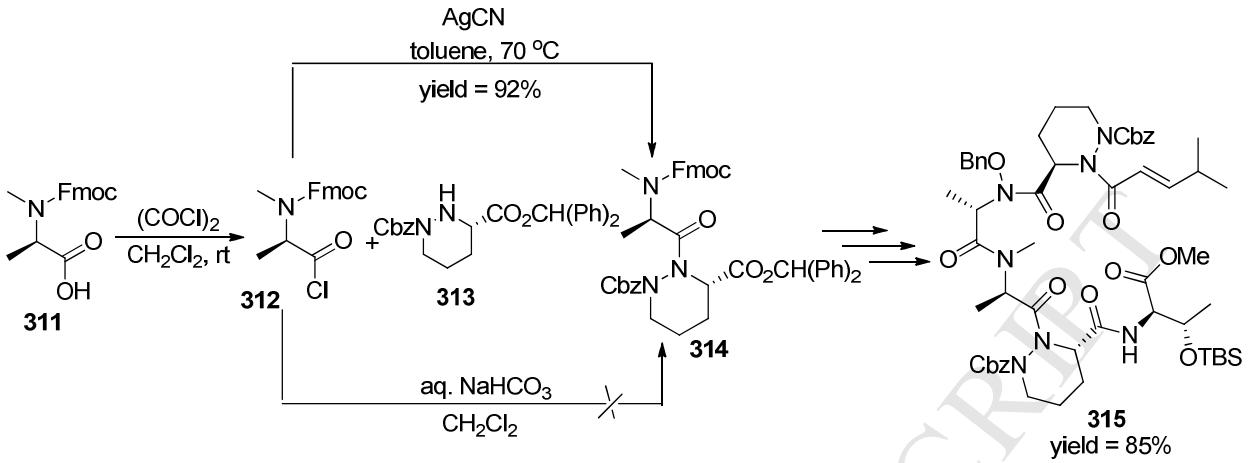
Hale and coworkers employed acid chloride activation for coupling of key fragments in a sequential 3+2+1 fragment condensation strategy for the preparation of hexapeptide precursor for azinothricin family of antitumor antibiotic A83586C (Scheme 76).[292] The dipeptide segment **310** was constructed by coupling the acid chloride of Fmoc-protected piperazic acid derivative **309** with the α-hydroxamic acid derivative **308** in a mixture of CH_2Cl_2 and 12% aqueous Na_2CO_3 followed by treatment with TFA in CH_2Cl_2.



Scheme 76. Coupling of Fmoc-protected piperazic acid chloride derivative **309** with the α-hydroxamic acid derivative **308**.

Synthesis of tripeptide fragment involved initial coupling of Fmoc-MeAla-Cl **312** with (3*S*)-piperazic acid derivative **313** in the presence of AgCN in toluene at 70 ^oC for 1 h, to afford the dipeptide **314** in 92% yield. However efforts to make use of the two-phase protocol using aqueous $NaHCO_3/CH_2Cl_2$ were unsuccessful. Besides, other carboxyl activating agents such as DCC, $Ph_2P(O)Cl$, $(PyS)_2/PPh_3$ failed to produce the desired dipeptide which can be attributed to the very poor nucleophilicity of the N(2)-atom in N(1)-acylated α-hydrazino acid derivative owing to the strong electron withdrawing effect of *N*-acyl unit and the sterically hindered environment around the N(2)-atom. The dipeptide was eventually converted into the required tripeptide fragment.

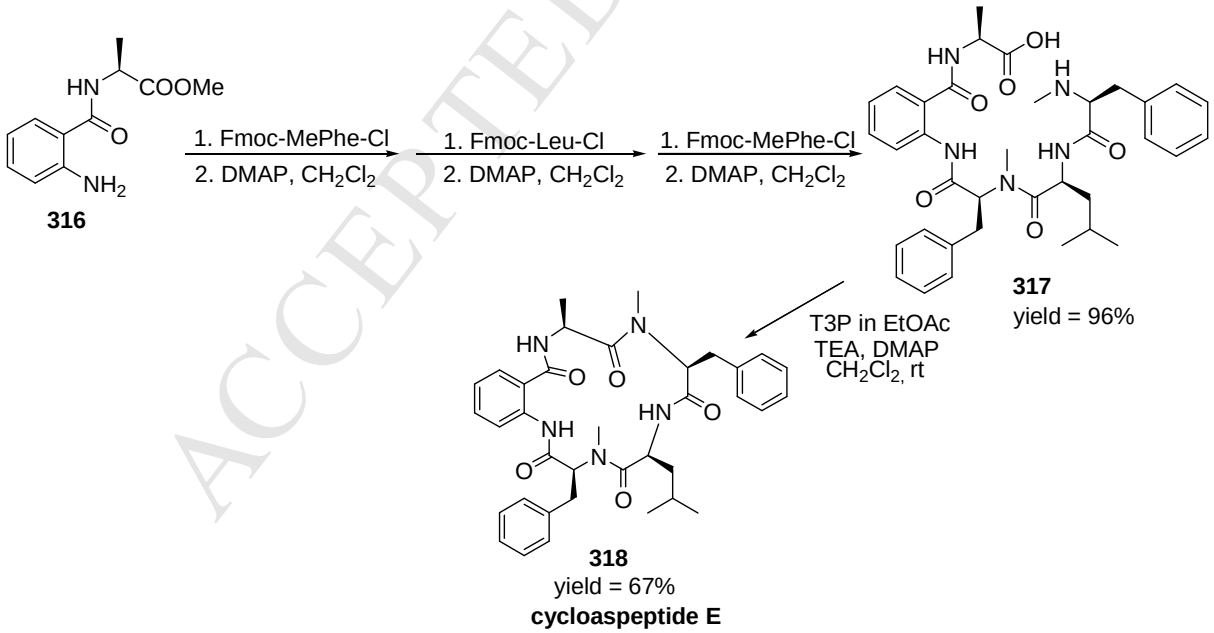
The dipeptide fragment was then coupled to the Fmoc deprotected tripeptide fragment by BOP-Cl activation. The Fmoc protected pentapeptide was deprotected using diethylamine and the partially liberated hydrazine was coupled to the final acid chloride unit under reflux in toluene in the presence of AgCN to afford the desired hexapeptide **315** (Scheme 77).



Scheme 77. Synthesis of hexapeptide precursor of antitumor antibiotic A83586C.

6.4.5. Cycloaspeptide E

Total synthesis of cycloaspeptide E involved the preparation of acyclic pentapeptide precursor by Fmoc solution phase synthesis using oxalyl chloride/cat. DMF in good overall yield starting from methyl alaninate hydrochloride (Scheme 78).[293] Acyclic pentapeptide **317** was then cyclized to cycloaspeptide E **318** using the cyclic anhydride propane-1-phosphonic anhydride (T3P)[294] in 67% yield.

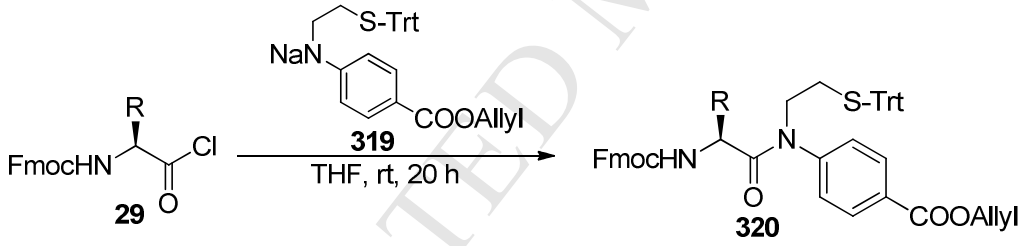


Scheme 78. Synthesis of cycloaspeptide E using Fmoc-acid chloride strategy.

6.5. Miscellaneous applications

6.5.1. *N*-Fmoc-amino acyl-*N*-sulfanylethylaniline linkers

Sakamoto et al.[295] reported an efficient synthesis of *N*-Fmoc-amino acyl-*N*-sulfanylethylaniline linkers **320**, which serve as crypto-peptide thioester precursors for native chemical ligation[296] applications (Scheme 79). The protocol involved reaction of Fmoc-amino acid chlorides with sodium anilides preformed by treating aniline with NaH, at ambient temperature. It was found that for sterically less hindered Gly and Ala derivatives, corresponding acid chlorides prepared using $SOCl_2$ and catalytic DMF yielded better results. In case of other protienogenic amino acids including those with acid labile side chain protecting groups, an equimolar mixture of Fmoc amino acid, TEA, and $POCl_3$ (five fold excess over anilide) in CH_2Cl_2 was used for coupling with sodium anilide at ambient temperature for 24 h. The coupling conditions lead to good isolated yields of products with negligible racemization. Even in case of highly racemization prone Ser(^{t}Bu) (< 1%), Cys(Trt) (not detected), His(Mbom) (< 4%) [Mbom = 4-methoxybenzyloxymethyl] derivatives, negligible or no racemization was reported.

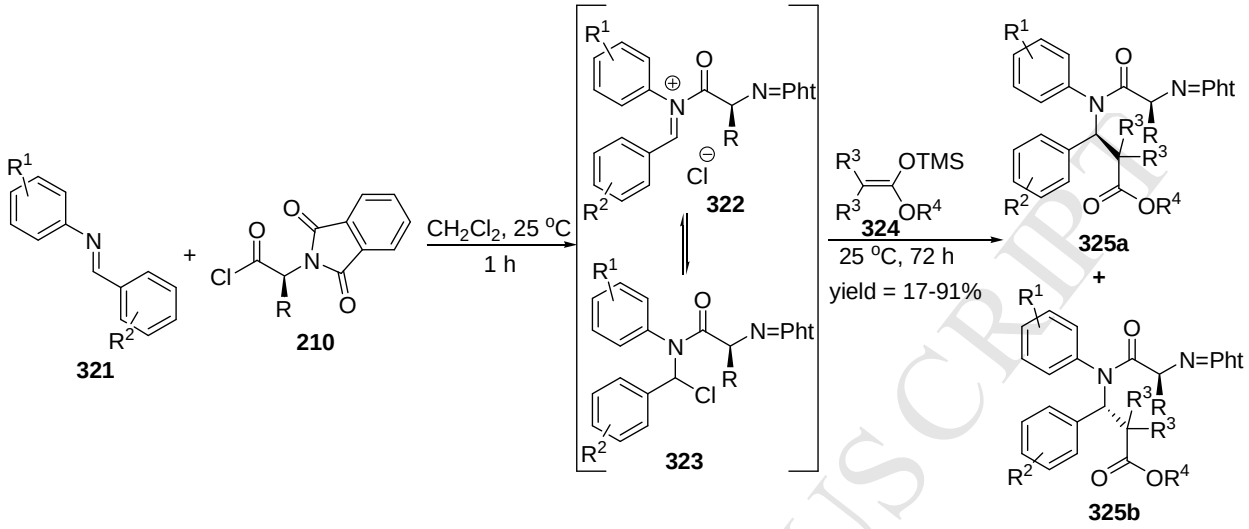


R = H (yield = 94%), CH_3 (yield = 80%), $CH(CH_3)_2$ (yield = 87%), $CH(CH_3)CH_2CH_3$ (yield = 88%), $CH_2CH(CH_3)_2$ (yield = 74%), CH_2Ph (yield = 83%), $-(CH_2)_3-$ (yield = 48%), CH_2O^tBu (yield = 89%)

Scheme 79. Synthesis of *N*-Fmoc-amino acyl-*N*-sulfanylethylaniline linkers.

6.5.2. Mannich type reaction: *N*-Acylated β-amino acid esters

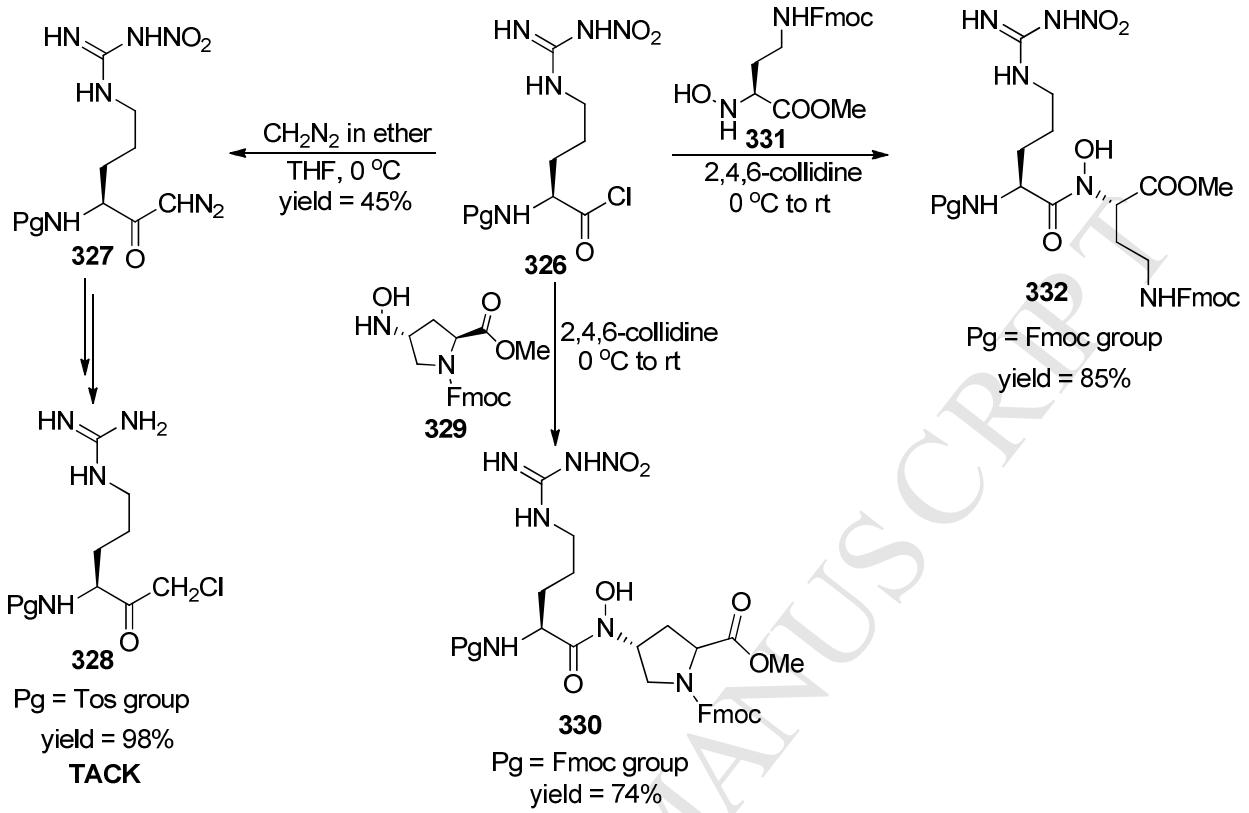
In a Mannich-type reaction, Schiff bases **321** are treated with *N,N*-phthaloyl amino acid chlorides **210** and then with the silylketene acetals at room temperature to afford the *N*-acylated β-amino acid esters **325** in moderate to high yields with high diastereomeric ratios (Scheme 80).[297] The stereoselectivity of the reaction found to depend on the steric demand of the amino acid side chain as well as the aromatic imine substituents. Whereas the imine from benzylamine provided lower diastereomeric ratio, the ortho substituents at either of the aromatic group at the imine nitrogen or the carbon atom of the C=N bond tend to increase the stereoselectivity.



Scheme 80. Synthesis of *N*-acylated β-amino acid esters by reaction of Schiff bases with *N*,*N*-phthaloyl amino acid chlorides.

6.5.3. Arginine compounds: Hydroxamate dipeptidomimetics and Tos-L-Arg chloromethyl ketone (TACK) derivatives

Seo and Silverman reported arginine containing hydroxamate dipeptidomimetics using Fmoc-Arg(NO_2)-Cl **326** in good yields.[298] Due to the weak nucleophilicity of *N*-alkylhydroxylamines, use of uronium- or phosphonium-based peptide coupling reagents resulted in no isolable product. Formation of lactam side product could be observed in these cases (Scheme 81). The use of PyBroP/DIEA system lead to only 8% isolated yield of *N*-hydroxy derivative. However reaction of Fmoc-Arg(NO_2)-Cl using $SOCl_2$ at -10 °C to 0 °C followed by coupling with *N*-alkylhydroxylamines in presence of 2,4,6-collidine resulted in hydroxamates **332** and **330** in 85% and 74% yield respectively.



Scheme 81. Synthesis of hydroxamate dipeptidomimetics and Tos-L-Arg chloromethyl ketone (TACK) derivatives.

Tos-Arg(NO_2)-Cl **326** (prepared by the treatment of Tos-Arg(NO_2)-OH with PCl_5 in THF at -10 to 0 °C) was employed efficiently in the synthesis of N^{α}-tosyl-L-arginine chloromethyl ketone (TACK) in good yield. Tos-Arg(NO_2)-Cl was converted to corresponding diazoketone, followed by treatment with HCl in acetic acid to yield N^{G}-nitro-TACK. Finally, treatment with anisole and anhydrous HF was carried out at 0 °C to yield TACK **328** in 98% yield.[299]

N^{α}-Fmoc-N^{G}-tosylarginine esters were synthesized by the reaction of corresponding acid with oxalyl chloride in presence of catalytic amount of DMF, followed by treatment with an appropriate alcohol and pyridine. Reaction with methanolic ammonia afforded carboxamide. These were then tested as HIV-1 protease inhibitors and found to be relatively specific and nontoxic.[300]

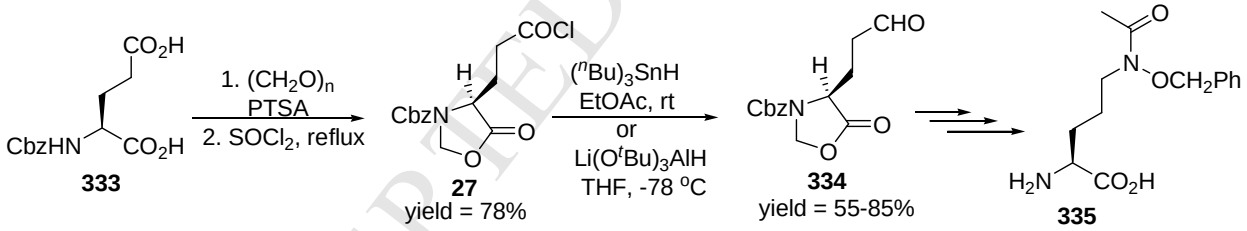
6.5.4. Acylation of Wang resin

Akaji et al. demonstrated esterification of 4-alkoxybenzyl alcohol polystyrene resin in high yields with practically no racemerization (< 0.7%) using Fmoc-amino acid chlorides.[301] The crude Fmoc-amino acid chloride was dissolved in 40% pyridine in CH_2Cl_2 and vortexed with polystyrene-supported Wang resin at 25 ^oC for 60 min. Except for His(Bom) various amino acids with bulky side chain could be obtained quantitatively. The amount of D-isomer was found below 0.7% with exception of Met (1.7%). Almost similar results were reported by others also.[302]

6.5.5. Side chain acid chlorides

6.5.5.1. *N*-Hydroxy-L-ornithine

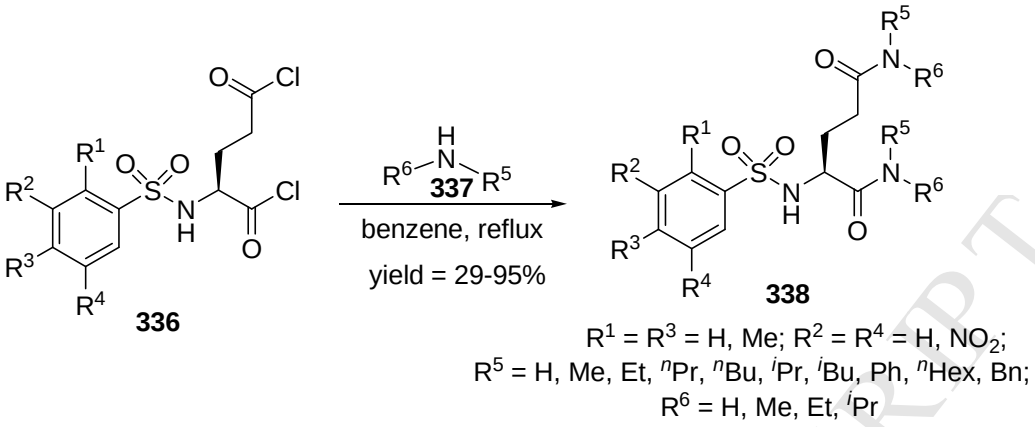
δ-*N*-Hydroxy-L-ornithine derivatives **335** were reported by Miller et al. starting from Glu. The sequence involved the reduction of γ-acid chloride **27** to the aldehyde **334**, formation of the substituted oxime and reductive acylation (Scheme 82).[71] Cbz-Glu was treated with paraformaldehyde, cat. *p*-TsOH in toluene to protect the α-amino and carboxyl groups. Further it was converted to the corresponding acid chloride followed by reduction to the corresponding aldehyde.



Scheme 82. Synthesis of δ-*N*-hydroxy-L-ornithine derivatives.

6.5.5.2. 1,5-*N*,*N*'-Disubstituted-2-(substituted benzenesulfonyl)glutamamides

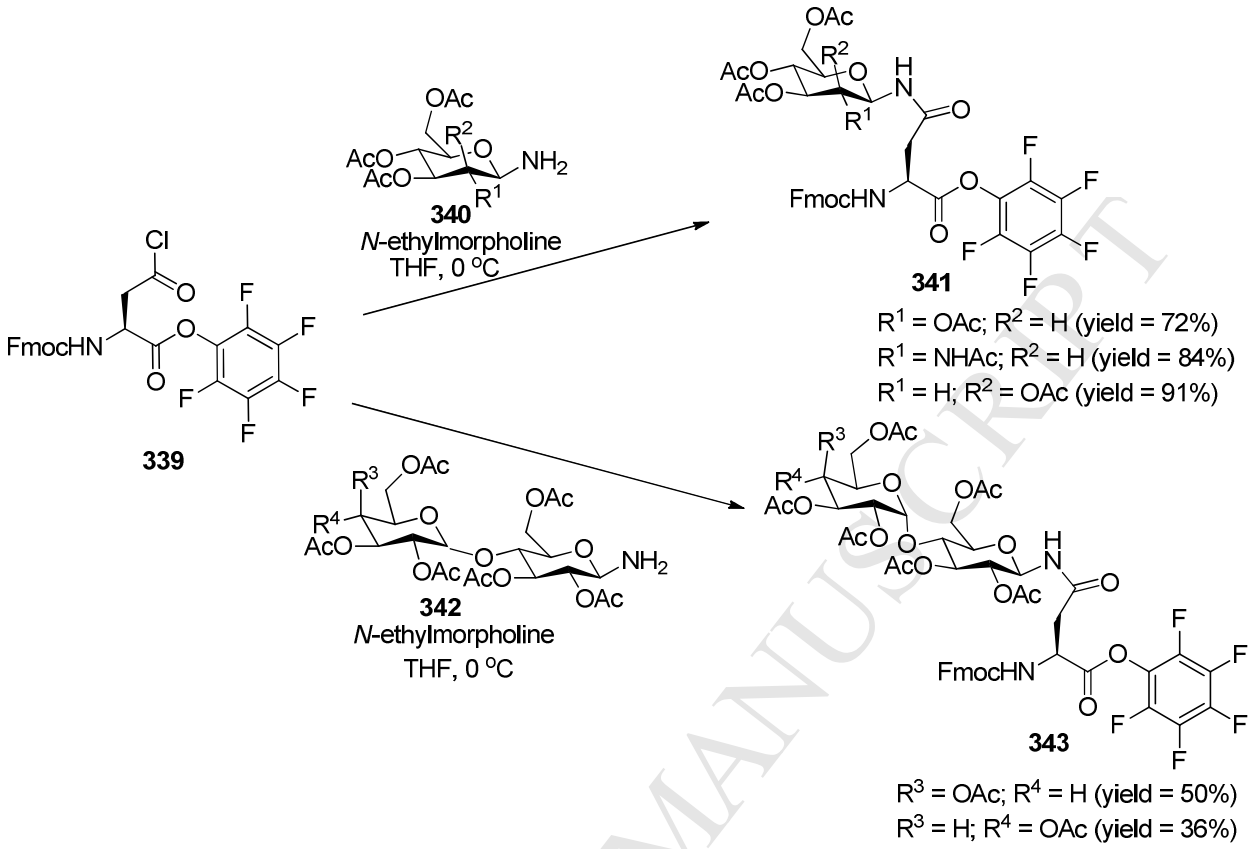
Srikanth et al.[132] reported 1,5-*N*,*N*'-disubstituted-2-(substituted benzenesulfonyl)glutamamides **338** for the study of quantitative structure activity relationship of antitumor activity. Various substituted benzenesulfonyl glutamic acids were prepared by the reaction of corresponding benzenesulfonyl chlorides with Glu in 2 N NaOH solution. The resultant diacid was converted to the corresponding diacid chloride using $SOCl_2$ under reflux. At the end, 2-(substituted benzenesulfonyl)-1,5-*N*,*N*-dialkyl glutamamides **338** were obtained by addition of acyl chloride **336** to excess of amine under reflux for 30 min in benzene (Scheme 83).



Scheme 83. Synthesis of 1,5-*N*,*N'*-disubstituted-2-(substituted benzenesulfonyl)glutamamides.

6.5.5.3. Glycosylated amino acids

Meldal et al. demonstrated synthesis of fully protected glycosylated asparagine building blocks activated as their pentafluorophenyl esters using N^{α}-Fmoc-Asp(Cl)-OPfp.[303] The acid chloride was prepared (0.025-5 g scale) from commercially available N^{α}-Fmoc-Asp(O^{t}Bu)-OPfp by simultaneous treatment with TFA and $SOCl_2$ at 40 ^{o}C for 24 h quantitatively. N^{α}-Fmoc-Asp(Cl)-OPfp **339** was then glycosylated with per-*O*-acetylated β-D-glucose, *N*-acetyl-β-D-glucosamine, β-D-mannose, 4-*O*-β-D-glucopyranosyl-β-D-glucose (cellobiose), 4-O-α-D-glucopyranosyl-β-D-glucose (maltose) and 4-*O*-β-D-galactopyranosyl-β-D-glucose (lactose) in single step to yield the glycosylated building blocks **341** and **343** (Scheme 84). The condensation of the per-*O*-acetylated glycosyl amines and acid chloride was carried out at 0 ^{o}C to result in 36-91% yield of the desired product with no reaction with the Pfp ester.



Scheme 84. Synthesis of glycosylated asparagine building blocks.

7. Conclusions

Emil Fischer introduced acid chlorides as peptide coupling agents and the journey came to full circle with Louis Carpino reasserting them as efficient and appropriate economical choice with the use of Fmoc group. Especially in the sterically hindered peptide couplings involving α,α-dialkyl amino acids, *N*-alkyl amino acids and *N*-aryl amino acids, clearly the acid chlorides are the most efficient when compared with the expensive reagents such as HATU. They can be introduced in an automated synthesizer by virtue of being stable in organic solvents like DMF, CH_2Cl_2. Also, in situ generation of acid chlorides has given convenience of not handling them directly owing to the problems of hydrolysis and stability. While the diversity of amino acid chemistry render a peptide bond formation as a combination of several parameters, as Albericio puts it "there is more than one way to skin a cat" and no best single coupling agent yet or in future. Though numerous activating agents starting from carbodiimides to active esters, azides, anhydrides and other fancy reagents decorated the armory of a synthetic peptide chemist; acid

chlorides undoubtedly remain the troubleshooter in the case of a difficult synthesis in hand, albeit with necessary precautions/modifications. In this regard, new directions to both the preparation as well as coupling conditions are the need of the hour.

8. Acknowledgement

Vommina V. Sureshbabu is grateful to late Professor K. M. Sivanandaiah, Bangalore University, Bangalore for his guidance in the initial stages of establishment of peptide research group at Central College, Bangalore (CCB) and to late Prof. B. S. Sheshadri for his untiring support in providing laboratory space at CCB in 1998. He is ever thankful to Drs. H. N. Gopi and K. Ananda for their toiling work in establishing the group during its infancy. He also place on record sincere thanks to all the former students, in particular, Drs. R. Venkataramanarao, Chennakrishnareddy, H. P. Hemantha and S. A. Shankar for their sincere involvement and hard work during their stay in the group. He is grateful to Professor M. S. Thimmappa and Dr. N. Prabhudev, formerly Vice-Chancellors of Bangalore University and in particular, Prof. B. Thimme Gowda (present Vice-Chancellor) for extending academic support for the sustenance of research group at CCB. The Department of Science and Technology, Council of Scientific and Industrial Research, Department of Biotechnology, University Grants Commission, Govt. of India, New Delhi and Board of Research in Nuclear Sciences, DAE, Mumbai are thanked for generous financial support.

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$$\overset{+}{X}NH_3R + NR'_3 \rightleftharpoons NH_2R + \overset{-}{X}\cdot\overset{+}{H}NR'_3$$

Deviations from the addition of stoichiometric quantities of a base can result in catalysis of the formation of O-acylation, succinimide and glutamide formation, diketopiperazine ring closure and racemization.

The above side reactions can be avoided by i) using a weak base (tertiary amine) as possible; ii) using a hindered base as possible and iii) avoiding salts, if possible (i.e., prefer to use amino free amino acid ester as amine component during the coupling. For detailed investigations primarily by Bodanszky and others, see the series of publications entitled coupling in the absence of base.[38-42]

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10. Biographical sketches

Girish Prabhu was born in Karkala, Karnataka (India). He obtained his B. Sc. from Sri Bhuvanendra College, Karkala in 2004 and M.Sc. in Organic Chemistry from Mangalore University, Mangalore in 2006. He joined Syngenta Biosciences Pvt. Ltd., Goa, India in 2006 as Junior Research Scientist, where he worked on nitrogen heterocyles of agrochemical interest. In January 2010, he joined the research group of Prof. V. V. Sureshbabu at the Department of Chemsitry, Central College, Bangalore for his Ph.D. His research interests include peptides, peptidomimetics, synthetic methodologies, nanochemistry.

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N. Narendra was born in Bangalore, Karnataka, India in 1981. He completed M.Sc. in Organic Chemistry from Bangalore University, Bangalore in 2005. He worked on peptides and peptidomimetics under the guidance of Dr. V.V. Sureshbabu at the Department of Chemsitry, Central College, Bangalore for his Ph.D. Presently he is working as assistant professor at the University College of Science, Tumkur University.

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Professor Vommina V. Sureshbabu was born in Nellore, Andhra Pradesh, India in 1961. He obtained M.Sc. in Chemistry from Sri Krishnadevaraya University, Ananthapur, India in 1983. He was invited by Prof. K.M. Sivanandaiah to join for Ph.D at Central College, Bangalore to work in the area of peptide chemistry. After the completion of Ph.D in 1989, he was appointed as Lecturer at the same department. Later, he went to USA for a postdoctoral assignment to CUNY, New York where he worked on the synthesis of GPCR fragments through native chemical ligation. At present, he is working as a Professor at the Department of studies in Chemistry, Central College, Bangalore. His research interests include development of new reagents for efficient peptide synthesis, design and synthesis of peptidomimetics, incorporation of unnatural linkages into peptide backbone, native chemical ligation, C-terminal versus N-terminal modifications for peptidomimetic synthesis and utility of Fmoc-group in solution-phase synthesis. Recently, V.V.S. has contributed a chapter entitled 'Protection Reactions' to the volume 'Amino acids, Peptides and Proteins in Organic Chemistry' Vol. 4. Protection Reactions, Combinatorial and Medicinal Chemistry: (Ed. Andrew Hughes), 2011, Wiley Int. Ltd and a report entitled "Total chemical synthesis of polypeptides and proteins: Chemistry of ligation techniques and beyond" (Tetrahedron 2012, 68, 9491-9537).

Graphical Abstract

Amino acid chlorides

A journey from instability and racemization towards broader utility in organic synthesis including peptides and their mimetics

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Dedicated to Professor Padmanabhan Balaram, IISc, Bangalore on the occasion of his superannuation