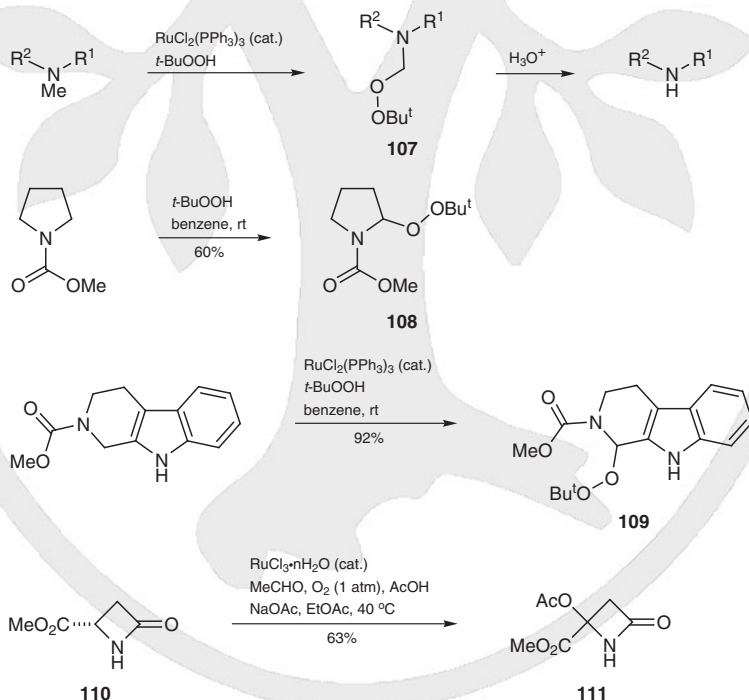
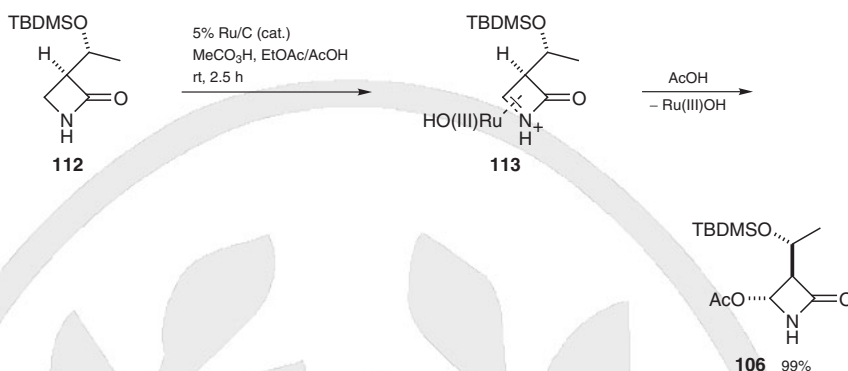


21.3.2.2.8

**Method 8:
Ruthenium-Catalyzed Oxidation of Amides and Carbamates**

The biomimetic oxidation of tertiary amines to afford the corresponding α -alkyl peroxides **107** (Scheme 32) has been developed into a valuable and efficient method for the α -oxygenation of C—H bonds adjacent to the nitrogen atom of amides and carbamates.^[123–126] Thus, dichlorobis(triphenylphosphine)ruthenium(II)-catalyzed oxidation of amides with *tert*-butyl hydroperoxide takes place under mild conditions to afford the corresponding α -(*tert*-butylperoxy) amides.^[123] Two specific examples of this procedure are shown in Scheme 32 leading to the peroxides **108** and **109**. Peroxy compounds can be replaced by employing aldehydes and molecular oxygen in the presence of a catalyst, and here ruthenium(III) chloride alone is shown to be more effective than its complexes.^[124] This convenient procedure rivals the anodic oxidation method (Section 21.3.2.2.7) in scope and efficiency, and there is also a similarity of mechanistic features between the two methods. It is speculated that the active species is an oxoruthenium(V) species, which abstracts a hydrogen atom from the carbon α to the nitrogen functionality; subsequent electron transfer generates the corresponding *N*-acyliminium ions. Finally, ensuing attack by a peroxy acid or an acid affords the α -oxygenation products. In the case of the azetidinones **110** and **112** this method can be used to form the corresponding 2-acetoxyated derivatives **111** and **106**, respectively. The scrambling of stereochemistry in the first case and the induction of stereochemistry at the site of acetoxylation in the second provide further strong support for the intermediacy of an *N*-acyliminium–metal complex, e.g. **113** (Scheme 32).^[123,124]

Scheme 32 Ruthenium-Catalyzed Oxidation of Amides and Carbamates^[123,124]



When this approach is applied to the oxidation of dipeptides, glycine-selective oxidation occurs to give the respective oxo amides.^[127] It may be noted that the glycine backbone is inert to ruthenium(VIII) oxide, which is commonly used for the oxidation of amides to imides.^[128]

(2*R*,3*R*)-3-[1-(*tert*-Butyldimethylsiloxy)ethyl]-4-oxoazetidin-2-yl Acetate (106**); Typical Procedure:**^[123]

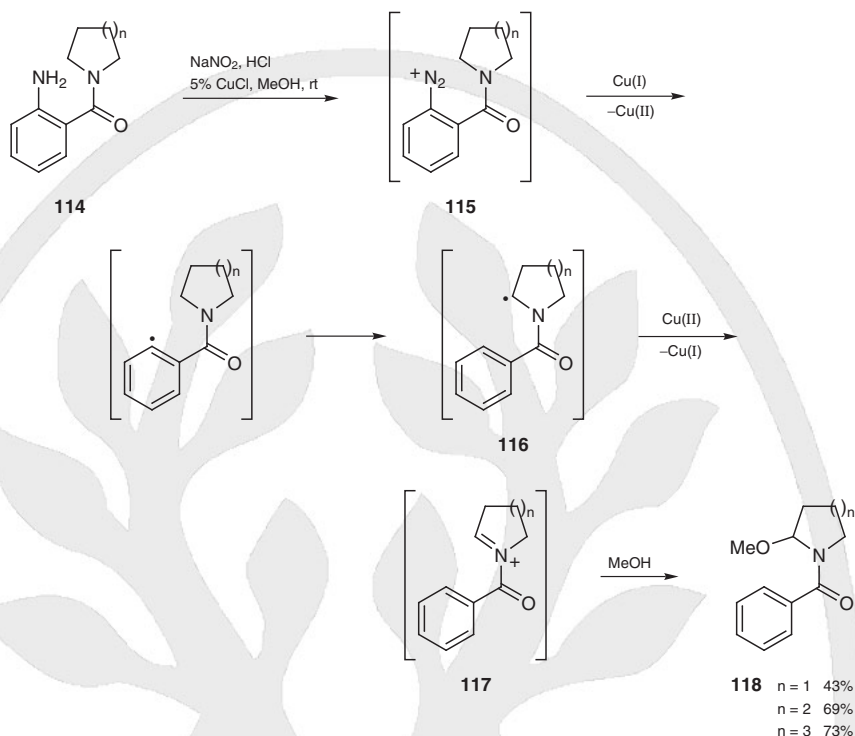
30% MeCO₃H (2.41 g, 9.61 mmol) in EtOAc was added dropwise to a stirred mixture of azetidinone **112** (1.00 g, 4.37 mmol), 5% Ru/C (0.25 g), and anhyd NaOAc (0.36 g, 4.37 mmol) in AcOH (4.4 mL) over a period of 2.5 h at rt. After filtration, the mixture was poured into H₂O and extracted with hexane. Evaporation of the solvents gave a colorless solid; yield: 1.24 g (99%); mp 108.5 °C; [α]_D +51.2 (c 1.0, CHCl₃).

21.3.2.2.8.1

Variation 1:

Decomposition of Diazonium Salts of 1-(2-Aminobenzoyl)azacycloalkanes

Copper(I) ion promoted decomposition of the diazonium salts **115**, which are generated in situ from the 1-(2-aminobenzoyl)azacycloalkanes **114** (*n* = 1, 2, 3), in methanol provides the methoxylated compounds **118**. The reaction mechanism is rationalized by initial conversion of the diazonium salt by the copper(I) cation into an aryl radical, followed by a 1,5-hydrogen atom transfer, oxidation of the resulting α -amidyl radical **116**, and trapping of an *N*-acyliminium species **117** by methanol (Scheme 33).^[129,130] When the heterocyclic component is an unsymmetrical 2-substituted pyrrolidine or piperidine ring the oxidation step may display good regioselectivity; this is attributed to preferences within the populations of amide rotamers.

Scheme 33 Copper(I)-Mediated Methoxylation of 1-(2-Aminobenzoyl)azacycloalkanes^[129]**1-Benzoyl-2-methoxyazacycloalkanes 118; General Procedure:**^[129]

NaNO₂ (2 equiv) and CuCl (5 mol %) were added to a stirred soln of the 2-aminobenzamide (1–3 mmol) in MeOH (0.05 M soln). Methanolic HCl (3%, 3 equiv) was added during 5–10 min, and stirring was continued at rt. The mixture was diluted with aq sat. NaHCO₃, and MeOH was removed under reduced pressure. The residue was extracted with EtOAc (3 × 30 mL); the extracts were washed with brine, dried (MgSO₄), and concentrated under reduced pressure; purification of the residue was achieved by preparative TLC (EtOAc/hexanes 1:2 to 1:1).

21.3.2.2.8.2

Variation 2:**Oxidation of Amines by 2-Iodoxybenzoic Acid**

There are several papers dealing with the oxidation or oxidative fragmentation of amides and related compounds.^[131–133] 2-Iodoxybenzoic acid is utilized for the oxidation of primary and secondary amines to the corresponding functionalized imines^[134] and, since imines (see Sections 21.3.1.2.1 and 21.3.2.2.5) serve as suitable precursors for *N*-(chloroalkyl) or *N*-(alkoxyalkyl) amides and carbamates, this may prove useful in the future.

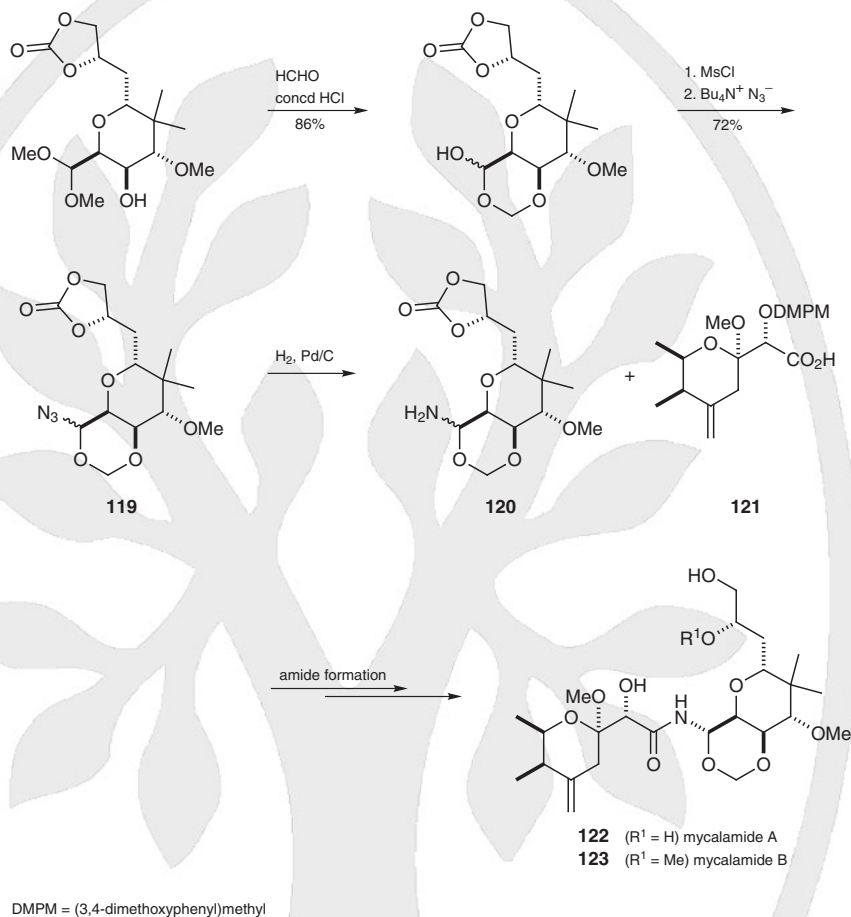
21.3.2.2.9

Methods 9:**Miscellaneous Procedures**

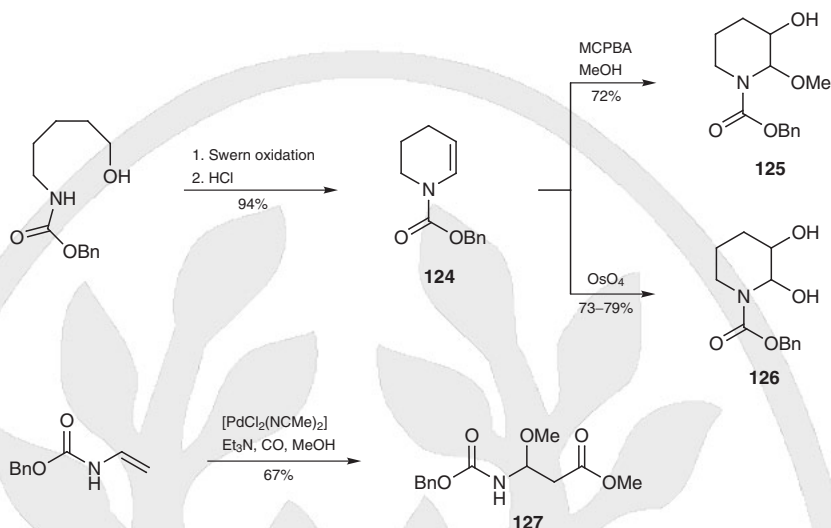
Other methods of potentially general applicability exist although they have not been investigated extensively; however, their synthetic utility is well demonstrated in the total synthesis of natural products. For example, a key step in the syntheses of the mycalamides A (**122**) and B (**123**) (as well as onnamide A), natural products that display a strikingly close structural relationship to pederin (**90**; see Scheme 25, Section 21.3.2.2.6), relies

on conventional amide formation from the configurationally unstable amine **120** and the acid **121**.^[135,136] Here the amine **120** is prepared from the corresponding alcohol via the reduction of an azide intermediate **119** (Scheme 34).

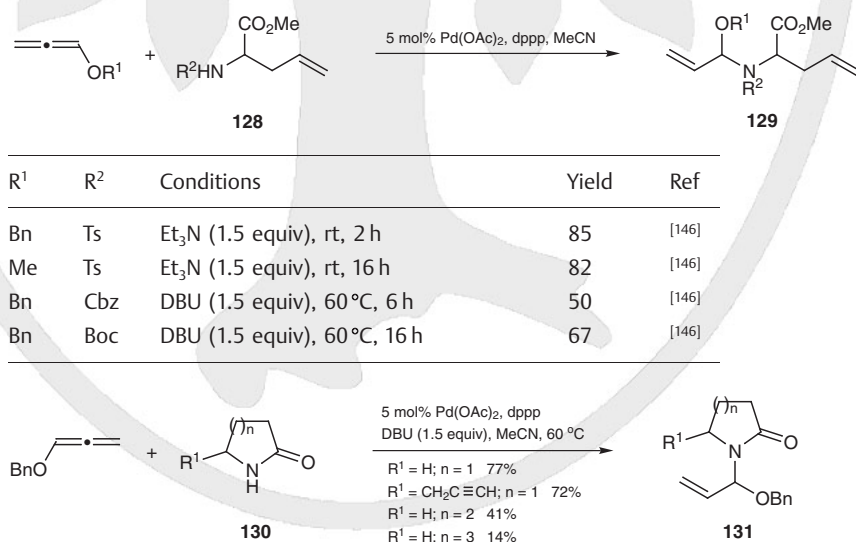
Scheme 34 Syntheses of the Mycalamides A and B by the Reaction of an Aminal and an Acid^[135]



Another method is based on the electrophilic addition reactions of acyclic and cyclic N-acylated enamines.^[137–140] One convenient method for preparing N-acylated enamines is through the acylation of imines.^[92,142,143] Five- and six-membered derivatives are also readily available by either partial reduction of the corresponding lactams, or by cyclodehydration of open-chain aldehydic amides or carbamates. Subsequent elaboration of the product enamines can be initiated by epoxidation, dihydroxylation, or halogenation. An example of this approach is shown in Scheme 35 where an amino alcohol is first oxidized by the Swern method and then cyclodehydrated to afford the tetrahydropyridine **124**. This compound is then converted into either the 2-methoxypiperidin-3-ol **125** or the related diol **126**.^[141] Although the yields are not high, oxidative cyclization of enamides has been achieved by the action of manganese(III) acetate in refluxing methanol.^[144] Palladium(II)-mediated carboacylation of enamides has been developed for preparation of functionalized β -amino acids, as in the formation of the ester **127** from the benzyl vinylcarbamate (Scheme 35).^[145]

Scheme 35 Formation and Functionalization of Ene-Carbamates^[141,145]

Direct access to suitably functionalized N-acylated N,O-acetals is possible by palladium-catalyzed amidopalladation of alkoxyallenes (Scheme 36). Triethylamine is used as the base to transform the sulfonamide **128** (R² = Ts) into the appropriate alkoxyated carbamates **129**.^[146] Not only sulfonamides, but less acidic carbamates and imides are suitable when 1,8-diazabicyclo[5.4.0]undec-7-ene is employed as the base. Two different mechanisms have been proposed to account for the difference in reactivity among these amide derivatives.^[146] Moreover, the conversion of the cyclic lactams **130** into the N-alkylated products **131** can also be carried out using 1,8-diazabicyclo[5.4.0]undec-7-ene (Scheme 36); however, as the various amide precursors in the scheme show different reactivities it is probable that they utilize different reaction mechanisms.^[146]

Scheme 36 Amidopalladation of Alkoxyallenes^[146]

In more specialized cases, highly functionalized polycyclic alkoxyated lactams have been prepared in good yields by elegant applications of cycloadditions.^[147–150]

21.3.2.2.10

Method 10:**Further Applications of Iminium and *N*-Acyliminium Ions in Total Synthesis**

Iminium ions have long been extensively used in the formation of C—C bonds, as illustrated in classical Mannich and Pictet–Spengler reactions. The introduction of an electron-withdrawing acyl group at nitrogen makes the resulting *N*-acyliminium ion intermediates more electrophilic than the parent iminium ions; this enhanced electrophilicity was pointed out as early as 1957 in studies directed toward the syntheses of Erythrina alkaloids.^[151–154] Additionally, the presence of the *N*-acyl group augments the stability of *N*-(α -hydroxyalkyl) and (α -alkoxyalkyl) amides and derivatives, which serve as the most convenient precursors of the requisite *N*-acyliminium ions. These advantageous characteristics of *N*-acyliminium ions are exploited in a wide variety of inter- and intramolecular C—C bond-forming reactions (amidoalkylations).^[1, 15, 16, 95, 135, 136, 155–168] Particularly noteworthy are *N*-acyliminium ion initiated cyclizations that provide a powerful method for stereoselective syntheses. The synthetic utility of *N*-acyliminium chemistry is well illustrated in many total syntheses, detailed descriptions of which can be found in a number of comprehensive reviews, including those that relate to alkaloids^[155–164] and to β -lactams.^[165]

21.3.3

Product Subclass 3:***N*-(1-Amino- or 1-Acylaminoalkyl) Amides and Carbamates**

In general, *N,N'*-methylene bisamides are stable solids and many have been prepared. The main uses for these compounds include α -amidoalkylation and partial modifications of polypeptides. However, owing to the rather harsh conditions required, most α -amidoalkylation and *N*-acyliminium ion cyclizations typically utilize alkoxy derivatives instead of the bisamides (Section 21.3.2.1).

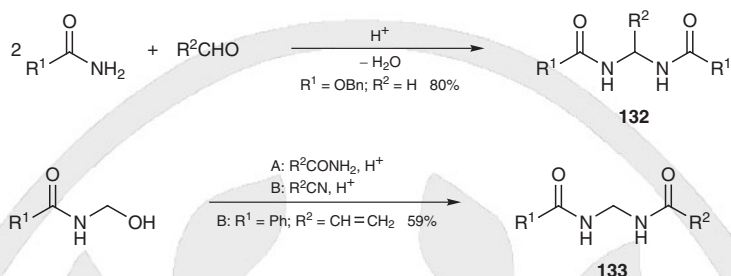
21.3.3.1

Synthesis of Product Subclass 3

21.3.3.1.1

Method 1:**Condensation of Amides and Aldehydes**

A long-established, reliable procedure for the preparation of *N*-(1-amidoalkyl) amides involves condensation of *N*-unsubstituted or *N*-monosubstituted amides and derivatives with aliphatic or aromatic aldehydes (Scheme 37).^[1, 15, 16] *N,N*-Methylenedibenzamide was first prepared in 1876 from dimethoxymethane and benzonitrile in the presence of sulfuric acid. Numerous examples involving amides, carbamates, nitriles, and arylsulfonamides have since appeared in the literature. For example, dibenzyl methylenebiscarbamate **132** ($R^1 = \text{OBn}$; $R^2 = \text{H}$) is formed from benzyl carbamate and paraformaldehyde (Scheme 37).^[169] It is not surprising that acetals or vinyl acetate can be used in place of aldehydes; the generality of this simple procedure is clearly due to the stability of the product bisamides and biscarbamates. Unlike aldehydes, however, simple ketones are not suitable for condensations with amides. Higher yields are often obtained by the treatment of readily available *N*-(hydroxymethyl) amides (see Section 21.3.2.1.1) with amides (Method A) or with nitriles (Method B) in acid solution; but, although ready access to unsymmetrical bisamides **133** is desirable, in the case of *N*-(benzamidomethyl)propanamide (**133**, $R^1 = \text{Ph}$; $R^2 = \text{CH}=\text{CH}_2$) (obtained from *N*-hydroxymethylbenzamide and propenenitrile) the yield is only 59% (Scheme 37).^[170]

Scheme 37 Preparation of Bisamides by the Condensations of Amides and Aldehydes^[1,15,169,170,16]**Dibenzyl Methylenebiscarbamate (132, $\text{R}^1 = \text{OBn}$; $\text{R}^2 = \text{H}$); Typical Procedure:**^[169]

A mixture of benzyl carbamate (30.2 g, 0.2 mol), paraformaldehyde (3.0 g, 0.1 mol), and TsOH (0.04 g) was refluxed in CH_2Cl_2 for 30 min. The mixture was cooled to rt, and CHCl_3 (300 mL) was added. The mixture was washed with 5% NaOH and then with H_2O , dried (Na_2SO_4), and concentrated under reduced pressure to give a colorless solid; yield: 25.2 g (80%); mp 154°C [recrystallized from CH_2Cl_2 /petroleum ether (bp $30\text{--}60^\circ\text{C}$)].

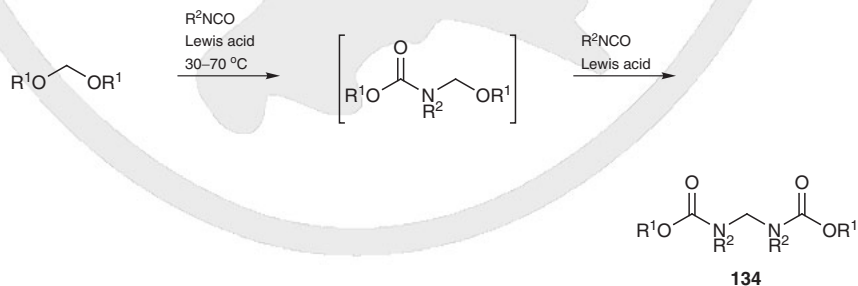
***N*-[(Propenoylamino)methyl]benzamide (133, $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{CH=CH}_2$); Typical Procedure:**^[170]

Method B: A mixture of *N*-hydroxymethylbenzamide (7.6 g, 0.05 mol) and propenenitrile (3.7 g, 0.05 mol) was added slowly to 96% H_2SO_4 (50 mL) with stirring, while the temperature was maintained at 30°C by cooling. After 1 h, the mixture was poured onto ice (200 g) and H_2O . The precipitate was collected by filtration and crystallized (H_2O); yield: 6.0 g (59%). This compound polymerized in the melting point tube when it was heated above 150°C .

21.3.3.1.1.1

**Variation 1:
Treatment of Acetals with Isocyanates**

Another method that can be used for the preparation of *N,N'*-methylene biscarbamates **134** entails treatment of dimethoxymethane (or other acetals) with two molar equivalents of an isocyanate in the presence of a Lewis acid (e.g., BF_3 , ZnCl_2 , or AlCl_3) at $30\text{--}70^\circ\text{C}$ (Scheme 38). In principle, this approach should be amenable to preparation of mixed biscarbamates by controlling the quantities of the acid catalyst, as well as the isocyanate added.^[171] A related procedure requires the condensations of isocyanates and formamide acetals.^[172]

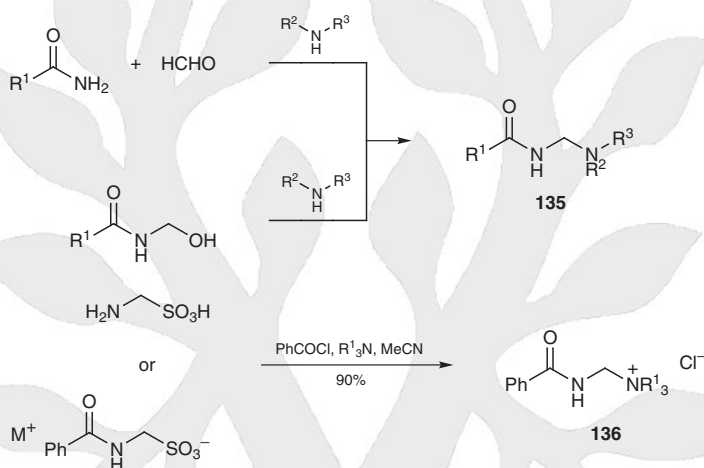
Scheme 38 Reactions of Isocyanates with Acetals^[171]Lewis acid = BF_3 , ZnCl_2 , AlCl_3

21.3.3.1.1.2

Variation 2:**Condensation of Amides, Formaldehyde, and Amines**

Mannich-type reactions of amides with formaldehyde and amines have often been used for the preparation of *N*-(α -aminomethyl) amides **135**;[1] condensations of *N*-(hydroxymethyl) amides with amines can also be utilized. An attempted *N,N*-dibenzoylation of aminomethanesulfonic acid with benzoyl chloride in the presence of a tertiary amine results in the elimination of sulfur dioxide and the formation of the appropriate mono-benzoylated ammonium salt **136**, as does a similar attempt to benzoylate (benzoylamino)methanesulfonates (Scheme 39).[173]

Scheme 39 Preparation of *N*-(α -Aminoalkyl) Amides from Secondary Amines or Amides^[1,173]

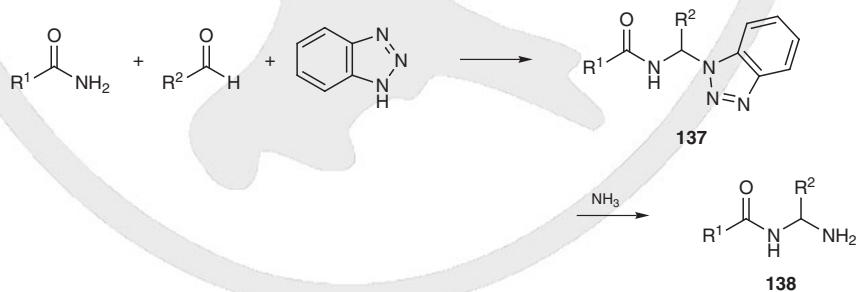


21.3.3.1.1.3

Variation 3:**Use of Benzotriazole in a Mannich-Type Reaction**

Another modification of a Mannich-type reaction of amides and formaldehyde involves the use of benzotriazole and, upon exposure to ammonia, the adducts **137** thus obtained provide the corresponding monoacylated amins **138** (Scheme 40).[174,175]

Scheme 40 Preparation of *N*-(α -Aminoalkyl) Amides from Benzotriazole^[174,175]

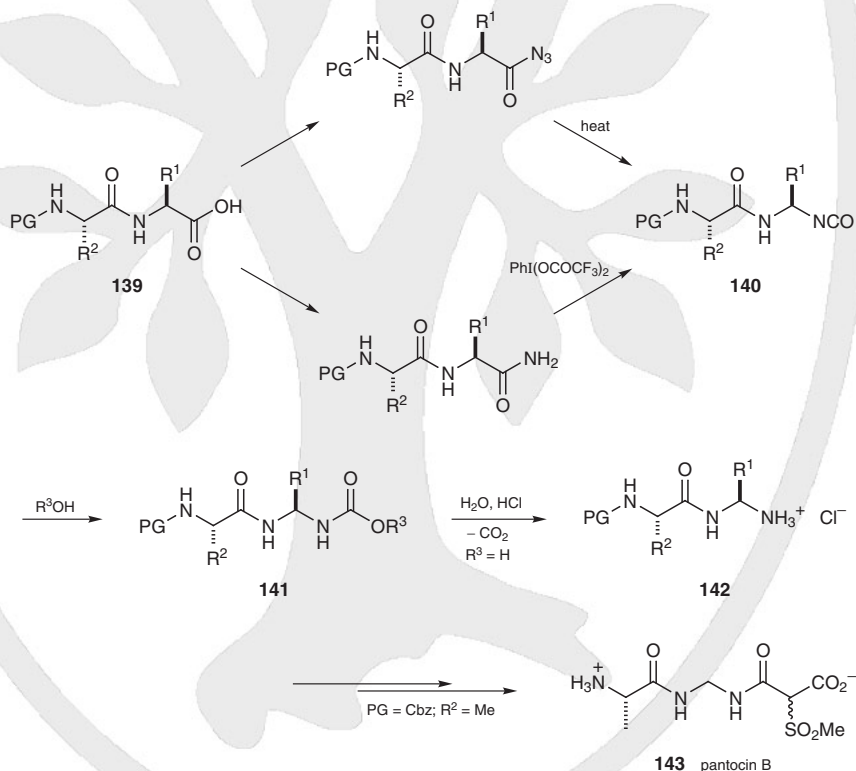


21.3.3.1.2

**Method 2:
Curtius Rearrangement**

Another apparently general route to unsymmetrical combinations of amides and carbamates has evolved from the Curtius rearrangement of acyl azides. This mild procedure is utilized for the stepwise degradation of polypeptides and the partial modification of peptides.^[176–180] For example, treatment of hydrazides derived from *N*-acylpeptides with nitrous acid and subsequent rearrangement in an alcoholic solvent provides *gem*-diacylamino derivatives.^[176] An improved procedure includes a Hofmann rearrangement under mildly acidic conditions using bis(trifluoroacetoxy)iodobenzene.^[179] Both variants are shown in Scheme 41 from various dipeptides **139** (PG = protecting group) as starting materials; the intermediate *N*-acyl- α -aminoalkyl isocyanates **140** can be trapped by an alcohol or water to afford the corresponding carbamates or amines, respectively. The *N*-(1-aminomethyl) amides **141** are remarkably stable toward hydrolysis under both acidic pH (≥ 1) and moderately basic conditions (pH ≤ 11). A synthesis of pantocin B (**143**), an unusual antibiotic from *Erwinia herbicola*, starts with the amine **142** ($R^1 = \text{H}$; $R^2 = \text{Me}$; PG = Cbz) derived from *N*-benzyloxycarbonyl-L-alanylglycinamide (Scheme 41).^[181]

Scheme 41 Curtius or Hofmann Rearrangements Leading to *N,N*-Diacylated Methylenediamines^[176–181]



***N*-[(Benzyloxy)carbonyl]-L-alanylglycinamide Hydrochloride Salt (**142**, $R^1 = \text{H}$; $R^2 = \text{Me}$; PG = Cbz); Typical Procedure:**^[181]

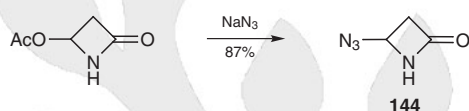
An equal volume of deionized H_2O was added to bis(trifluoroacetoxy)iodobenzene (2.48 g, 5.7 mmol) in MeCN (15 mL), followed by *N*-(benzyloxy)carbonyl-L-alanylglycinamide (**141**; 1.64 g, 5.7 mmol). The mixture was stirred at rt for 12 h, diluted with 1 M HCl and washed with Et_2O (2 \times). The aqueous layer was concentrated under reduced pressure and the resi-

due was crystallized (MeOH/Et₂O) to give a colorless solid; yield: 0.77 g (48%); mp 168–171 °C; [α]_D –11.3 (*c* 0.63, MeOH).

21.3.3.1.3

Method 3:**Treatment of *N*-(1-Haloalkyl) or *N*-(1-Acyloxyalkyl) Amides and Carbamates with Amines or Azides**

As noted in Section 21.3.1.2.1 the use of *N*-(1-haloalkyl) amides and carbamates, as α -amidoalkylating agents, along with amine nucleophiles represents another traditional route to members of this subclass and related compounds. *N*-(1-Acyloxyalkyl) amides are also suitable for displacement reactions. Prominent examples occur in β -lactam chemistry where readily available 4-acetoxyzetidin-2-ones are convenient substrates for reactions with various nucleophiles; for example, treatment of 4-acetoxyzetidin-2-one with sodium azide gives the corresponding azido- β -lactam **144** in excellent yield (Scheme 42).^[182] Additional examples are described in several reviews.^[165,183]

Scheme 42 Displacement of 4-Acetoxyzetidinone by Sodium Azide^[182]

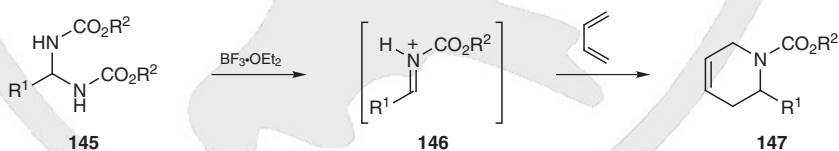
21.3.3.2

Applications of Product Subclass 3 in Organic Synthesis

21.3.3.2.1

Method 1: **α -Amidoalkylation**

Early applications of bisamides and carbamate derivatives lie in α -amidoalkylation.^[1,15,16] Typically, heating in the presence of an acid is required to generate the respective *N*-acyliminium ion intermediates but, due to the rather harsh conditions required, these reactions are limited in value and, in all but a handful of special cases,^[184] they have given way to the use of more versatile *N*-(1-hydroxyalkyl)- or alkoxyalkyl derivatives (Section 21.3.2.1).^[155–164] Since the first report of hetero-Diels–Alder reactions involving biscarbamates,^[185] generation and cycloadditions of the imino dienophiles have been extensively investigated in the syntheses of heterocycles; thus, treatment of the carbamates **145** with boron trifluoride–diethyl ether complex and then capture of the intermediate iminium cations **146** with buta-1,3-diene gives the tetrahydropyridines **147** (Scheme 43).^[38]

Scheme 43 Synthesis of *N*-Acyltetrahydropyridines from Iminium Dienophiles^[38,185]

R¹ = H, alkyl, CO₂R², aryl

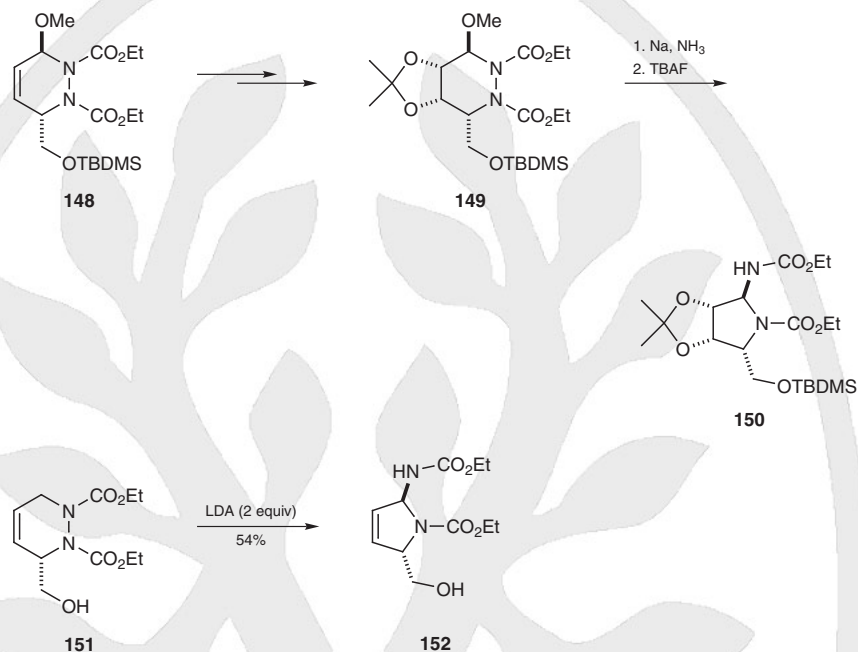
21.3.3.2.2

Method 2:**Reductive Cleavage of Reduced Pyridazines**

Other applications involve the cleavages of tetrahydropyridazines, which are themselves easily prepared by Diels–Alder reactions of dienes with diethyl diazocarboxylate. Two examples are shown in Scheme 44; in the first the hexahydropyridazine **149** is formed in

several steps from the adduct **148** and affords the pyrrolidine **150**, after ring scission and rearrangement. In the second illustration the dihydropyrrole **152** is obtained from the tetrahydropyridazine **151** by treatment with lithium diisopropylamide (Scheme 44).^[186–187]

Scheme 44 Reduced Pyrroles from the Cleavage of Pyrazines^[186,188]



21.3.3.2.3

Method 3: α -Azidation of Amides and Carbamates

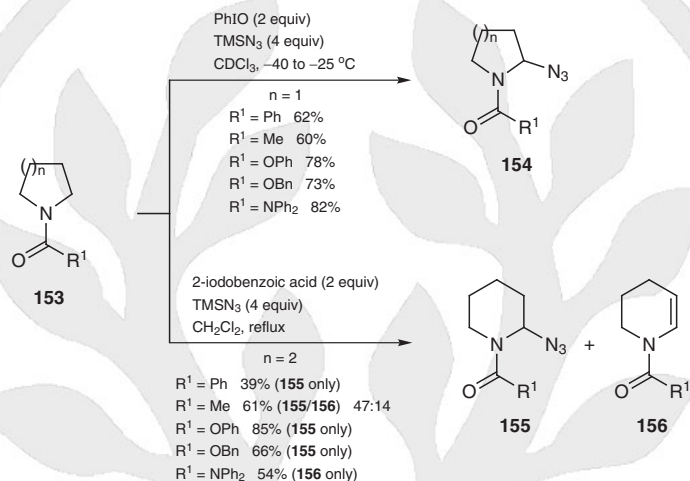
A new method for the direct introduction of an α -azide group into amides, carbamates, and ureas (Scheme 45),^[189,190] as well as into *N,N*-dimethylanilines,^[191,192] has been developed by the combined use of iodosobenzene/azidotrimethylsilane or 2-iodosobenzoic acid/azidotrimethylsilane. The reaction rate increases with the electron-donating ability of the *N*-acyl group in the starting materials **153** ($n = 1, 2$). Similarly, prolines are less reactive than the corresponding pyrrolidines.^[190] Competition experiments show that the pyrrolidines **153** ($n = 1$) are considerably more reactive than their piperidine counterparts **153** ($n = 2$). Thus, although iodosobenzene/azidotrimethylsilane can be used to form the corresponding azides **154** from *N*-acylpyrrolidines in modest yields, substitution of 2-iodosobenzoic acid for iodosobenzene is preferred in the pyridine series in order to circumvent decomposition of the reactive intermediate $[\text{PhI}(\text{OTMS})\text{N}_3]$.^[189] Even so, the α -azido products **155** are less stable, often leading to the elimination of azoic acid to give the corresponding enamides **156** (e.g., when $\text{R}^1 = \text{Me}$ or NPh_2). The α -azidation reactions (including those of triisopropyl enol ethers) appear to be specific for the hypervalent tricoordinate reagents. The detailed mechanism is not known, but a mechanistic hypothesis has been advanced for the role and fate of iodosobenzene/azidotrimethylsilane.^[193] The unique chemistry of hypervalent iodine compounds is the subject of several reviews.^[194–199]

Although the chemistry of these α -azido amides and derivatives is not fully investigated, they do act as *N*-acyliminium ion precursors;^[189] for example, treatment of the α -azido products **154** and **155** with methanol in the presence of silica gives the correspond-

for references see p 381

ing α -methoxy derivatives.^[189,190,193] It may be noted that conversions of α -methoxylated carbamates, which are readily available by means of anodic oxidation (Section 21.3.2.2.7), to the corresponding α -azido carbamates can be achieved by the action of azidotrimethylsilane in the presence of a Lewis acid (e.g., SnCl_4 or $\text{BF}_3 \cdot \text{OEt}_2$).¹⁹⁸ The azide group may be reduced to the respective amines and is utilized for 1,3-dipolar cycloadditions to introduce the triazole group.^[189,200]

Scheme 45 α -Azidonation of Amides and Carbamates^[189–191]



1-Acyl-2-azidopyrrolidines **154**; General Procedure:^[189]

CAUTION: Trimethylsilyl azide (azidotrimethylsilane) is toxic by inhalation, skin absorption, and orally. When dry, this reagent may explode and there is also a risk of explosion when it is exposed to heat or a shock.

TMSN₃ (0.64 mL, 4.8 mmol) was added at -40 °C to a suspension of freshly prepared PhIO (532 mg, 2.4 mmol) in CH₂Cl₂ (30 mL). After the suspension had been stirred for 5 min and had turned yellow in color, an amide or a carbamate (2 mmol) was added. The mixture was allowed to warm to -25 °C and was stirred overnight. The solvent was concentrated under reduced pressure. Purification of the residue was achieved by column chromatography (Florisil 200 mesh).

1-Acyl-2-azidopiperidines **155** and/or 1-Acyl-1,2,3,4-dihydropyridines **156**; General Procedure:^[189]

CAUTION: Trimethylsilyl azide (azidotrimethylsilane) is toxic by inhalation, skin absorption, and orally. When dry, this reagent may explode and there is also a risk of explosion when it is exposed to heat or a shock.

TMSN₃ (0.64 mL, 4.8 mmol) was added to a stirred suspension of 2-iodosobenzoic acid (630 mg, 2.4 mmol) in CH₂Cl₂ (30 mL) at 25 °C, followed by an amide or a carbamate (2 mmol). The mixture was refluxed overnight. The solvent was concentrated under reduced pressure and the residue was purified by column chromatography (Florisil 200 mesh) to give the appropriate azidopiperidine **155** and/or the corresponding enamide **156**.

21.3.4

**Product Subclass 4:
N-(1-Thioalkyl) Amides and Carbamates**

Since the structures of penicillins and cephalosporins were first elucidated many studies have been directed at the preparation and elaboration of related *N*-(1-alkylsulfanyl) amides and carbamates. α -Sulfur substituents possess inherent versatility, as each of the three different oxidation levels (sulfide, sulfoxide, and sulfone) is readily available and is well suited to subsequent elaboration. Useful transformations are found in a diverse range of *N*-acyliminium ion reactions, free-radical cyclizations, and in the coupling of α -amido carbanions with electrophiles.

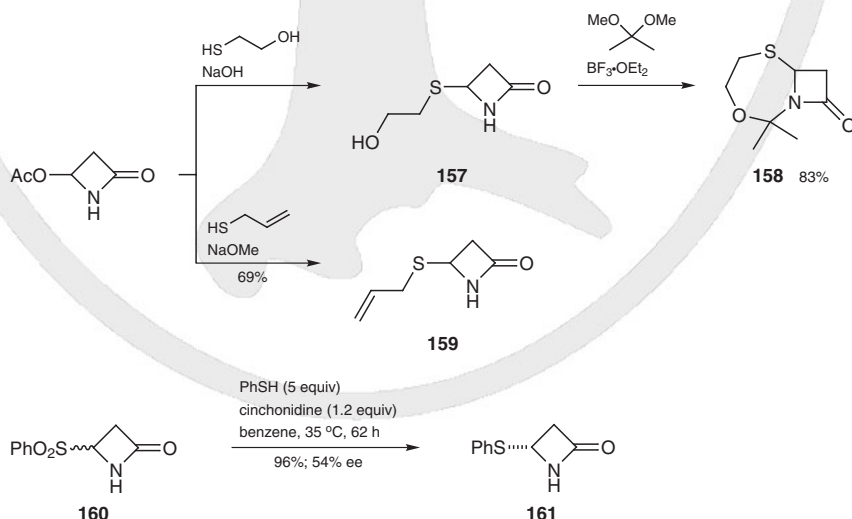
21.3.4.1

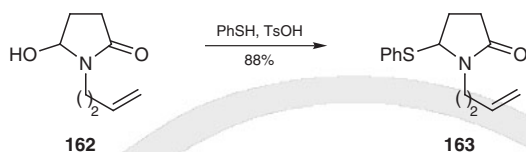
Synthesis of Product Subclass 4

21.3.4.1.1

**Method 1:
By Displacement Reactions**

α -Alkylsulfanyl, α -arylsulfanyl, and cognate selenium substituents can be easily introduced to amides and carbamates by displacement of suitable leaving groups such as halo, alkoxy, acyloxy, hydroxy, and sulfonyl functionalities (see Sections 21.3.1.2.1, 21.3.2.1.1 and 21.3.3.1.3). Owing to the high nucleophilicity of the sulfur-based nucleophiles, the substitution reaction proceeds smoothly under basic conditions;^[182,201,202] for example, 4-acetoxyazetidinone combines with 2-sulfanylethanol to give the hydroxylated sulfide **157**, which reacts with 2,2-dimethoxypropane and boron trifluoride–diethyl ether complex to afford 2,2-dimethyl-3-oxa-6-thia-1-azabicyclo[5.2.0]nonan-9-one (**158**),^[201] whereas a reaction with prop-2-enethiol gives the propenyl sulfide **159** (Scheme 46).^[202] This approach has been extensively utilized for the preparation and derivatization of β -lactams.^[118–120,165,183] Although enantioselectivity for the addition to the presumed azetidinone intermediate is not high (only 54% ee), treatment of the sulfone **160** with an excess of benzenethiol in the presence of cinchonidine gives the phenylsulfanylazetidinone **161** in 96% yield (Scheme 46).^[203] Relatively mild acidic conditions can also be employed by taking advantage of *N*-acyliminium ion intermediates;^[162,204,205] thus, for example, the alcohol **162** reacts with benzenethiol in the presence of 4-toluenesulfonic acid to afford the phenyl sulfide **163** (Scheme 46).^[204]

Scheme 46 Preparation of α -Sulfanylated Amides by Substitution Reactions^[201–204]



4-(2-Hydroxyethylsulfanyl)azetidin-2-one (**157**); Typical Procedure:^[201]

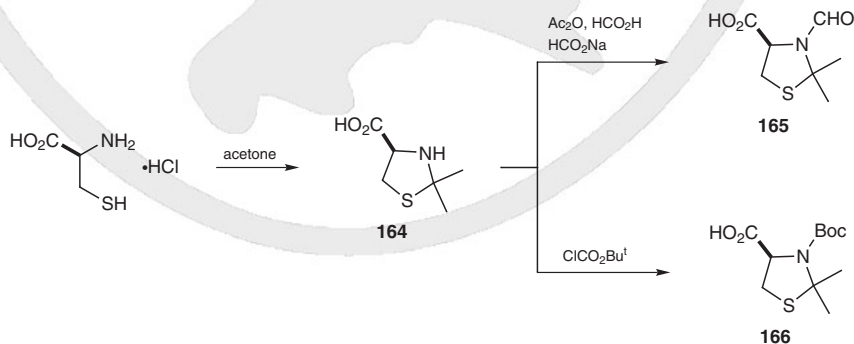
2 M NaOH (55 mL) was added dropwise during 30 min to a stirred soln of 4-acetoxyazetidin-2-one (12.9 g, 0.1 mol) and 2-sulfanylethanol (10 mL, 0.142 mol) in 95% EtOH (75 mL) at -10°C under N_2 . The mixture was allowed to warm to 0°C and it was stirred for an additional 1 h at this temperature, before it was neutralized by the addition of TFA (2 mL). The solvent was removed under reduced pressure and the residue was dried under high vacuum, treated with Na_2SO_4 (100 g), and extracted several times with portions of CHCl_3 (200 mL). The combined extracts were filtered, the solvent was removed under reduced pressure, and the residue was dried under high vacuum, affording a viscous liquid; yield: 14.7 g (100%). An analytical sample was purified by column chromatography (silica gel, EtOAc); mp 36°C .

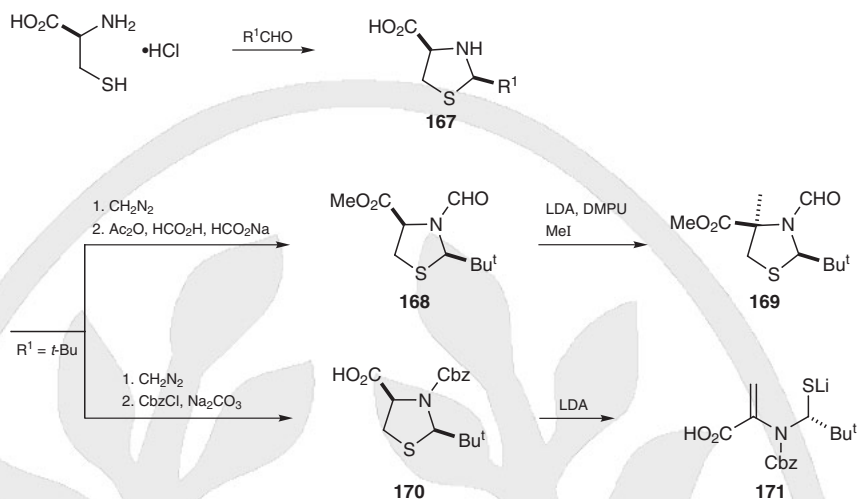
21.3.4.1.2

Method 2: Acylation of Thiazolidines

Another classical approach entails the acylation of readily available thiazolidines. For example, condensation of cysteine with acetone with removal of water provides 2,2-dimethylthiazolidine-4-carboxylic acid **164**.^[206] Subsequent acylation with the mixed anhydride of formic and acetic acids gives easy access to the formamide **165**, whereas pivaloyl chloride affords the carbamate **166**. Similarly, formaldehyde or pivaldehyde react with cysteine and give thiazolidine-4-carboxylic acid **167** ($\text{R}^1 = \text{H}$), or its *tert*-butyl analogue **167** ($\text{R}^1 = t\text{-Bu}$), respectively. In the case of the carboxylic acid **167** ($\text{R}^1 = \text{H}$) treatment with diazomethane leads to the methyl ester, which can then be N-acylated;^[207–212] surprisingly, there is a drastic difference in the reactivity of the N-acylated derivatives (Scheme 47). Thus, the formamide **168** undergoes clean deprotonation and subsequent C-methylation at low temperatures to yield the methyl ester **169** when treated with lithium diisopropylamide and iodomethane in the presence of 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1H)-one,^[212] but the carbamate **170** is ring opened by this base to afford the lithium sulfide **171**.^[211] Other examples utilize ester-tethered aldehydes for γ -lactam formation to prepare highly constrained bicyclic systems, one application of which is to develop a β -turn peptide mimetic.^[213–215]

Scheme 47 Acylation of Thiazolidines Derived from Cysteine^[206–208,210–212]





(2*R*,4*R*)-3-[(Benzyloxy)carbonyl]-2-*tert*-butyl-1,3-thiazolidine-4-carboxylic Acid (170**); Typical Procedure:**^[210]

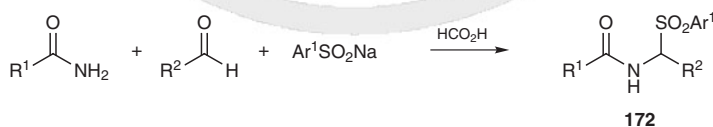
(-)-L-Cysteine hydrochloride monohydrate (100 g, 0.57 mol) was stirred overnight at rt with pivaloyl aldehyde (124 mL, 1.14 mol) in EtOH (500 mL). The soln was concentrated under reduced pressure, and the resulting colorless oil was dried under high vacuum to give the acid **167** ($R^1 = t\text{-Bu}$); yield: ca. 100%. CbzCl (98.3 mL, 0.62 mol) was slowly added dropwise to a soln of this acid (128.4 g, 0.57 mol) in 0.37 M Na_2CO_3 (1.5 L) and the suspension that formed was stirred for 12 h at rt. Excess CbzCl was removed by extraction with Et_2O and the aqueous layer was treated with concd H_3PO_4 to pH 1, and extracted several times with Et_2O . The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure to give the title compound as a colorless oil; yield: 169.4 g (92%); $[\alpha]_D -88.0$ (c 2.9, CHCl_3).

21.3.4.1.3

Method 3:
Mannich Condensations Involving Sulfinic Acids

The sulfide functionality can be converted by straightforward oxidation into the corresponding sulfoxides and sulfones, expanding the synthetic utility of amides containing α -sulfur substituents. An alternative method involves displacement of the acyloxy substituent in *N*-(1-acyloxyalkyl) amides by use of sodium sulfinate in an analogous manner to Section 21.3.4.1.1.^[182] Another general method involves Mannich condensations of sulfinic acids or sulfonates with aldehydes and amides, carbamates, or sulfonamides). In the case of an amide and an aldehyde the addition of sodium 4-toluenesulfinate leads to the *N*-(1-arylsulfonylalkyl) amides **172** ($\text{Ar}^1 = 4\text{-Tol}$) (Scheme 48).^[216,217] Such amides and their carbamate analogues are stable and can be stored at room temperature, provided exposure to traces of acid is avoided. They are versatile α -amidoalkylating agents owing to the excellent nucleofugal properties of the sulfonyl group under mild conditions.

Scheme 48 Mannich Condensations of Aldehydes, Amides, and Sulfonates^[216,217]



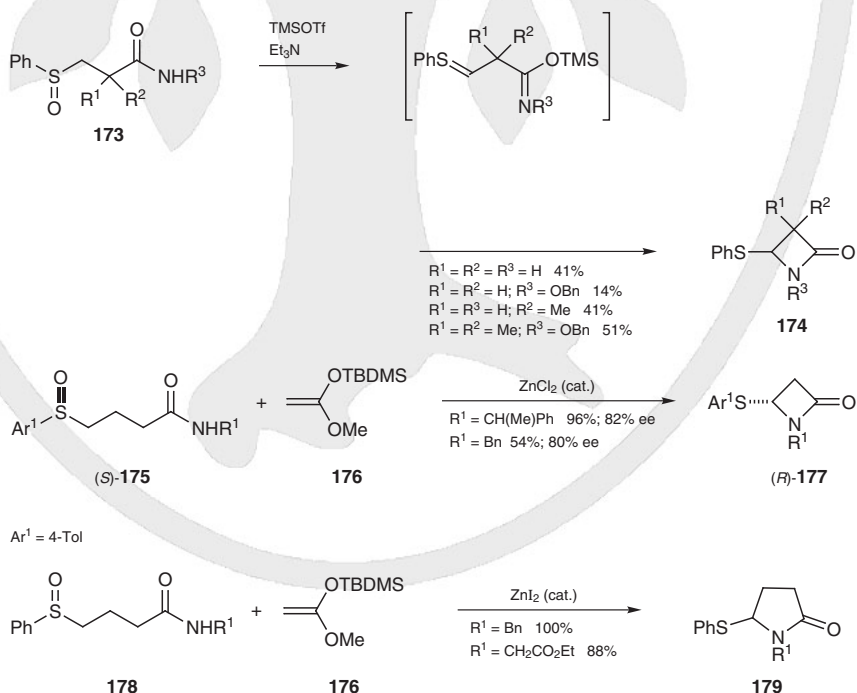
(Acylamino)methyl 4-Toluenesulfonates 172 (Ar¹ = 4-Tol); General Procedure:^[216]

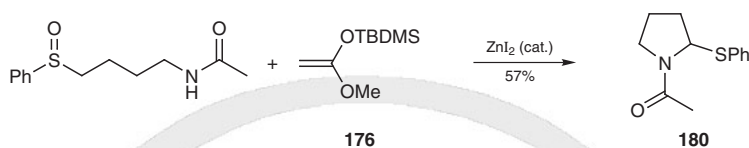
A mixture of sodium 4-toluenesulfinate (20 mmol), an aldehyde (22 mmol), and an amide (20 mmol) in H₂O (20 mL) was acidified with HCO₂H (5 mL) and then heated for 5 h at 80 °C. After the mixture had been allowed to cool, the 4-toluenesulfonate partly crystallized out and was collected by filtration. The aqueous filtrate was carefully neutralized with 2 M NaOH, extracted with CH₂Cl₂, and the combined extracts were dried (MgSO₄). The solvent was removed under reduced pressure to give an additional quantity of the title compound.

21.3.4.1.3.1

Variation 1:**Pummerer Reactions of Amido Sulfoxides**

In place of Mannich-type condensations the Pummerer reactions of certain amido sulfoxides afford 2-phenylsulfanyl substituted lactams in poor to excellent yields.^[218–223] The requisite thionium ions for an intramolecular Pummerer reaction can be generated by using the reagents trimethylsilyl trifluoromethanesulfonate and triethylamine, as in the conversions of the sulfoxides **173** into the azetidinones **174** (Scheme 49). The diastereoselectivity of this type of cyclization has been examined, and for the sulfoxide **173** (R¹ = R³ = H; R² = Me) the ratio of the *cis/trans* products **174** (R¹ = R³ = H; R² = Me) is 2.7:1.^[218] The use of O-silylated ketene acetals, such as the methoxyethene (**176**), in the presence of a catalytic amount of zinc(II) chloride or zinc(II) iodide is particularly effective.^[219] For example, implementation of this procedure gives the azetidin-2-ones **177** from the chiral sulfoxides **175**. In a similar manner the sulfoxides **178** afford the phenylsulfanylpyrrolidinones **179** and **180** (Scheme 49). Although the precise mechanistic details are unknown for the intramolecular asymmetric Pummerer reaction, the formation of a transient dihydroisothiazolone, subsequent to silylation of the sulfoxide, and a formal 1,2-rearrangement is likely.^[220]

Scheme 49 Intramolecular Pummerer Reactions of Amido Sulfoxides^[218–220]

**4-(Phenylsulfanyl)azetidin-2-one (174, $R^1 = R^2 = R^3 = H$); Typical Procedure:**^[218]

Et_3N (0.25 mL, 1.8 mmol) and TMSOTf (0.35 mL, 1.8 mmol) were added to the sulfoxide (**173**, $R^1 = R^2 = R^3 = H$; 99 mg, 0.5 mmol) in CH_2Cl_2 (20 mL) at -20°C . The mixture was stirred at -20°C for 15 min, and then quenched with 5% NaHCO_3 . The organic layer was washed with 0.5% aq HCl and brine, and then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a colorless oil, which was purified by preparative TLC (silica gel, $\text{MeOH}/\text{CH}_2\text{Cl}_2$ 1:19); yield: 37 mg (41%); mp $72\text{--}73^\circ\text{C}$ (recrystallized from Et_2O). Some starting material (18%) was also recovered, plus (*E*)-3-(phenylsulfanyl)propenenitrile (8%).

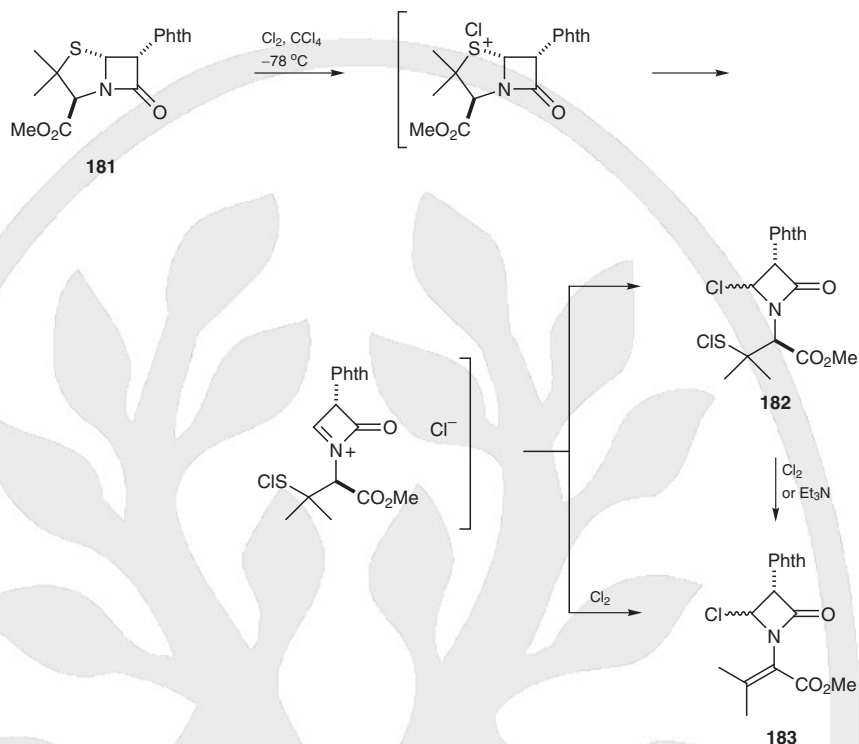
21.3.4.2

Applications of Product Subclass 4 in Organic Synthesis

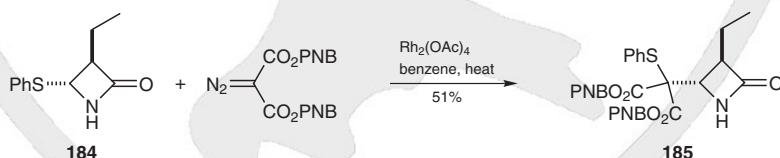
21.3.4.2.1

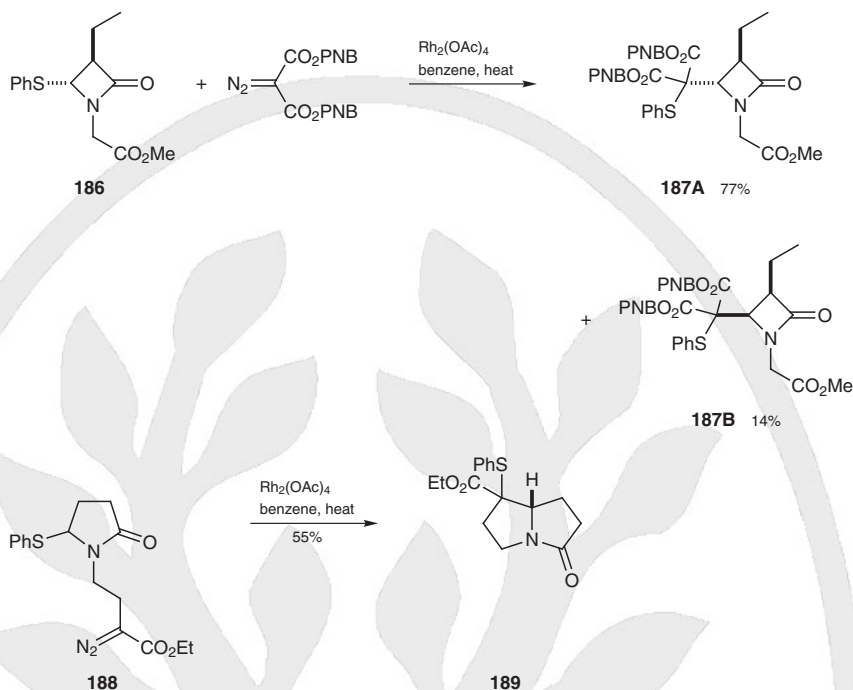
**Method 1:
Ring Cleavage via *N*-Acyliminium Ions**

Upon activation of the sulfur-bearing functions of α -alkylsulfanyl amides and carbamates the *N*-acyliminium ions are readily generated. Examples of this type of cleavage are involved in the electrophilic opening of the thiazolidine ring in penicillins; thus, treatment of methyl 6-phthalimidopenicillanate (**181**) with 1 equivalent of chlorine, or thionyl chloride in carbon tetrachloride at room temperature gives the chloroazetidinone **182** as a 4:1 epimeric mixture in nearly quantitative yield. When 2 equivalents of the electrophile are used the sulfur atom is lost and the *N*-vinyl analogue **183** is obtained; alternatively, this last compound can be formed when the sulfenyl chloride **182** is treated with triethylamine (Scheme 50).^[224]

Scheme 50 Cleavage of Methyl 6-Phthalimidopenicillanate via an *N*-Acyliminium Ion^[224]

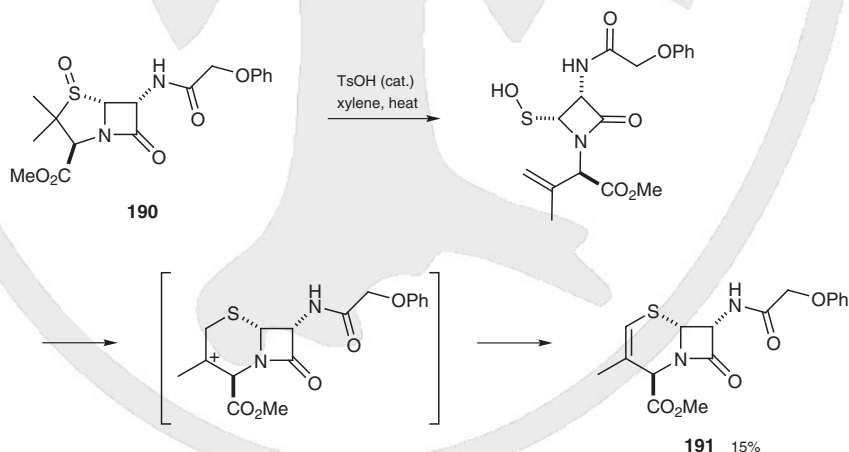
Various thiophilic reagents have been used to induce thioether cleavage and these include mercury(II) acetate,^[225] chloramine-T,^[226] alkynylzinc reagents,^[227] copper(II) acetate,^[228] and boron trifluoride–acetic acid complex.^[221] Another approach involves the generation of sulfonium ylides, by employing diazo compounds in the presence of appropriate transition metal ions [e.g., copper(II) or rhodium(II)].^[229–233] Alkylations are then possible as demonstrated in the formation of the diesters **185** and **187A/B** from the azetidinones **184** and **186**, respectively, in the presence of di(4-nitrobenzyl) malonate.^[230] With α -diazoacetates, 4-oxazetidinones are formed instead.^[230] In the case of the diazoacetate **188** intramolecular cyclization occurs leading to the hexahydropyrrolizin-3(3*H*)-one **189** (Scheme 51).^[232]

Scheme 51 Generation of Sulfonium Ylides from Carbenoid Species^[229–233]



The oxidation of a sulfur atom (to the sulfoxide or sulfone equivalents) allows additional elaborations. One classical example is the Morin rearrangement of the sulfoxide **190** to the cephalosporin **191** under typical Pummerer rearrangement conditions (Scheme 52).^[223,234–236] Here the starting material can be regarded as one of the least expensive natural products, whereas the cephalosporin is not readily available in large quantities from fermentation. A similar transformation has been noted during studies directed toward the synthesis of a spiroquinazoline.^[237]

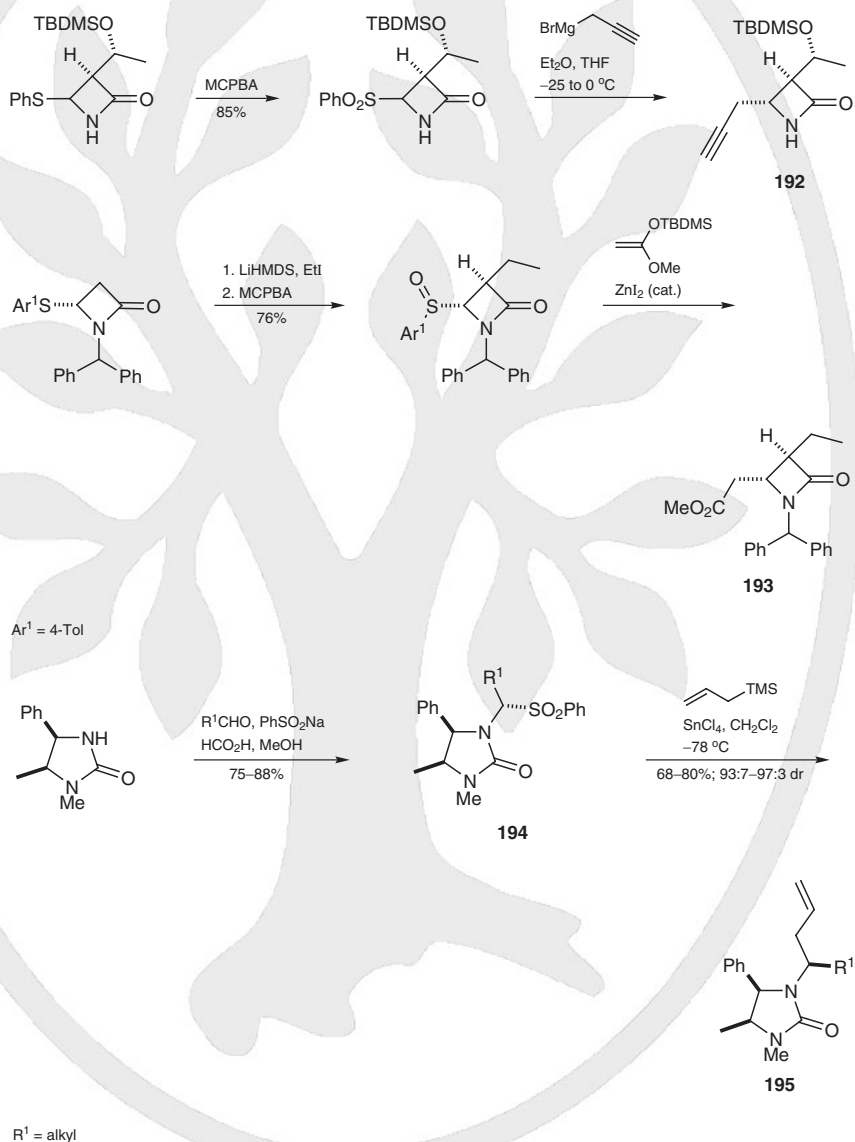
Scheme 52 Morin Rearrangement of a Penicillin under Pummerer Conditions^[223,234–236]

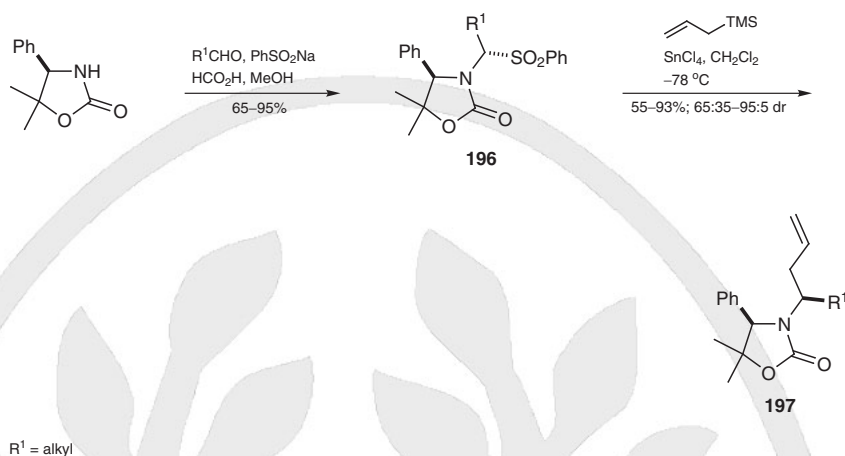


A number of carbon and heteroatom nucleophiles readily undergo displacement reactions with α -sulfonylalkylated amides and carbamates, including β -lactams. These reactions often proceed in high yields under mild conditions^[203,220,238] and two typical examples are depicted in Scheme 53, where the final products are the azetidinones **192**^[203] and **193**.^[220] Another study focuses on 2-phenylsulfonylated pyrrolidines and piperidines,

and typical nucleophiles include organozinc reagents, silyl enol ethers, silyl ketene acetals, allylsilanes, and trimethylsilyl cyanide in the presence of a Lewis acid.^[238] Efficient elimination to enamides is also achieved by the action of magnesium bromide and triethylamine under sonication.^[238,239] In work dealing with asymmetric induction by means of chiral auxiliaries,^[240–242] the imidazolidin-2-ones **194** react with prop-2-en-1-yltrimethylsilane to afford the propenylated products **195**,^[240] with the opposite diastereofacial bias to that shown by the oxazolidinones **196**, which combine with the same reagent to afford the propenes **197** (Scheme 53).^[241]

Scheme 53 Substitution Reactions of α -Sulfonyl and α -Sulfanylalkyl Amides^[203,220,240,241]



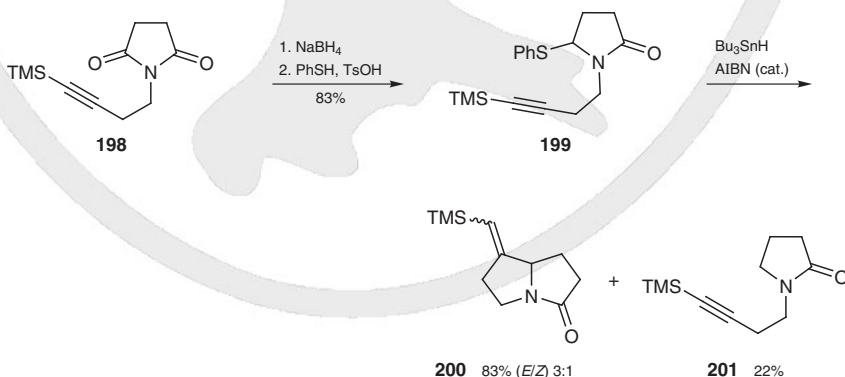


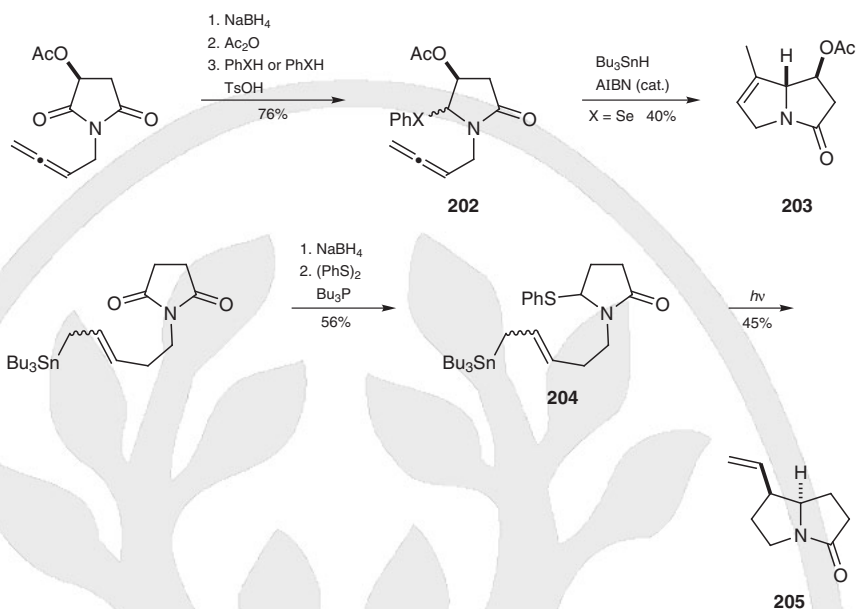
21.3.4.2.2

Method 2: Generation of α -Acylamino Radicals

The generation of α -acylamino radicals represents another useful application of *N*-(α -aryl-sulfanylalkyl) amides.^[20,162,204,205,243–246] For example, when the sulfide **199**, obtained from the pyrrolidone **198** by sodium borohydride reduction in the presence of benzene thiol, is reacted with tributyltin hydride and a catalytic amount of 2,2'-azobisisobutyronitrile cyclization takes place to form the isomeric hexahydropyrrolizinones **200**, but some reductive desulfurization also occurs affording the pyrrolidone **201** (Scheme 54).^[243] Similar treatment of *N*-(α -arylsulfanylalkyl) amides or the cognate seleno derivatives with tributyltin hydride and subsequent intramolecular addition of the resultant α -acylamino radicals to tethered alkenes, alkynes, and allenes have been explored in the syntheses of a wide variety of alkaloids and β -lactams. Although radical cyclization cannot be achieved with the sulfide **202** ($X = \text{S}$) (because of preferential addition of tributyltin radical to the allene side chain), radical generation and cyclization does proceed with its selenium analogue **202** ($X = \text{Se}$) to afford the bicyclic acetate **203**.^[244] An alternative procedure employs photochemical rather than chemically induced cleavage of the C—Sn bond and, for example, the sulfide **204** can be cyclized to the hexahydropyrrolizinone **205** when it is irradiated in a Pyrex vessel; unfortunately the yield is only 45% (Scheme 54).^[246]

Scheme 54 Generation and Synthetic Applications of α -Acylamino Radicals^[243–246]





The sulfides can be readily oxidized to the corresponding sulfones. Owing to the ability of the sulfone function to stabilize a negative charge and to undergo reductive desulfonylation,^[239] α -amido or α -amino carbanions can be readily generated in situ from the appropriate substrates and used for synthetic applications.^[247,248]

21.3.5 Product Subclass 5: *N*-(1-Phosphoniumalkyl) or *N*-(1-Phosphonylalkyl) Amides and Carbamates

21.3.5.1 Synthesis of Product Subclass 5

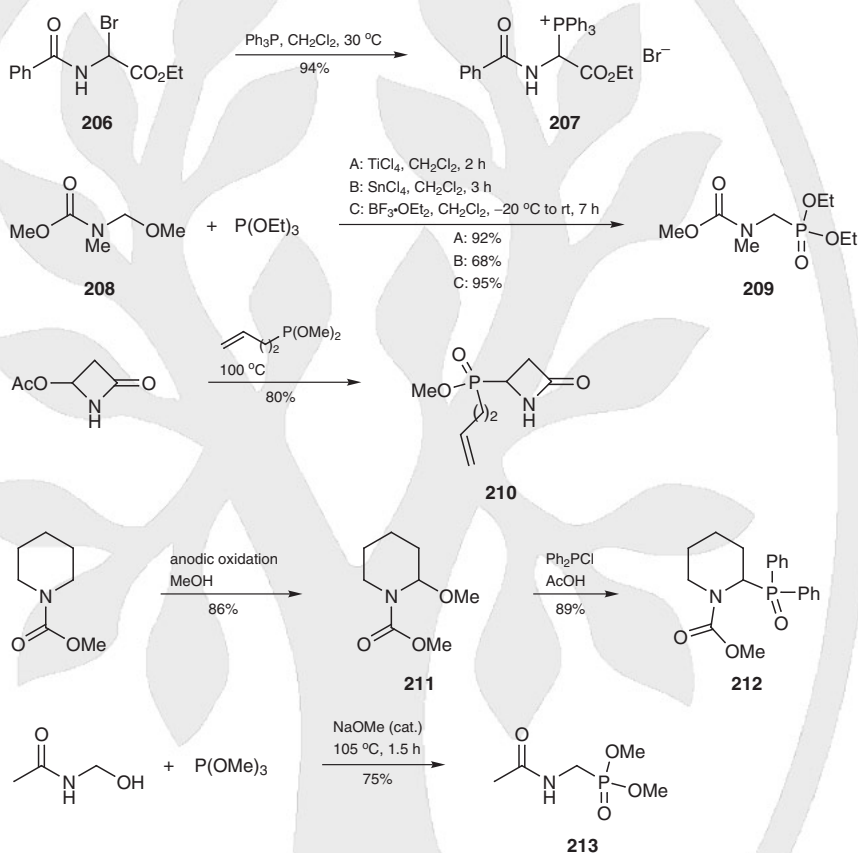
A large number of aminoalkylphosphonic acids and their *N*-acyl derivatives, along with related members of phosphorus-based acid families, have been prepared, since they are known to possess fungicidal, herbicidal, insecticidal, and antibacterial activity. Applications include uses as peptide isosteres, enzyme inhibitors, and as haptens in catalytic antibody synthesis. As synthons, their main uses are in Wittig alkenations. Generation of α -acylamino carbanions is also possible under the influence of electron-withdrawing functionalities such as phosphine oxides.

21.3.5.1.1 Method 1: Displacement by Phosphine or Phosphite

A phosphorus substituent can be readily introduced at the α -position of an amide or a carbamate by the displacement of a suitable leaving group by a phosphine or a phosphite. Treatment of the bromide **206** with triphenylphosphine, for example, provides the corresponding phosphonium salt **207** in 94% yield.^[24,249,250] Similarly, the Arbuzov reaction of phosphites can be achieved under thermal or Lewis acid mediated conditions depending on the nature of the substituents;^[251,252] thus, in the case of triethyl phosphite the carbamate **208** can be reacted under a variety of Lewis acid conditions (Methods A–C) to afford the diethyl phosphonate **209** (Scheme 55), but the reaction fails when the Lewis Acid is zinc(II) chloride.^[251] In an example of a thermal process 4-acetoxiazetidinone can be transformed into the azetidinone phosphonate **210** by heating it with but-3-enyl(dimethyl) phosphonite (Scheme 55).^[252] Other frequently used nucleophiles include chloro(diphenyl)phosphine, alkyl phosphonites, and bis(trimethylsilyl)ethoxycarbonylphosphon-

ite that may be used in the preparations of the respective phosphine oxide, phosphinic acid, and phosphonous acid derivatives.^[253–256] Illustrations include the reaction of the carbamate **211** (which is available by the electrochemical α -methoxylation of methyl piperidine-1-carboxylate) with chlorodiphenylphosphine to afford the phosphonate **212**,^[253] and the combination of *N*-hydroxymethylacetamide with trimethyl phosphite to give its dimethylphosphonomethyl derivative **213** (Scheme 55).^[257] Products such as these are amenable to further functional group manipulations.

Scheme 55 Reactions of α -Alkoxy Amides and Carbamates with Phosphines and Phosphites^[249,251–253,257]



Methyl [(Diethoxyphosphonyl)methyl]methyl Carbamate (209); Typical Procedure:^[251]

Method C: $\text{BF}_3 \cdot \text{OEt}_2$ (10 mmol) was added dropwise to the carbamate **208** (10 mmol) and $\text{P}(\text{OEt})_3$ (10 mmol) in CH_2Cl_2 (20 mL) at -20°C . The mixture was allowed to warm to rt, stirred for an additional 7 h, before being poured into H_2O and then extracted with CH_2Cl_2 . The extracts were dried (MgSO_4), concentrated under reduced pressure, and the residue was distilled to give the title compound; yield: 95%.

21.3.5.1.2

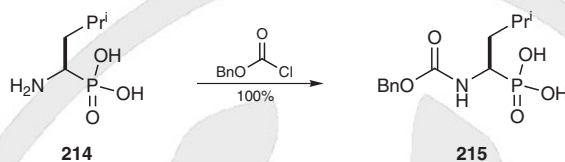
Method 2:

Acylation of Amino Phosphonic and Phosphinic Acids

A reverse mode of reaction is possible as, for example, by the amination of (dibenzylphosphono)methyl trifluoromethanesulfonate, and this is particularly useful with unhindered, nucleophilic amines affording free amino phosphonic and phosphinic acid derivatives.^[258] Subsequent acylation of the product amines provides access to corresponding

amides and carbamates.^[255,259–261] An acylation of this type is the reaction of the aminophosphonic acid **214** with benzyloxycarbonyl chloride to yield the carbamate **215** (Scheme 56).^[260]

Scheme 56 N-Acylation of Aminophosphonic Acids^[260]

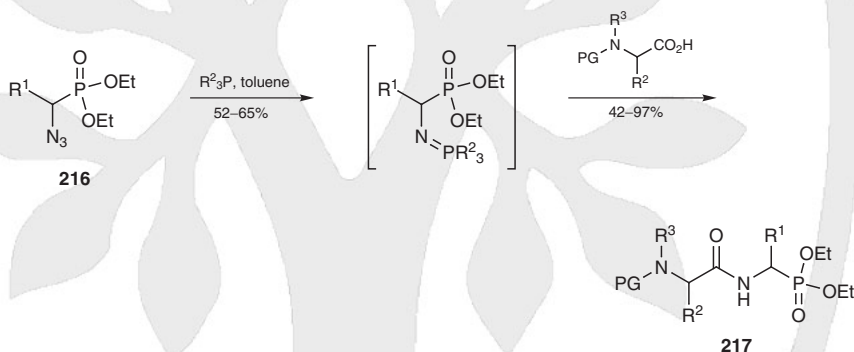


21.3.5.1.2.1

Variation 1: Staudinger Reactions of 1-Azidoalkylphosphonates

An alternate method for acylation can be realized through the Staudinger reactions of 1-azidoalkylphosphonates, which are easily prepared from the Mitsunobu reactions of 1-hydroxyalkylphosphonates with hydrazoic acid; thus, in the presence of a trialkylphosphine coupling of the diethyl azidophosphonate **216** with N-protected amino acids gives a convenient synthesis of the appropriate phosphonodipeptides **217** in moderate to good yields (Scheme 57).^[262]

Scheme 57 A Staudinger Approach to Phosphonodipeptides^[262]



Phosphonopeptides **217**; General Procedure:^[262]

1 M Me_3P (0.004 mol) in toluene was slowly added to a cooled (ice-water bath) soln of a diethyl 1-azidoalkylphosphonate (0.003 mol) in anhyd toluene (5 mL). Vigorous evolution of N_2 was observed. The water bath was removed and the soln was stirred for 1 h at rt. An N-protected amino acid (0.0036 mol) was then added in one portion, and the mixture was stirred at rt until TLC indicated complete disappearance of the starting material. After excess Me_3P had been removed under reduced pressure, the residue was diluted with toluene (100 mL), washed successively with H_2O (2 mL), 5% HCl (2 mL), H_2O (2 mL), 5% NaHCO_3 (2×2 mL), and H_2O (2 mL), and dried (Na_2SO_4). The toluene was evaporated and the residual volatile material was removed at $40^\circ\text{C}/0.04$ Torr to give the desired phosphonodipeptide.

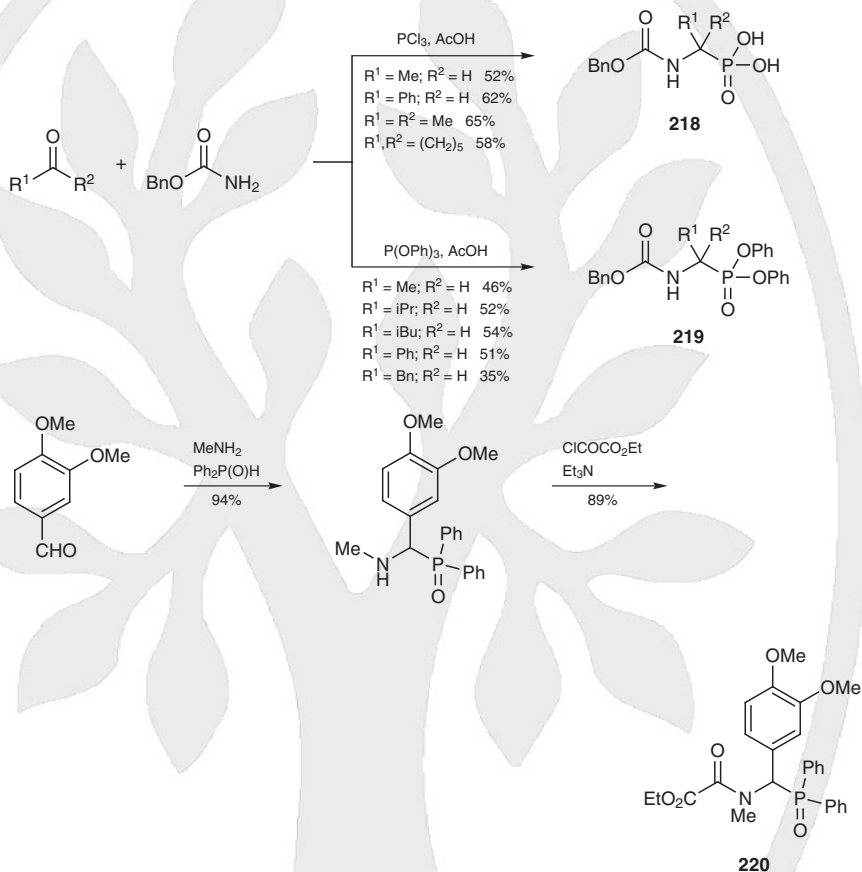
21.3.5.1.3

Method 3: Three-Component Coupling of Carbonyls, Amides, and Phosphorus-Based Nucleophiles

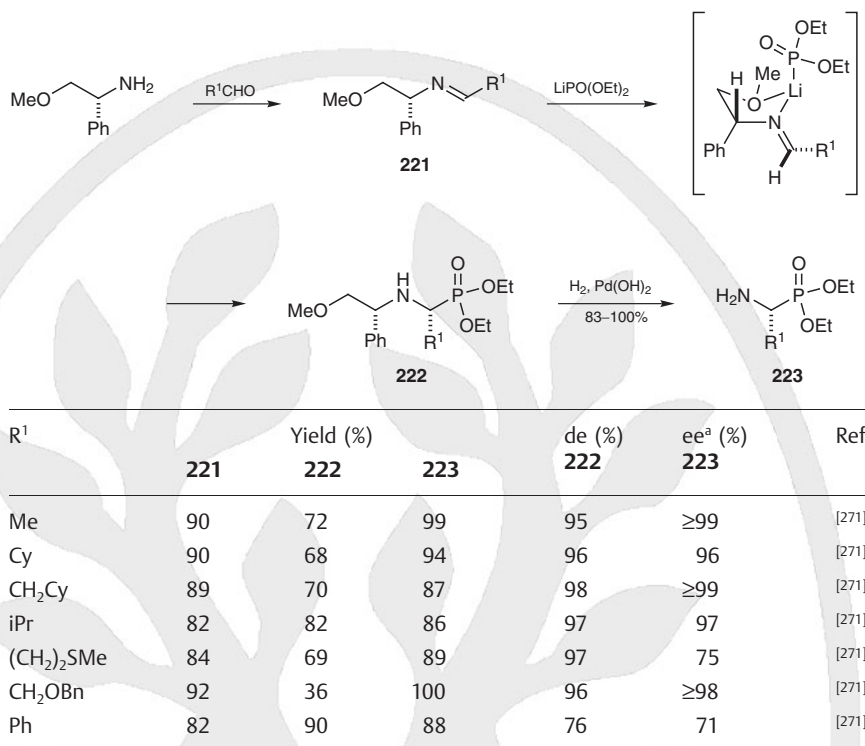
A versatile method, first reported in 1974, stems from a three-component condensation reaction involving an aldehyde or a ketone, an amide or a urea, and a phosphite.^[263] This

attractive procedure, which can also use other phosphorus-based nucleophiles (e.g., phosphorus trichloride, dialkyl phosphates, alkylphosphonites, etc), has since been extensively investigated.^[264–268] Examples of this procedure leading to the phosphonic acids **218** and the diphenyl phosphonates **219** are depicted in Scheme 58,^[264–266] together with the synthesis of the oxamate **220** by the *N*-acylation of the product from 3,4-dimethoxybenzaldehyde, methylamine and diphenylphosphine oxide.^[261]

Scheme 58 Three-Component Coupling Approach to α -Acylaminophosphonic Acids or Phosphonates^[261,264–266]



Also effective for convenient access to 1-aminoalkylphosphonic acid and phosphonous acid derivatives are Mannich-type condensations that employ amines in lieu of carbamates or ureas.^[258,268–270] As discussed in Section 21.3.5.1.2, acylation allows the formation of functionalized amides suitable for further elaboration.^[261] Central to the utilization of α -aminophosphonic acids as surrogates of biologically active amino acids is their availability in high enantiomeric purity. An efficient, enantioselective method has been developed by employing a chelating metal ion; the combined use of lithium diethyl phosphite (in place of its protio counterpart) and scalemic imines **221** derived from (*R*)- or (*S*)-2-phenylglycinol ethers provides α -aminophosphonates **222** in excellent yields and high diastereoselectivity.^[271,272] The observed diastereofacial selectivity is in accord with a rigid, five-membered chelate of the lithium cation held by the ether oxygen and the imine nitrogen, where the phosphite anion adds to the imine double bond away from the phenyl group. Subsequent removal of the chiral auxiliary is effected by hydrogenolysis to provide the aminophosphonate **223** without epimerization at the α -carbon atom (Scheme 59).

Scheme 59 Enantioselective Syntheses of α -Aminophosphonates^[271]

^a Enantiomeric excess determined from the Mosher's ester.

There are many related studies on asymmetric synthesis,^[273–275] including those that use Oppolzer's sultam.^[276]

Diphenyl 1-(N-Benzyloxycarbonyl)aminoalkylphosphonates 219 (R² = H); General Procedure:^[265]

A mixture of P(OPh)₃ (0.1 mol), freshly distilled aldehyde (0.15 mol), and benzyl carbamate (0.1 mol) in glacial AcOH (15 mL) was stirred for 1 h until the exothermic reaction had subsided. The mixture was then heated at 80–85 °C for 1 h, and volatile products were removed under reduced pressure with gentle heating. The oily residue was redissolved in MeOH (180 mL) and the soln was left at –10 °C to induce the crystallization of the product.

Diethyl {(1R)-1-[(1R)-(2-Methoxy-1-phenylethyl)amino]ethyl}phosphonate (222, R¹ = Me); Typical Procedure:^[271]

Freshly distilled MeCHO (0.3 mL, 5.37 mmol) was added to a soln of (–)-(1R)-2-methoxy-1-phenylethanamine (202 mg, 1.33 mmol) in benzene (2 mL) (**CAUTION: carcinogen**) at 0 °C. The mixture was allowed to warm to rt, and then it was treated with Na₂SO₄. The resulting mixture was then stirred for 1 h, filtered, and concentrated under reduced pressure to provide the imine **221** as a colorless oil, which was used immediately; yield: 212 mg (90%).

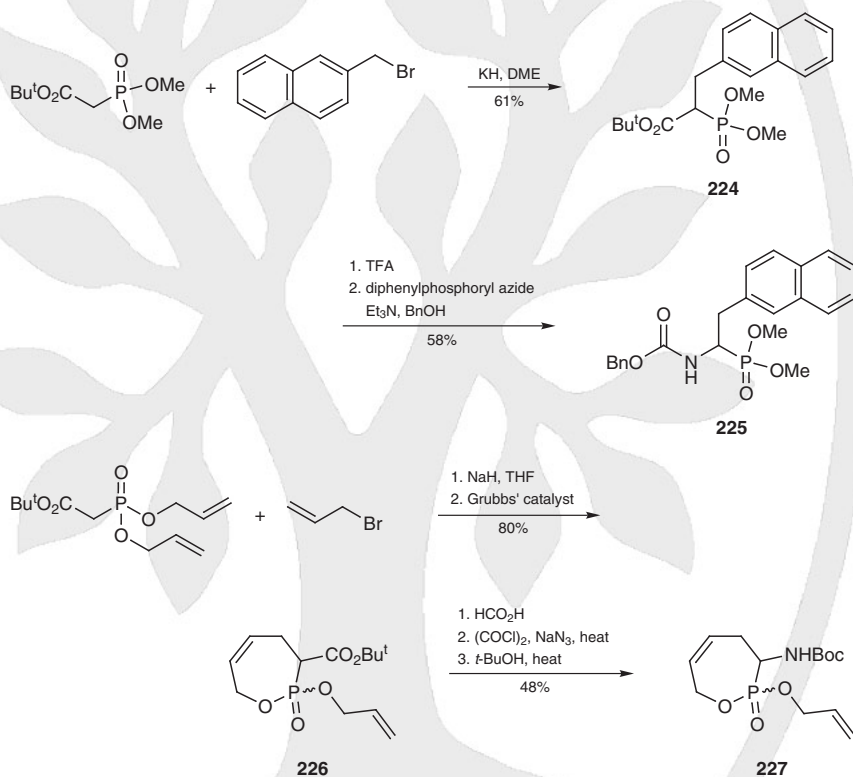
1.59 M BuLi (0.72 mmol) in hexane was added dropwise to freshly distilled P(OEt)₃ (0.31 mL, 2.4 mmol) in THF (1.5 mL) at 0 °C. The soln was stirred for an additional 30 min at 0 °C, warmed to rt, and then added via cannula to a soln of **221** in THF (2.4 mL). The mixture was stirred at rt for 21 h, and then quenched with H₂O (5 mL). After most of the THF had been removed under reduced pressure, the aqueous layer was saturated with NaCl, filtered, and concentrated under reduced pressure. Flash chromatography (silica

gel, EtOAc/hexanes 1:1 to 2:1) gave **222** as a colorless oil; yield: 275 mg (72%); $[\alpha]_D -83$ (c 2.5, CHCl_3).

21.3.5.1.4

Method 4:**Curtius Rearrangements of α -Acylazido Phosphonates**

Another convenient and general method makes use of the Curtius rearrangement of α -acylazido phosphonates; thus the ester **224** can be converted into the *N*-acylamino phosphonate **225** via its acyl azide.^[277] The diastereomeric tetrahydro-1,2-oxaphosphepin-3-yl]carbamate **227** is formed similarly from the corresponding ester **226**, which is prepared as a 1:1 diastereomeric mixture by the reaction of allyl bromide and *tert*-butyl phosphorylacetate (Scheme 60).^[278]

Scheme 60 Curtius Rearrangements of Acylazido Phosphonates^[277,278]

2-(Allyloxy)-3-*tert*-butyloxycarbonylamino-2,3,4,7-tetrahydro-1,2-oxaphosphepine 2-Oxide (227**):**^[278]

The *tert*-butyl ester **226** was dissolved in neat HCO_2H . Once hydrolysis was complete, excess HCO_2H was removed under reduced pressure. The crude acid was then redissolved in CH_2Cl_2 in a round-bottomed flask equipped with a drying tube and the soln was cooled to 0°C . Oxalyl chloride was added along with one drop of DMF, which caused the evolution of CO_2 . Once the evolution of gas had subsided the mixture was concentrated under reduced pressure and the residue was redissolved in MeCN and treated with sat. aq NaN_3 . The mixture was stirred for 5 h, diluted with EtOAc, washed with H_2O , and then brine, dried (Na_2SO_4), and then concentrated under reduced pressure. The crude acyl azide was dissolved in toluene in a flame-dried pressure tube, 4-Å molecular sieves were added, and the mixture was refluxed. Once the acyl azide had reacted and an isocyanate peak was de-

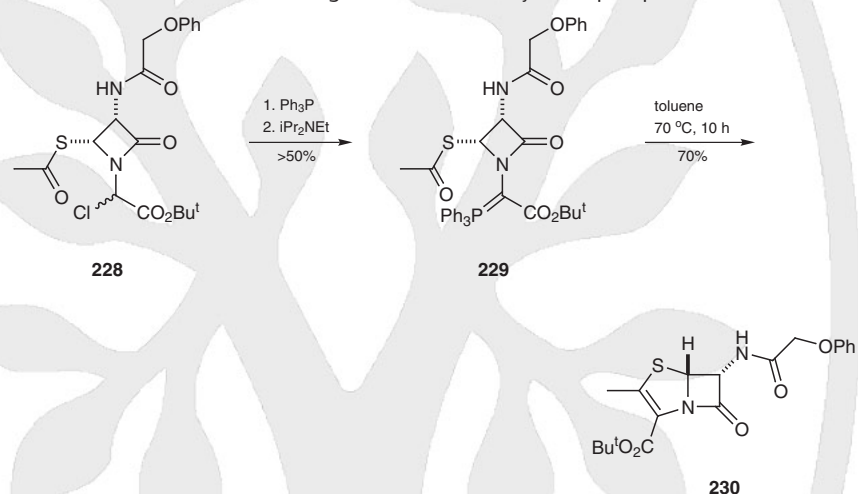
tected in the IR spectrum, excess *t*-BuOH was added and the mixture was refluxed until the reaction was complete (IR). The crude carbamate was purified by flash column chromatography (silica gel, hexanes/EtOAc); yield: 48%.

21.3.5.2 Applications of Product Subclass 5 in Organic Synthesis

21.3.5.2.1 Method 1: Wittig Alkenation

The most common application of this subclass is in Wittig alkenation reactions; an illustration starts with the chloride **228**, which is converted into the phosphorane **229** with triphenylphosphine.^[24] Intramolecular cyclization of the phosphorane to the penem **230** is induced by heating in toluene (Scheme 61). This type of cyclization is very sensitive to steric and electronic effects.

Scheme 61 Intramolecular Wittig Alkenation of *N*-Acylaminophosphoranes^[24]



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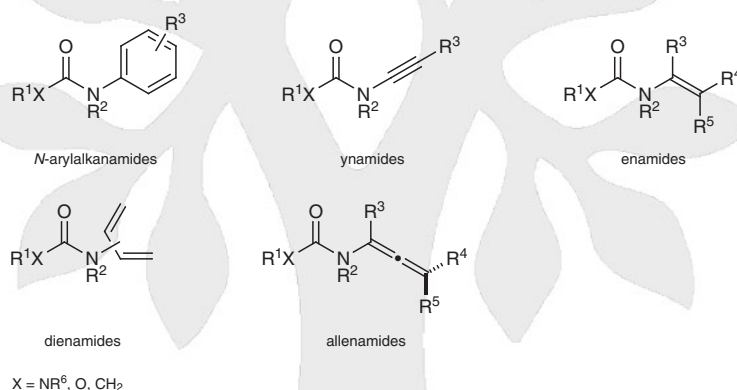
Product Class 4: *N*-Arylalkanamides, Ynamides, Enamides, Dienamides, and Allenamides

M. R. Tracey, R. P. Hsung, J. Antoline, K. C. M. Kurtz, L. Shen, B. W. Slafer,
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General Introduction

The types of *N*-arylalkanamides, ynamides, enamides, dienamides, and allenamides that form the main subject of this review are shown in Scheme 1; all are based upon an acylated amino unit where the substituent X can be a methylene group, or groups, an oxygen atom or a substituted amino group; thus, for the last two cases the definition alkanamide is widened to include certain carbamates, ureas, and other related compounds. Similarly, in important new methodology, the chemistry of ynamides and ynesulfonamides is intimately intertwined and a discussion of synthetic routes to both types is necessary.

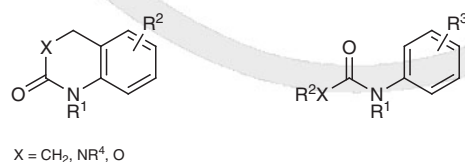
Scheme 1 Structures of *N*-Arylalkanamides, Ynamides, Enamides, Dienamides, and Allenamides



Product Subclass 1: *N*-Arylalkanamides

N-Arylalkanamides are compounds that have an aromatic ring bonded to the nitrogen atom of an alkanamide. The amide function can be fused to the aromatic ring (cyclic) as well as being independent of the aromatic ring (acyclic). Scheme 2 shows both structural types.

Scheme 2 Structures of *N*-Arylalkanamides



21.4.1.1 Synthesis of Product Subclass 1

As many N-arylalkanamides occur as natural products and some are potential drug candidates, there is a need for efficient, low-cost methods of preparation. N-Acylation of the requisite aromatic amine is probably the easiest approach, as long as the parent aniline is readily available. Direct N-arylation of an alkanamide is more difficult, but many investigations of the coupling of aryl halides and alkanamides have been undertaken; where possible aryl chlorides are employed as the least expensive of the aryl halides. Although aryl halides react with various amides under Ullmann-type conditions, the conditions are often harsh [e.g., the Goldberg reaction, requires stoichiometric amounts of copper salts, high temperatures (>150 °C), and polar solvents, such as dimethylformamide, collidine, or pyridine]. In these procedures only relatively stable compounds survive,^[1] and a number of milder palladium-catalyzed processes can now be used that, when appropriate, replace the traditional copper-mediated procedures. However, these innovations tend to reflect the piecemeal development of coupling systems for individual amide equivalents and aryl halides rather than a complete solution to the problem. Thus, few of these newer methods are universally applicable, the most efficient being those used for intramolecular amidations. The lack of a convenient general catalytic synthesis for intermolecular amidations is partly overcome by using a palladium(II) acetate/9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos) system; this accelerates the coupling of most amide types to electron-poor aryl halides.^[2] For electron-rich aryl halides a dipalladium tris(dibenzylideneacetone)/9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene catalyst is somewhat more effective. The common feature of both catalyst systems is the incorporation of an aryl ring from the 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos) ligand into the product by an aryl group exchange reaction.^[2]

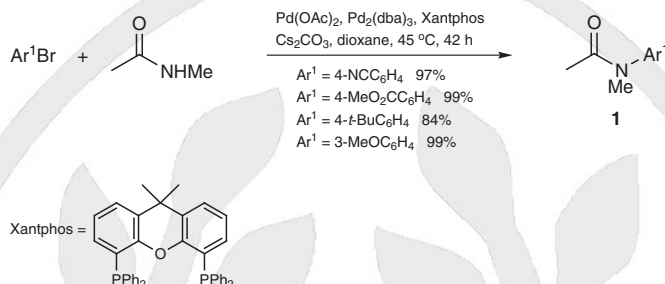
Despite significant improvements in the palladium-mediated N-arylation of alkanamides, some limitations still remain.^[3] Most notably, the amidation of electron-rich or *ortho*-substituted electronically neutral aryl halides is difficult; another factor is the high cost of palladium. In addition, the removal of palladium residues from polar reaction products, particularly at a late stage in the synthesis of a pharmaceutical substance, can be challenging.^[3] An important alternative procedure uses aryl boronic acids as arylating agents instead of aryl halides.^[4] Unfortunately, even this method has a limited scope and it suffers from high cost and the poor availability of functionalized boronic acids. In the search for a more general, cost-effective, and efficient method, interest has shifted back to copper-mediated coupling reactions. The traditional Goldberg amidation reaction employs simple copper salts or often copper metal as the catalyst and there was little interest in the deliberate use of ligands to facilitate copper-catalyzed aryl amidations.^[3] However, a combination of air-stable copper(I) iodide and inexpensive 1,2-diamine ligands in the presence of potassium phosphate or carbonate is now shown to provide an extremely efficient and general catalytic system for the N-amidation of aryl and heteroaryl iodides and bromides and, in some cases, even unactivated aryl chlorides.^[3] This methodology may prove to be an excellent complement to palladium-catalyzed methodology, particularly if aryl halides containing strongly electron-donating groups, or secondary amino functions are to be amidated.

21.4.1.1.1 Method 1: Palladium-Catalyzed Intermolecular Coupling of Aryl Halides and Amides

A method for the formation of an intermolecular C—N bond uses a palladium-catalyzed coupling of aryl halides and amides to afford the N-aryl-N-methylacetamide **1**. A 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos) ligand is required, together with cesium carbonate as the base (Scheme 3).^[2,5] The key to the reaction is probably the ability of Xantphos to undergo transcoordination to the palladium atom of the catalyst,

presumably enhancing the ultimate coupling of the aryl ring and the amidic functional group.

Scheme 3 Intermolecular Palladium(II)-Catalyzed C–N Bond Formation between Aryl Halides and Amides^[5]



***N*-(Aryl)-*N*-methylacetamides 1; General Procedure:**^[5]

A flame-dried resealable Schlenk tube was charged with $\text{Pd}(\text{OAc})_2$ or $\text{Pd}_2(\text{dba})_3$ (1 mol% of Pd), Xantphos (L/Pd = 1.5), the aryl halide (1 equiv), *N*-methylacetamide (1.2 equiv), and Cs_2CO_3 (1.4 equiv). Before the experiment the Schlenk tube containing the solids was capped with a rubber septum, evacuated, and backfilled with argon; the evacuation/backfilling cycle was repeated. The liquid reactants and anhyd 1,4-dioxane (1 mL·mmol^{−1} aryl halide) were then added by syringe through the septum. The septum was replaced by a Teflon screw cap. The Schlenk tube was sealed, and the mixture was stirred at 100 °C until the starting aryl halide had been completely consumed (GC). The mixture was then allowed to cool to rt, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel).

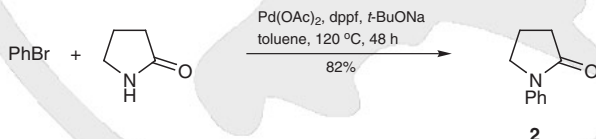
21.4.1.1.1

Variation 1:

Palladium(II)-Catalyzed Intermolecular Coupling of Aryl Halides and Lactams

An early palladium(II)-catalyzed intermolecular C–N bond formation leading to lactams utilizes both electron-rich and electron-poor aryl bromides.^[6] An example is shown in Scheme 4, 1-phenylpyrrolidin-2-one (**2**) is formed in 82% yield from the coupling of bromobenzene and pyrrolidin-2-one. In general the method is only applicable to the amidation of lactams of a certain ring size and success may also depend upon their latent acidity.

Scheme 4 Intermolecular Palladium(II)-Catalyzed C–N Bond Formation between an Aryl Halide and a Lactam^[6]



1-Phenylpyrrolidin-2-one (2); Typical Procedure:^[6]

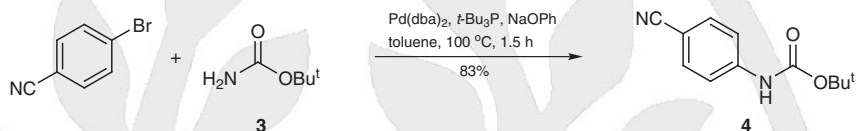
Pyrrolidin-2-one (151 μL , 2.0 mmol), PhBr (316 μL , 3.0 mmol), dppf (66 mg, 0.12 mmol), $\text{Pd}(\text{OAc})_2$ (22 mg, 0.10 mmol), and *t*-BuONa (0.29 g, 3.0 mmol) in toluene (10 mL) under N_2 were heated in a sealed tube at 120 °C for 48 h. The mixture was cooled to rt, filtered through Celite, and concentrated onto silica gel. Chromatography (silica gel, EtOAc/hexanes 1:1) afforded a colorless solid; yield: 0.27 g (82%).

21.4.1.1.1.2

Variation 2:
Palladium(0)-Catalyzed Intermolecular Coupling of Aryl Halides and Carbamates

The first palladium(0)-catalyzed amidations of carbamates used bis(dibenzylideneacetone)palladium and the bulky, electron-rich tris(*tert*-butyl)phosphine ligand.^[7] With the carbamate **3** the arylated product **4** is obtained (Scheme 5). However, this methodology is only effective with acyclic carbamates, indole, and various other amines.

Scheme 5 Intermolecular Palladium(0)-Catalyzed C–N Bond Formation between an Aryl Halide and a Carbamate^[7]


***tert*-Butyl N-(4-Cyanophenyl)carbamate (4); Typical Procedure:**^[7]

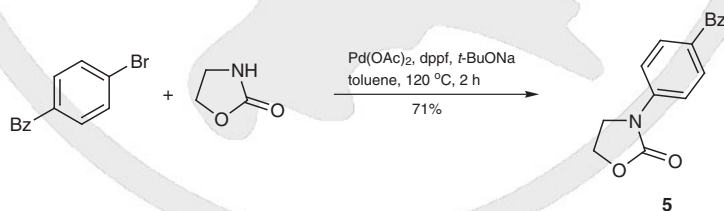
A small round-bottomed flask, contained within a dry box, was charged with Pd(dba)₂ (14.4 mg, 0.025 mmol, 2.5 mol%), *t*-Bu₃P (10.1 mg, 0.05 mmol), NaOPh (174 mg, 1.5 mmol), 4-bromobenzonitrile (1.00 mmol), and *tert*-butyl carbamate (176 mg, 1.5 mmol). Toluene (3 mL) was added to give a thick suspension. The flask was sealed with a septum, removed from the dry box, and placed in an oil bath and heated to 100 °C. The reaction was vigorously stirred until the aryl halide was completely consumed (GC). The toluene was removed under reduced pressure and the residue loaded onto silica gel. Chromatography (silica gel, CH₂Cl₂/hexanes 1:1) gave a pale yellow oil. Crystallization (hexanes) gave colorless needles; yield: 83%.

21.4.1.1.1.3

Variation 3:
Palladium(II)-Catalyzed Intermolecular Coupling of Aryl Halides and Oxazolidinones

Five- and six-membered cyclic carbamates can be synthesized through palladium(II)-catalyzed N-arylations with aryl bromides in the presence of various phosphine ligands. Unfortunately, the method is only really effective with N-unsubstituted oxazolidinones. For example, a coupling reaction between oxazolidin-2-one and 4-bromobenzophenone affords the arylated compound **5** in 71% yield (Scheme 6).^[8]

Scheme 6 Intermolecular Palladium(II)-Catalyzed C–N Bond Formation between an Aryl Halide and Oxazolidin-2-one^[8]


N-(4-Benzoylphenyl)oxazolidin-2-one (5):^[8]

A soln of dppf (25.0 mg, 0.045 mmol) and Pd(OAc)₂ (8.4 mg, 0.019 mmol) in toluene (1 mL) was stirred under argon at rt for 20 min. 4-Bromobenzophenone (150 mg, 0.75 mmol), oxazolidin-2-one (82 mg, 1.13 mmol), *t*-BuONa (101.4 mg, 1.056 mmol), and toluene (2 mL)

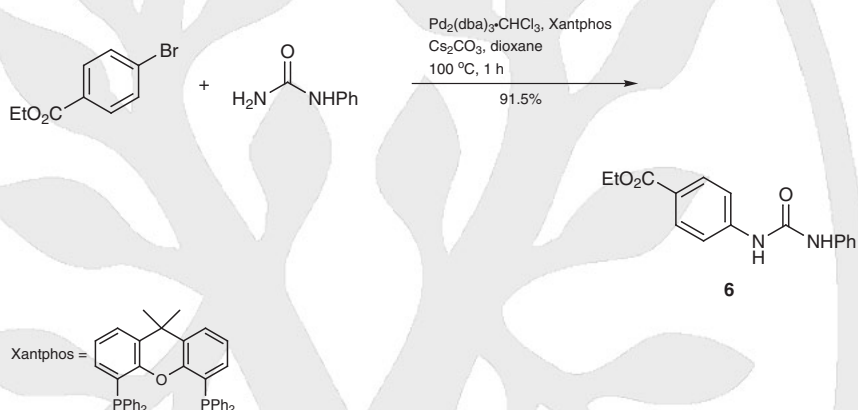
were added. The mixture was heated at 120 °C for 2 h, and then cooled, diluted with EtOAc, and washed with H₂O. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, EtOAc/hexane 2:3); yield: 109 mg (71%).

21.4.1.1.1.4

Variation 4:**Palladium(0)-Catalyzed Intermolecular Coupling of Aryl Halides and Ureas**

The palladium(0)-catalyzed coupling of *N*-phenylurea with an aryl bromide using dipalladium tris(dibenzylideneacetone), chloroform, and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos) provides an *N*-arylated urea **6** in good yield (Scheme 7);^[9] however, once again, the method is restricted to the formation of this type of product.

Scheme 7 Intermolecular Palladium(0)-Catalyzed C—N Bond Formation between an Aryl Halide and a Urea^[9]

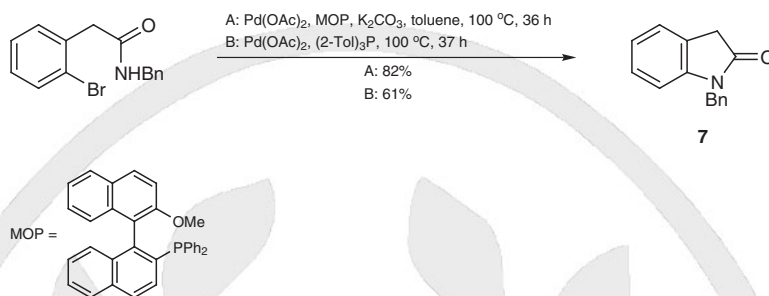
***N*-[(4-Ethoxycarbonyl)phenyl]-*N'*-phenylurea (**6**):^[9]**

Ethyl 4-bromobenzoate (143 mg, 0.60 mmol), *N*-phenylurea (81 mg, 0.60 mmol), Pd₂(dba)₃·CHCl₃ (6.3 mg, 0.006 mmol), Xantphos (11.0 mg, 0.019 mmol), dry Cs₂CO₃ (280 mg, 0.858 mmol), and 1,4-dioxane (3 mL) were purged with argon and placed in an argon-filled reactor. The mixture was degassed by several freeze–pump–thaw cycles and the reactor was again filled with a positive pressure of argon. The mixture was stirred and heated at 100 °C. After 1 h, TLC showed the absence of the starting urea. The mixture was cooled to rt, diluted with EtOAc (40 mL), filtered, and concentrated to dryness. The residue was purified by chromatography (silica gel, EtOAc/petroleum ether 1:2) to give a colorless solid; yield: 156 mg (91.5%).

21.4.1.1.1.5

Variation 5:**Palladium(II)-Catalyzed Intramolecular Cyclization of Amides**

An intramolecular palladium(II)-catalyzed C—N bond-formation procedure is used in an efficient synthesis of five-, six-, and seven-membered rings from *N*-monosubstituted amides or carbamates. In some cases the choice of the ligand and the base has been optimized; so that, for example, 2-methoxy-2'-diphenylphosphinyl-1,1'-binaphthalene (MOP) proves to be a superior ligand (Method A) than monodentate phosphorus-based ligands (Method B) for the formation of the indol-2(3*H*)-one **7** from *N*-benzyl-2-(2-bromophenyl)acetamide (Scheme 8).^[10,11]

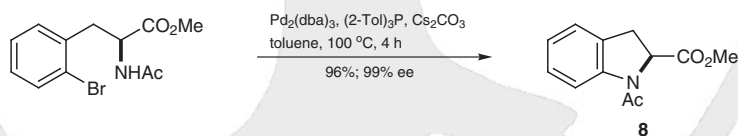
Scheme 8 Synthesis of an N-Arylalkanamide by Palladium(II)-Catalyzed Intramolecular Cyclization of an N-Monosubstituted Amide^[10,11]**1-Benzylindol-2(3H)-one (7):**^[10]

Method B: A Schlenk tube was charged with *N*-benzyl-2-(2-bromophenyl)acetamide (152 mg, 0.50 mmol), K_2CO_3 (97 mg, 0.7 mmol), $\text{Pd}_2(\text{dba})_3$ (9.0 mg, 0.01 mmol, 4.1 mol% Pd), and (2-Tol) $_3\text{P}$ (12.0 mg, 0.04 mmol). The tube was purged with argon for 1 min, then toluene (4 mL) was added, and the mixture was heated to 100 °C with stirring. After 15 h, GC showed that some substrate still remained. $\text{Pd}_2(\text{dba})_3$ (5.0 mg, 0.005 mmol, 2.0 mol% Pd), and (2-Tol) $_3\text{P}$ (6.0 mg, 0.02 mmol) were added. The mixture was heated for an additional 22 h, after which the starting material had been completely consumed (GC). The soln was allowed to cool to rt, diluted with Et_2O (15 mL), filtered, and concentrated. The crude product was then purified by chromatography (silica gel, EtOAc/hexane 1:8) to give a yellow oil; yield: 68 mg (61%).

21.4.1.1.1.6

Variation 6:**Palladium(II)-Catalyzed Intramolecular Cyclization of Chiral Amides**

A similar palladium(II)-catalyzed intramolecular cyclization can be extended to chiral amides and used to prepare enantiomerically enriched aniline derivatives in excellent yields and enantioselectivities.^[12,13] Thus, methyl *N*-acetyl-2-bromo-L-phenylalaninate can be cyclized to give the dihydroindole **8** in excellent stereoselectivity and yield (Scheme 9).^[12]

Scheme 9 Synthesis of an N-Arylalkanamide by Palladium(II)-Catalyzed Intramolecular Cyclization of an Optically Active Amide^[12]**Methyl (2S)-1-Acetyl-2,3-dihydroindole-2-carboxylate (8):**^[12]

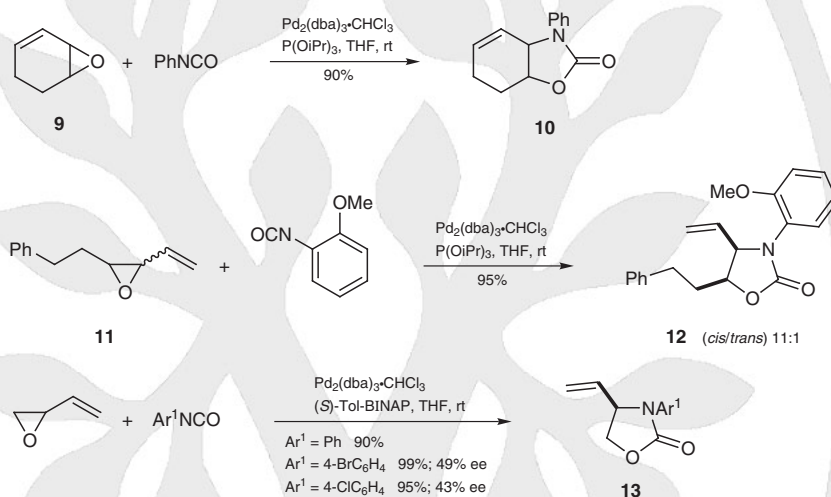
Methyl *N*-acetyl-2-bromo-L-phenylalaninate (100 mg, 0.33 mmol), $\text{Pd}_2(\text{dba})_3$ (15.7 mg, 0.017 mmol, 10 mol% Pd), (2-Tol) $_3\text{P}$ (18.3 mg, 0.06 mmol, 20 mol%), and Cs_2CO_3 (215 mg, 0.66 mmol) in toluene (0.6 mL) were heated to 100 °C in an oven-dried Schlenk flask under N_2 for 15 h. The mixture was then cooled to rt and purified directly by chromatography (EtOAc/hexanes 1:1) to give a clear oil; yield: 69 mg (96%).

21.4.1.1.2

Method 2:**Palladium(0)-Catalyzed Coupling of Epoxides and Isocyanates via a π -Allyl Intermediate**

A versatile synthesis of carbamates is achieved through palladium-mediated hydroxyaminations of monoepoxides with aryl isocyanates. It proceeds via the formation of a π -allyl intermediate.^[13] In the case of the epoxide **9** the product is the tetrahydrobenzoxazol-2(3*H*)-one **10**, and when a mixture of the *cis*- and *trans*-epoxides **11** is used the isomers are stereoselectively converted into the *cis*-oxazolidin-2-one **12**. In further examples 2-vinylloxirane reacts with aryl isocyanates and a chiral phosphine ligand to give the oxazolidin-2-ones, e.g. **13**; however, the enantioselectivity is poor (Scheme 10).^[14,15]

Scheme 10 Synthesis of *N*-Arylalkanamides by Palladium(0)-Catalyzed Coupling of Epoxides and Isocyanates via a π -Allyl Intermediate^[13–15]

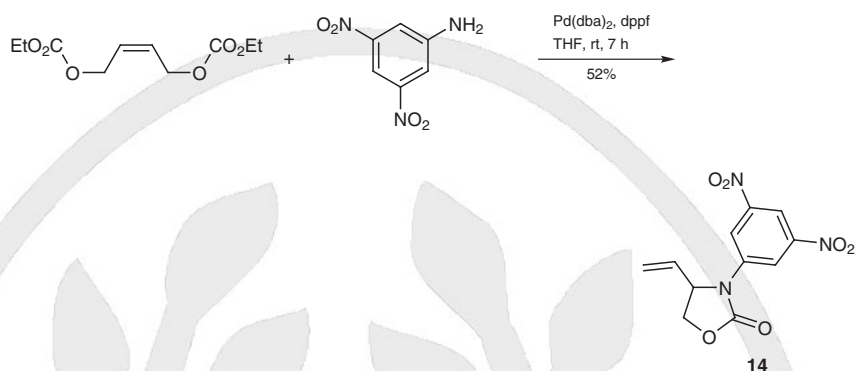
**(4*R*)-3-Aryl-4-vinylloxazolidin-2-ones **13**; General Procedure:**^[15]

A mixture of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (0.03 mmol), a chiral phosphine ligand (0.06 mmol), and THF was stirred at rt for 30 min. 2-Vinylloxirane (1.0 mmol) and an aryl isocyanate (1.0 mmol) were added, and the mixture was stirred under N_2 at either rt or 10 °C, until the conversion of the isocyanate was complete (as monitored by the replacement of the IR absorption band of the isocyanate function at about $\tilde{\nu}_{\text{max}}$: 2200 cm^{-1} by a band at ca. $\tilde{\nu}_{\text{max}}$: 1750 cm^{-1}). At this point the orange brown soln was concentrated under reduced pressure, and the residue was subjected to preparative TLC (silica gel). The product was again chromatographed to eliminate any residual chiral phosphine ligand and the enantiomeric excess was then determined by analytical HPLC.

21.4.1.1.2.1

Variation 1:**Palladium(0)-Catalyzed Coupling of Dicarbonates and Isocyanates via a π -Allyl Intermediate**

The palladium-catalyzed reactions of anilines (in which the ring is substituted by electron-withdrawing groups) with (*Z*)-but-2-ene-1,4-diyl dicarbonate afford a variety of *N*-aryl-4-vinylloxazolidin-2-ones, e.g. **14** (Scheme 11).^[16,17] Again the reactions proceed through π -allyl intermediates.

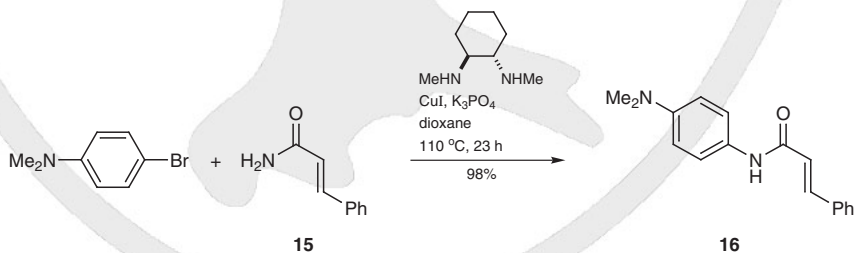
Scheme 11 Synthesis of an *N*-Arylalkanamide by Palladium(0)-Catalyzed Coupling of a Dicarbonate and an Isocyanate through a π -Allyl Intermediate^[17]***N*-(3,5-Dinitrophenyl)-4-vinyloxazolidin-2-one (**14**); Typical Procedure:**^[17]

A degassed soln of (*Z*)-but-2-ene-1,4-diyl dicarbonate (1.27 g, 5.47 mmol) in anhyd THF (5 mL) was added to a stirred and degassed mixture of 3,5-dinitroaniline (0.50 g, 2.73 mmol), Pd(dba)₂ (0.07 g, 0.137 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.23 g, 0.41 mmol), and anhyd THF (10 mL). The mixture was stirred at rt under argon for 7 h and, when the reaction was complete (GC), the solvent was removed, and the residue was purified by column chromatography (silica gel, hexanes to EtOAc/hexanes) to afford a solid; yield: 0.79 g (52%).

21.4.1.1.3

Method 3:**Copper(I)-Catalyzed Intermolecular Coupling of Aryl Halides and Amides (The Goldberg Reaction)**

A modification of the traditional Goldberg reaction^[18] is now available in which aryl bromides are reacted with acetanilides in the presence of copper(I) iodide, potassium phosphate, and diamine ligands to yield the corresponding *N*-arylated amides.^[3,19] This procedure is tolerant of *ortho*-substitution on both the carbocycle of the aryl bromide and that of the acetanilide. An example of this approach is found in the synthesis of the *N*-arylated amide **16** from cinnamamide (**15**) and 4-bromo-*N,N*-dimethylaniline (Scheme 12).^[3]

Scheme 12 Synthesis of an *N*-Arylalkanamide by Intermolecular Copper(I)-Catalyzed C—N Bond Formation between an Aryl Halide and an Amide^[3]***trans*-*N*-[(4-Dimethylamino)phenyl]-3-phenylpropenamide (**16**):**^[3]

A Schlenk tube was charged with CuI (9.6 mg, 0.05 mmol, 5 mol% Cu), 4-bromo-*N,N*-dimethylaniline (201 mg, 1.00 mmol), the amide **15** (178 mg, 1.21 mmol), and K₃PO₄ (430 mg, 2.03 mmol). The tube was evacuated, and backfilled with argon. Racemic *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine (0.1 mmol, 10 mol%) and toluene (1 mL) were add-

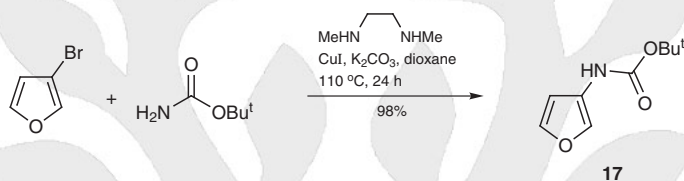
ed under argon. The Schlenk tube was sealed with a Teflon valve and the mixture was stirred at 110 °C for 23 h. The resulting bright yellow suspension was cooled to rt and filtered through a 0.5 × 1-cm column of silica gel (EtOAc/CH₂Cl₂ 1:1). The filtrate was concentrated, and the residue was dissolved in CH₂Cl₂ (10 mL), and purified by chromatography; yield: 260 mg (98%).

21.4.1.1.3.1

Variation 1:**Copper(I)-Catalyzed Intermolecular Coupling of Hetaryl Halides with Carbamates**

Cross-coupling between 3-bromofuran and *tert*-butyl carbamate to give the corresponding *N*-furylated carbamate **17** is achieved^[20] using the conditions described in the previous method,^[3] but with *N,N'*-dimethylethane-1,2-diamine as the ligand (Scheme 13).

Scheme 13 Synthesis of an *N*-Arylalkanamide by Intermolecular Copper(I)-Catalyzed C–N Bond Formation between a Hetaryl Halide and a Carbamate^[20]

***tert*-Butyl *N*-(Furan-3-yl)carbamate (**17**):**^[20]

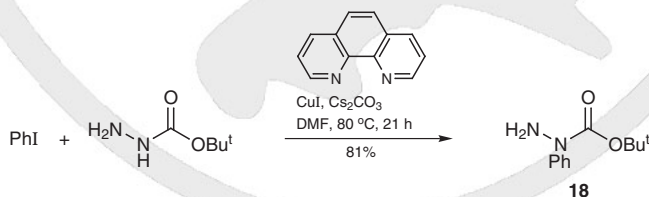
1,4-Dioxane (3 mL), followed by *N,N'*-dimethylethane-1,2-diamine (0.1 mmol, 10 mol%), 3-bromofuran (1.47 g, 1.0 mmol) and *tert*-butyl carbamate (1.2 mmol) were added to CuI (0.1 mmol, 10 mol% Cu) and K₂CO₃ (4.3 mmol) under argon. The mixture was stirred at 110 °C for 24 h, cooled to rt, diluted with CH₂Cl₂ (5 mL), filtered through a short plug of silica gel, and concentrated under reduced pressure. The crude residue was purified by chromatography (silica gel) to give a colorless solid; yield: 0.18 g (98%).

21.4.1.1.3.2

Variation 2:**Copper(I)-Catalyzed Intermolecular Coupling of Aryl Halides and Hydrazides**

The new copper(I)-catalyzed aryl coupling method can be extended to the synthesis of *N*-arylated hydrazides, e.g. **18**, by the use of dimethylformamide as a solvent (Scheme 14). With different types of substituted aryl iodides regioselective coupling can be achieved.^[21]

Scheme 14 Synthesis of an *N*-Arylalkanamide by Intermolecular Copper(I)-Catalyzed C–N Bond Formation between an Aryl Halide and a Hydrazide^[21]

***tert*-Butyl 1-Phenylhydrazinecarboxylate (**18**):**^[21]

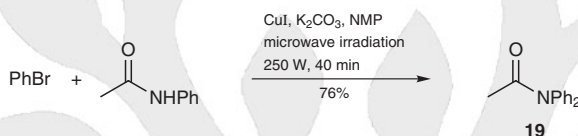
An oven-dried resealable Schlenk tube was charged with CuI (2 mg, 0.01 mmol, 1 mol% Cu), 1,10-phenanthroline (18 mg, 0.1 mmol, 10 mol%), Cs₂CO₃ (456 mg, 1.4 mmol), evacuated and backfilled with argon. *tert*-Butyl hydrazinecarboxylate (159 mg, 1.2 mmol), iodo-

benzene (110 μ L, 1 mmol) and DMF (1 mL) were added under argon. The Schlenk tube was sealed and the mixture was stirred at 80 °C for 21 h. The resulting suspension was cooled to rt and filtered through a silica gel plug (0.5 \times 1 cm) eluting with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography (2 \times 20-cm silica gel column, EtOAc/hexane 1:5) to give a pale yellow oil; yield: 202 mg (81%).

21.4.1.1.3.3 Variation 3: Microwave-Enhanced Goldberg Reaction

The traditional Goldberg procedure is usually quite drastic and unproductive; however, microwave irradiation greatly accelerates the process when 1-methylpyrrolidin-2-one is used as the solvent. For example, *N,N*-diphenylacetamide (**19**) is obtained within 40 minutes when *N*-phenylacetamide is reacted with bromobenzene under these conditions (Scheme 15).^[22]

Scheme 15 Synthesis of an *N*-Arylalkanamide by a Microwave-Enhanced Goldberg Reaction^[22]



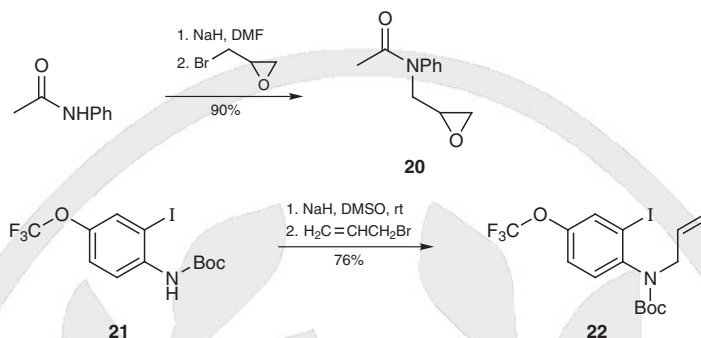
N,N-Diphenylacetamide (**19**):^[22]

CAUTION: Microwave-enhanced Goldberg reactions should be performed in an open reaction system in order that gaseous products can escape, thus avoiding the risk of explosion.

A stirred mixture of PhBr (3.95 mL, 37.5 mmol) and *N*-phenylacetamide (3.38 g, 25.0 mmol), NMP (5.0 mL, 52 mmol), CuI (0.50 g, 2.5 mmol, 0.10 equiv), and dry powdered K₂CO₃ (3.45 g, 25 mmol, 1 equiv) in a three-necked, round-bottomed flask, equipped with a reflux condenser, was irradiated in a microwave oven (Milestone Ethos 900) for 40 min at 250-W power under a gentle stream of N₂. The mixture was cooled to rt and diluted with Et₂O (200 mL). After filtration over Hyflo, the Et₂O layer was successively washed with three portions of 5% aq NaHCO₃. The aqueous layers were extracted with Et₂O, and the organic layer and extracts were dried (MgSO₄), filtered, and concentrated under reduced pressure to produce a brown oil (6.2 g). The oil was purified by chromatography (silica gel, EtOAc/petroleum ether 1:3) to give a colorless solid; yield: 4.0 g (76%).

21.4.1.1.4 Method 4: Alkylation of *N*-Aryl Amides with Alkyl Halides

In principal one of the easiest routes to *N*-arylalkanamides is the *N*-alkylation of arylated amides. There are a number of examples of this type, including the alkylation of acetanilide with epibromohydrin,^[23] and a reaction between the carbamate **21** and allyl bromide;^[24] in both cases sodium hydride is used to deprotonate the starting material. These reactions are shown in Scheme 16, where the products are the epoxide **20** and the allylated amide **22**, respectively. The same methodology can be used to *N*-methylate arylated amides using sodium hydride, or lithium isopropoxide as the base, and iodomethane as the alkylating agent;^[25,26] there is also an example of an intramolecular cyclization involving the displacement of a chloro substituent from the aryl ring of the substrate.^[27]

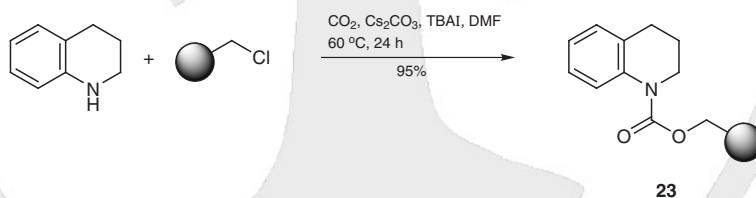
Scheme 16 Synthesis of *N*-Arylalkanamides by *N*-Alkylation of *N*-Arylated Amides^[23,24]***N*-Allyl-*N*-(*tert*-butoxycarbonyl)-2-iodo-4-(trifluoromethoxy)aniline (22):^[24]**

NaH (0.12 g, 3.0 mmol) was added to a soln of carbamate **21** (1.0 g, 2.5 mmol) in DMSO (5 mL) at rt. After 30 min, allyl bromide (0.24 mL, 0.33 g, 2.7 mmol) was added, and the mixture was stirred at rt for 17 h. H₂O (10 mL) was then introduced, the mixture was extracted with Et₂O (3 × 15 mL), the combined extracts were dried (Na₂SO₄), and the solvent was concentrated under reduced pressure. Chromatography of the residue (silica gel, Et₂O/hexane 1:9) gave a pale yellow oil; yield: 0.84 g (76%).

21.4.1.1.4.1

Variation 1:**Generation of Solid-Supported *N*-Arylalkanamides by Three-Component Coupling of *N*-Arylamines, Carbon Dioxide, and Merrifield's Resin**

The synthesis of *N*-arylalkanamides on Merrifield's resin allows the generation of large combinatorial libraries for the rapid screening of such products.^[27] In the formation of the resin-bonded carbamate **23**, 1,2,3,4-tetrahydroquinoline is treated with the chloromethylated resin, carbon dioxide, dimethylformamide, and tetrabutylammonium iodide (Scheme 17). If tetrabutylammonium iodide is absent some direct *N*-alkylation of the starting amine occurs.

Scheme 17 Synthesis of a Merrifield Resin-Bound *N*-Arylalkanamide from an Aryl Amine^[27]**Polymer-Bound 3,4-Dihydroquinoline-1(2H)-carboxylate (23):^[27]**

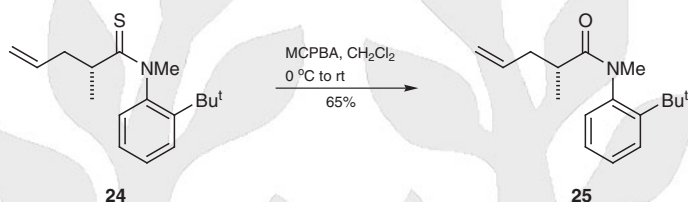
Cs₂CO₃ (2.44 g, 7.5 mmol, 3.75 equiv) and TBAI (2.77 g, 7.5 mmol, 3.75 equiv) were added to 1,2,3,4-tetrahydroquinoline (0.67 g, 5 mmol, 2.5 equiv) in DMF (40 mL) with vigorous stirring. The temperature of the mixture was raised to 60 °C, after which CO₂ was allowed to pass into the stirred suspension at the same temperature for 10 h. Merrifield's resin (1.0 g, 2.0 mmol, 1.0 equiv), was added and the mixture was continually stirred at 60 °C for 12 h, while CO₂ was bubbled in as a continuous stream. The resin was subsequently washed with aliquots (20 mL) of H₂O, MeOH/H₂O (1:1), H₂O, THF, CH₂Cl₂, and MeOH, in this order, and then the solid residue was dried under reduced pressure for 24 h; yield: 1.27 g (95%).

21.4.1.1.5

Method 5:**Oxidation of Thioamides with 3-Chloroperoxybenzoic Acid**

Thioamides are easily prepared, they are stable in air, and they have a number of valuable properties, such as high nucleophilicity, that can be utilized in synthesis; moreover, their ene-thiolates are regiospecifically *S*-alkylated. Thioamides are readily converted into the corresponding amides by treatment with 3-chloroperoxybenzoic acid and, for example, the thioamide **24** affords the amide **25** in 65% yield without loss of stereochemical integrity (Scheme 18).^[28]

Scheme 18 Synthesis of an *N*-Arylalkanamide from the Corresponding Thioamide^[28]



***N*-(2-*tert*-Butylphenyl)-*N*-methyl-(2*R*)-methylpent-4-enamide (**25**):^[28]**

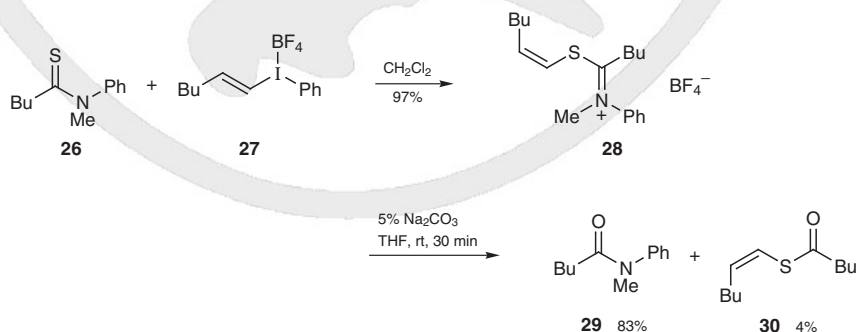
The thioamide **24** (0.11 g, 0.4 mmol) in CH₂Cl₂ (5 mL) was cooled to 0 °C. Purified MCPBA (0.14 g, 0.8 mmol, 2 equiv) was added, and the mixture was stirred at 0 °C for 3 h. The mixture was then slowly warmed to rt. After 2 h of stirring, TLC showed that the starting thioamide had disappeared. Sat. aq NaHCO₃ (2 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 30 mL). The combined extracts were washed with brine (5 mL), dried (MgSO₄), and the solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, EtOAc/petroleum ether 1:4) to give an oil; yield: 0.067 g (65%).

21.4.1.1.5.1

Variation 1:**Oxidation of Thioamides with Vinyl λ³-Iodanes**

Exposure of the tertiary thioamide **26** to (*E*)-hex-1-enyl(phenyl)-λ³-iodane **27** results in a vinylic S_N2 reaction to give the inverted (*Z*)-*S*-vinylthioimidonium salt **28**, which under alkaline hydrolysis affords the amide **29**. The thioester **30**, is obtained as a byproduct (Scheme 19).^[29] The procedure is effective with other thioamides and affords the corresponding amides in high yields. However, when acidic hydrolysis conditions are used thioesters are the main products.

Scheme 19 Synthesis of an *N*-Arylalkanamide from a Thioamide by Electrophilic Attack at the Sulfur Atom and Hydrolysis^[29]



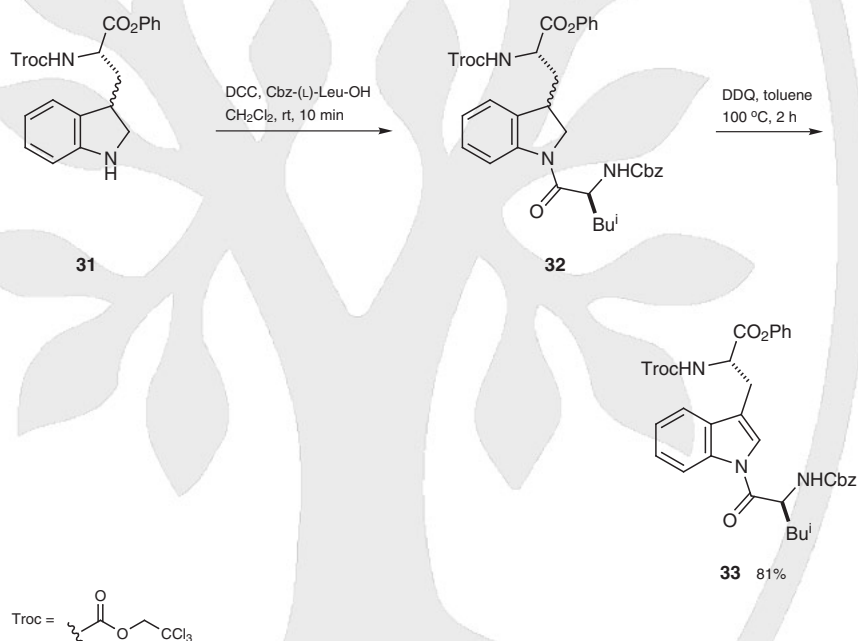
***N*-Methyl-*N*-phenylpentanamide (29):**^[29]

N-Methyl-*N*-phenylcarbothioamide (**26**; 0.29 mmol) was added to a stirred soln of the λ^3 -iodane **27** (0.27 mmol) in CH_2Cl_2 (5 mL) and the mixture was warmed at 50 °C for 17 h. After cooling, the mixture was concentrated. Purification of the crude product by repeated decantation with CH_2Cl_2 /hexane gave the (*Z*)-*S*-vinylthioimidonium tetrafluoroborate **28** (97%) as a colorless oil. The hydrolysis of the tetrafluoroborate **28** was carried out by treatment with 5% Na_2CO_3 in THF at rt for 20 min under N_2 to give the title compound; yield: 83%.

21.4.1.1.6

**Method 6:
Dicyclohexylcarbodiimide Peptide Coupling**

As an illustration of the use of dicyclohexylcarbodiimide in the formation of an amide bond the dihydroindole **31** can be coupled with a protected form of L-leucine to yield the amide **32**, which is then immediately oxidized to the acylated indole **33** in an overall yield of 81% (Scheme 20).^[30]

Scheme 20 Synthesis of an *N*-Arylalkanamide by 1,3-Dicyclohexylcarbodiimide Coupling^[30]**Phenyl *N*-(Benzyloxycarbonyl-L-leucyl)-*N*-(2,2,2-trichloroethoxycarbonyl)-L-tryptophanate (33):**^[30]

DCC (1.44 g, 7.0 mmol) in CH_2Cl_2 (2 mL) was added to *N*-benzyloxycarbonyl-L-leucine (1.77 g, 6.67 mmol) in CH_2Cl_2 (20 mL). After 5 min, a soln of the dihydroindole **31** (3.05 g, 6.67 mmol) in the same solvent was added. The resulting mixture was stirred at 25 °C for 10 min, an insoluble byproduct was removed by filtration, and the filtrate was concentrated under reduced pressure to give the acylated dihydroindole **32** as a colorless oil. This oil was redissolved in toluene (25 mL) and DDQ (2.0 g, 8.8 mmol) was added. The resulting black-red mixture was heated at 110 °C for 2 h. After cooling, the mixture was filtered, and the filtrate was washed with a sat. aq NaHCO_3 (2×30 mL), dried (Na_2SO_4), and concentrated to give a black-red oil. Chromatography (silica gel, EtOAc/ CH_2Cl_2 1:100) gave

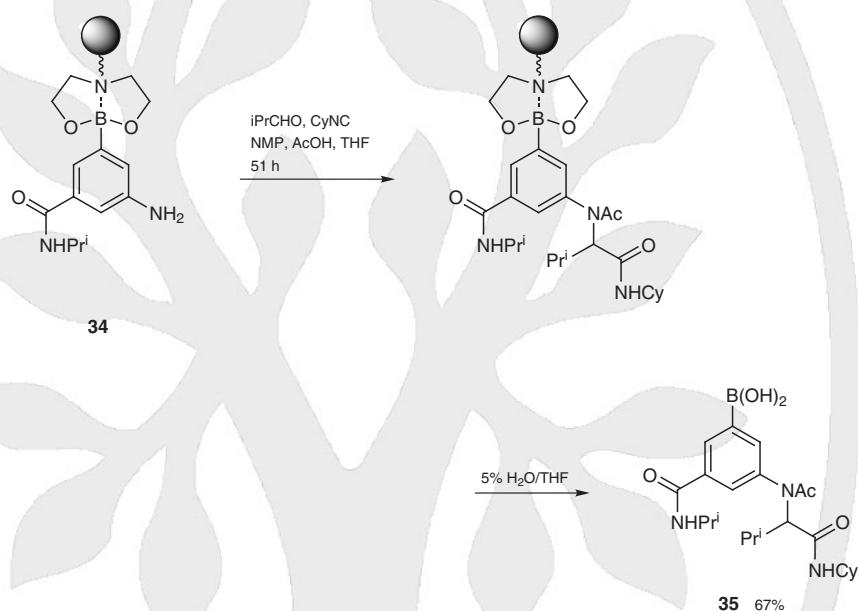
the title compound as a light red oil, which solidified upon refrigeration; yield: 3.78 g (81%).

21.4.1.1.7

Method 7:**Solid-Phase Synthesis of Boronic Acids Containing Amide Functionality via Ugi Reactions**

The resin-supported amine **34** undergoes an Ugi reaction with 2-methylpropanal and cyclohexylisocyanide.^[31] Subsequent removal of the resin provides the boronic acid **35** (Scheme 21). This route can be applied successfully to the synthesis of a large variety of other boronic acids.

Scheme 21 Solid-Phase Synthesis of a Boronated N-Arylalkanamide by the Ugi Reaction^[31]



N-{1-[(N'-Cyclohexylamino)carbonyl]-2-methylpropyl}-{3-(dihydroxyboryl)-5-[(isopropyl-amino)carbonyl]phenyl}acetamide (35**):^[31]**

The resin-bound amine **34** (122 mg, 0.115 mmol; theoretical loading $0.946 \text{ mmol}\cdot\text{g}^{-1}$) was added to a suitable peptide vessel (10 mL) and swollen in NMP (1 mL). 2-Methylpropanal (105 μL , 1.150 mmol), AcOH (66 μL , 1.150 mmol), and CyNC (120 μL , 1.150 mmol) were added in succession, and the vessel was shaken at rt for 51 h. The suspension was drained, and the resin was rinsed with five portions each of THF, CH_2Cl_2 , and THF. The resin-bound boronic acid was cleaved by vortexing the resin in 5% $\text{H}_2\text{O}/\text{THF}$ (2 mL) at rt for 1 min. The product-containing soln was drained and the resin was washed with 5% $\text{H}_2\text{O}/\text{THF}$ ($3 \times 2 \text{ mL}$). The filtrate and washings were combined, concentrated under reduced pressure, and dried under high vacuum overnight to afford a cream solid; yield: 26 mg (67%).

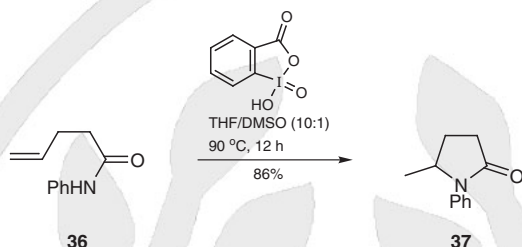
21.4.1.1.8

Method 8:**2-Iodoxybenzoic Acid Mediated Radical Cyclization of N-Arylated Amides and Carbamates**

The 2-iodoxybenzoic acid mediated radical cyclization of suitable aromatic amides and carbamates is used to form N-arylated γ -lactams and oxazolidinones. Although the meth-

od is suitable for the formation of simple heterocycles, such as 5-methyl-1-phenylpyrrolidin-2-one (**37**) from the amide **36** (Scheme 22),^[32] it can also be used to construct complex polycycles.

Scheme 22 Synthesis of an *N*-Arylalkanamide by Radical Cyclization Using 2-Iodoxybenzoic Acid^[32]



5-Methyl-1-phenylpyrrolidin-2-one (37**); Typical Procedure:**^[32]

Iodoxybenzoic acid (2.0 equiv) was added to a soln of the amide **36** (0.1 mmol) in THF/DMSO (10:1, 4 mL total volume). The soln was placed in a sealed tube and heated for 12 h at 90 °C, followed by the addition of more iodoxybenzoic acid (2.0 equiv), and heating for a further 12-h period at the same temperature. The mixture was diluted with EtOAc, and washed with 5% aq NaHCO₃, and then brine, dried (Mg₂SO₄), and concentrated. The residue was purified by preparative TLC (silica gel, EtOAc/hexane 1:2); yield: 86%.

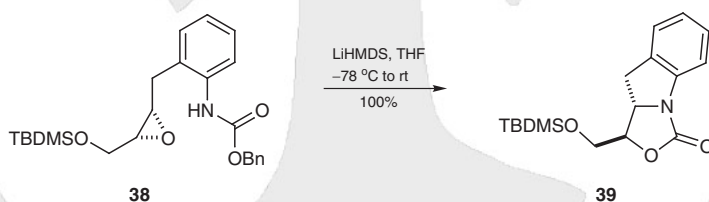
21.4.1.1.9

Method 9:

Intramolecular Epoxide Opening and Oxazolidinone Formation

A stereoselective intramolecular cyclization of the epoxide **38** to the tricyclic carbamate **39** occurs when it is treated with lithium hexamethyldisilazide (Scheme 23). Crucial to the success of this type of ring closure is the protection of a side-chain hydroxy group, in this example this protection is provided by a *tert*-butyldimethylsilyl unit.^[33]

Scheme 23 Synthesis of an *N*-Arylalkanamide by Intramolecular Epoxide Ring Opening and Oxazolidinone Formation^[33]



(1*R*,9*aS*)-1-[(*tert*-Butyldimethylsiloxy)methyl]-9,9*a*-dihydro-1*H*-[1,3]oxazolo[3,4-*a*]indol-3-one (39**):**^[33]

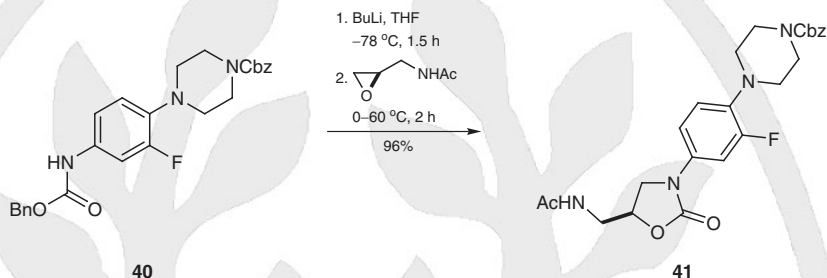
1.0 M LiHMDS in hexanes (1.14 mL) was added dropwise to the epoxysilane **38** (408 mg, 0.95 mmol) in THF (5 mL), at -78 °C. The temperature was maintained at -78 °C for 2 h, then the dry ice bath was allowed to slowly warm to rt, and stirring of the mixture was continued overnight. The soln was then cooled in an ice bath and quenched with sat. aq NH₄Cl, before it was extracted with EtOAc (4 × 5 mL). The extracts were combined, washed with brine, dried (Na₂SO₄), and evaporated to leave a yellow oil, which slowly crystallized upon standing; yield: 304 mg (100%). An analytically pure sample was obtained by recrystallization (hexanes) as colorless feathery crystals.

21.4.1.1.9.1

Variation 1:**Intermolecular Epoxide Opening and Oxazolidinone Formation**

The enantioselective synthesis of the N-arylated oxazolidinone **41** from the carbamate **40** and N-[(2S)-oxiran-2-ylmethyl]acetamide is achieved by base-catalyzed epoxide opening, followed by cyclization of an N-alkylated intermediate (Scheme 24).^[34]

Scheme 24 Synthesis of an N-Arylalkanamide by Intermolecular Epoxide Opening and Oxazolidinone Formation^[34]



This method is employed in the syntheses of many drug candidates including PNU-100592,^[34] PNU-100766,^[35] DuP 721,^[35] PNU-171933,^[36] and various analogues.^[37] The procedure may be slightly modified by using carbamates in place of epoxides for the syntheses of befloxatone analogues.^[38]

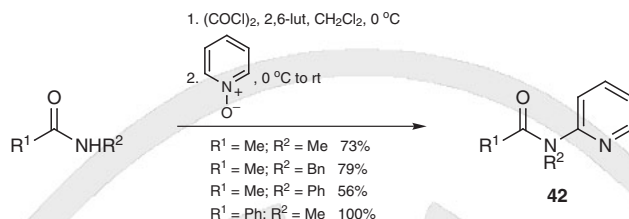
N-[(5S)-3-{3-Fluoro-4-[(4-benzylloxycarbonyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl]methylacetamide (41**):**^[34]

An oven-dried flask (10 mL) was charged with the carbamate **40** (156 mg, 0.0336 mmol). The flask was sealed and flushed with N₂. The starting material was taken up in THF (1.7 mL), cooled to -78 °C and 2.5 M BuLi (150 μL, 0.371 mmol) was added dropwise. The light yellow soln was stirred at -78 °C for 1.5 h, and then the flask was placed in an ice bath. A soln of N-[(2S)-oxiran-2-ylmethyl]acetamide (77.6 mg, 0.675 mmol) in THF (200 μL) was added and the resulting mixture was allowed to warm to rt over 30 min. Gentle heating at 60 °C for 2 h resulted in the formation of a suspension. This was allowed to cool to rt over 1 h, and then it was treated with sat. aq NH₄Cl. The resulting emulsion was rendered basic by the addition of sat. aq NaHCO₃, and then it was extracted three times with EtOAc/THF (1:1). The combined extracts were dried (Na₂SO₄), filtered, and concentrated to give a residue that was triturated (warm 30% EtOAc in hexanes) to give a nearly colorless solid; yield: 151 mg (96%).

21.4.1.1.10

Method 10:**N-Pyridinylation of Amides with Pyridine 1-Oxide**

Imidoyl chlorides are formed from the reactions of N-monosubstituted amides with a stoichiometric amount of oxalyl chloride and 2,6-lutidine in dichloromethane at 0 °C. Upon warming the mixture to room temperature in the presence of pyridine-1-oxide a rapid conversion into N-(2-pyridyl) amides **42** takes place with moderate to excellent efficiency (Scheme 25).^[39]

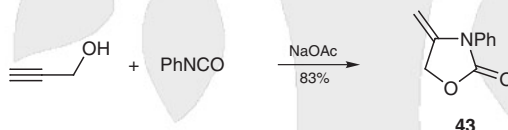
Scheme 25 Synthesis of *N*-(2-Pyridyl) Amides from Amides and Pyridine-1-Oxide^[39]***N*-(2-Pyridyl) Amides 42; General Procedure:**^[39]

2,6-Lutidine (2.5 equiv), and then oxalyl chloride (1.5 equiv) were added dropwise at 0 °C to a soln of an amide (1.5 equiv) in CH₂Cl₂ (0.2 M with respect to pyridine 1-oxide); an evolution of gas occurred. After stirring the mixture for 15 min, pyridine-1-oxide (1 equiv) was added all at once and the cooling bath was removed. After the *N*-oxide had been consumed (TLC or LC/MS) the mixture was diluted with sat. aq NaHCO₃ and extracted three times with CH₂Cl₂. The combined extracts were dried (Mg₂SO₄), filtered, and concentrated. The residue was purified by chromatography (MeOH/CH₂Cl₂ or EtOAc/hexanes).

21.4.1.1.11

Method 11:**Anionic Additions of Prop-2-yn-1-ols to Isocyanates**

Prop-2-yn-1-ol may be condensed with phenyl isocyanate to yield an intermediate carbamate, which further cyclizes to 4-methylene-3-phenyloxazolidin-2-one (**43**) under basic conditions.^[40] A large variety of other alkynic alcohols and isocyanates can be used to generate many different *N*-arylated oxazolidinones. Sodium acetate is used as the base in the reaction depicted in Scheme 26, but pyridine and potassium hydroxide can also be used.

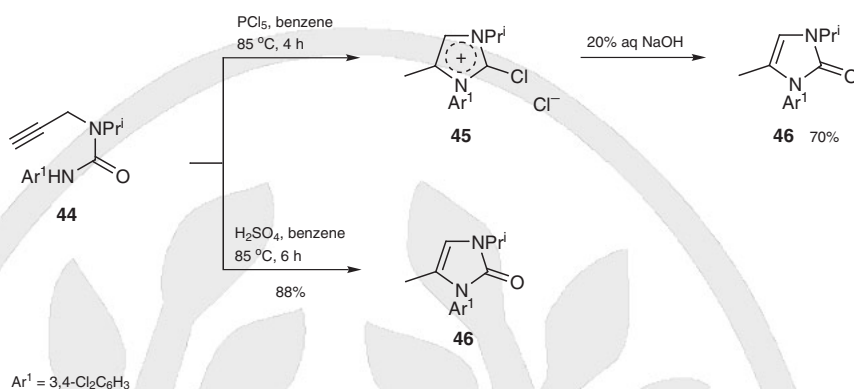
Scheme 26 Synthesis of an *N*-Arylalkanamide by Anionic Addition of Prop-2-yn-1-ol to an Isocyanate^[40]**4-Methylene-3-phenyloxazolidin-2-one (43):**^[40]

Phenyl isocyanate (11.9 g, 0.1 mol), prop-2-yn-1-ol (5.6 g, 0.1 mol), and NaOAc (0.1 g) were stirred until a strongly exothermic reaction had subsided. Workup and two crystallizations from MeOH gave small colorless granules; yield: 13.6 g (82.5%).

21.4.1.1.12

Method 12:**Hydrolysis of Imidazolium Chlorides under Basic Conditions**

In the presence of phosphorus pentachloride and aqueous base the *N*-propargyl-substituted urea **44** cyclizes to the dihydroimidazolone **46** via the imidazolium intermediate **45**.^[41] The overall yield is 70%. The same substrate **44** can also be cyclized to the dihydroimidazolone **46** under either acidic or basic conditions. When concentrated sulfuric acid in hot benzene is used the yield of the heterocycle is 88% (Scheme 27).^[42,43]

Scheme 27 Synthesis of an N-Arylalkanamide by the Ring Closure of an N-Propargyl-Substituted Urea^[41–43]**2-Chloro-3-(3,4-dichlorophenyl)-1-isopropyl-4-methylimidazolium Chloride (45):^[41]**

The urea **44** (67.0 g, 0.24 mol) and PCl₅ (50.0 g, 0.24 mol) in benzene (150 mL) (**CAUTION: carcinogen**) were refluxed for 4 h. A trace of hydrogen chloride was evolved and a colorless granular product gradually separated. The product was collected by filtration and washed with Et₂O (2 × 5 mL); yield: 69 g (85%). Two recrystallizations (CHCl₃) gave the title compound as fine colorless needles; yield: 60.5 g (77%).

3-(3,4-Dichlorophenyl)-1-isopropyl-4-methyl-1,3-dihydroimidazol-2(2H)-one (46):^[41]

The imidazolium salt **45** (17.0 g, 0.056 mol) was dissolved in H₂O (50 mL) and the soln was made slightly alkaline with 20% aq NaOH. A colorless granular product separated and was collected by filtration. Two recrystallizations (EtOAc) gave small stout prisms; yield: 13.1 g (82%).

3-(3,4-Dichlorophenyl)-1-isopropyl-4-methyl-1,3-dihydroimidazol-2(2H)-one (46); Typical Procedure:^[42]

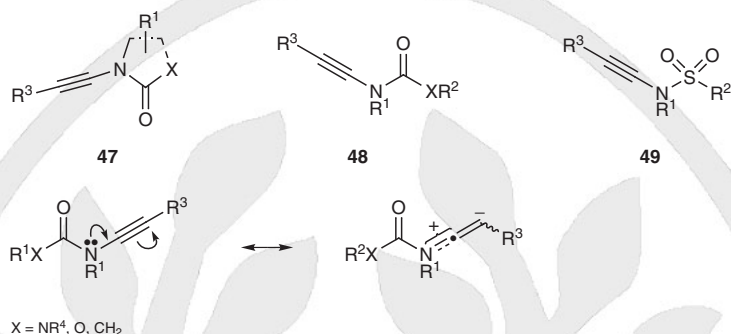
A soln of the urea **44** (28.3 g, 0.10 mol) and concd H₂SO₄ (10.5 g, 0.12 mol) in benzene (100 mL) (**CAUTION: carcinogen**) was refluxed for 6 h. A dark blue acid layer separated from the benzene soln. The acid layer was stirred into H₂O (500 mL) and made alkaline with 50% aq NaOH. The product was collected by filtration and crystallized (MeOH) to yield colorless prisms; yield: 25g (88%).

21.4.2 Product Subclass 2: Ynamides

For the purposes of this survey ynamides are electron-deficient compounds in which an alkyne is bonded via C1 to the nitrogen atom of an electron-withdrawing unit comprised of an imidazolidinone, oxazolidinone, lactam, or a simple amide represented by the structural types **47** and **48**. Their reactions, especially those where regioselectivity is concerned, are strongly influenced by the electronic bias associated with resonance within the chromophores (Scheme 28). Although sulfonamides **49** are not strictly within the scope of this review, they are deliberately included here as their syntheses are representatives of new methodology likely to have applications across the whole field. More information about the chemistry of ynamides can be found in a recent review.^[44] The electron-withdrawing unit, whether it be carbonyl- or sulfonyl-based, serves to diminish the electron-donating ability of the nitrogen atom, thereby offering stability superior to that of ynamines,^[45] and which allows the ready introduction of an additional group. Cyclic variants, particularly sulfonamides, are excellent choices because rotameric problems,

which have their origins in resonance effects, are eliminated and thus these compounds provide scaffolds for easy access to chiral “ynamides”.

Scheme 28 Ynamides and the Regioselective Bias Imposed by the Nitrogen Atom



Sulfonyl substitution not only serves to introduce an easily removable protecting group, but more significantly, it can tune the electron density of yne-sulfonamides leading to different reactivities compared to carbonyl-based types.^[45] Until recently, the limitations of the existing methods blocked the wider exploitation of ynamides; however, the first use of alkynyliodonium trifluoromethanesulfonate salts for the N-alkynylation of sulfonamides was accidentally discovered,^[46] and the emergence of iodonium trifluoromethanesulfonate salts for the general and efficient preparation of sulfonylated ynamides was demonstrated in 1998,^[47] leading to a resurgence in the chemistry of ynamides as a whole. While this methodology is effective in the synthesis of sulfonylated ynamides, it is inefficient in the case of oxazolidinone ynamides. However, the choice of base used to deprotonate the starting material is important and with a potassium, rather than a lithium, base yields are improved considerably; this simple change then provides an efficient route to oxazolidinone ynamides.^[48] Other progress in the area^[5,18,49] led to the development of the direct copper-catalyzed coupling of amides and alkynes as an economical and efficient approach to the corresponding ynamides. This work culminated in syntheses using copper(I)-mediated couplings that were first unveiled in 2003.^[50] These disclosures prompted further interest in this methodology and the development of a stoichiometric copper(I) coupling for acyclic ynamides.^[51] A catalytic copper(II) coupling that provides access to sulfonyl-, oxazolidinone-, imidazolidinone-, and lactam-based ynamides is now available;^[52] this methodology is also efficient for the coupling of pyrroles, indoles, and benzimidazolidin-2-ones with 1-bromoalkynes.

The reactivity of ynamides is still relatively unexplored and research in this area could prove to be a fertile ground for developing useful synthetic methods because of the enhanced stability of ynamides over ynamines. For example, the applications of ynamides in an array of methodologies such as cobalt- or iron-mediated Pauson–Khand cycloadditions^[47,53] and cyclotrimerizations,^[54,55] Suzuki couplings via hydroboration,^[56] Sonogashira couplings via hydrohalogenation,^[57] cross-couplings via hydro- or silylstannylated,^[48] ene-ynamide and tandem diene-ynamide ring-closing metathesis,^[58,59] Sonogashira couplings of aryl and vinyl iodides,^[60] Negishi coupling of aryl halides,^[61] Eschenmoser–Ficini–Claisen and Saucy–Marbet rearrangements,^[62,63] pericyclic reactions,^[64,65] and Lewis acid mediated additions to aldehydes and alkynes,^[66] have all been unveiled.

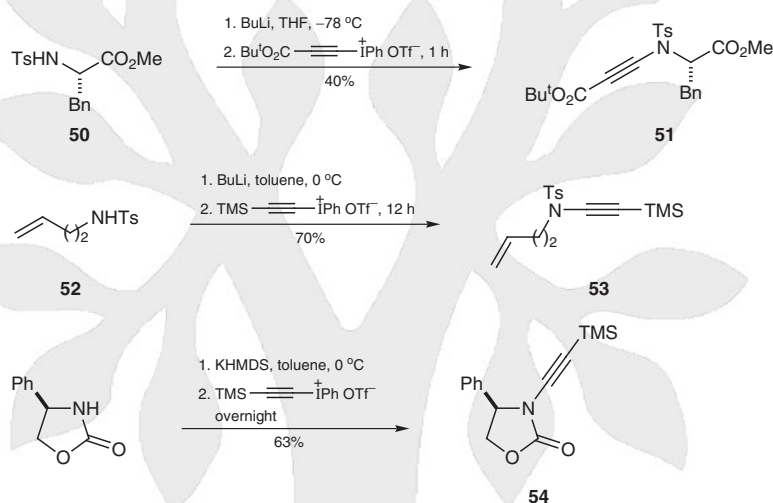
Most alkyl and silyl ynamides are oils, whereas most arylated ynamides are solids. All ynamides appear to be stable enough for purification by silica gel chromatography. However, ynamides are usually stored under nitrogen in the freezer to prevent decomposition; the most common decomposition pathway being hydrolysis to the imide. Ynamides have an IR band at ca. $\tilde{\nu}$ 2260 cm^{−1} corresponding to the N—C≡C bond stretching frequency.

21.4.2.1 Synthesis of Product Subclass 2

21.4.2.1.1 Method 1:
Addition of Amides to Alkynyliodonium Trifluoromethanesulfonates

Unexpectedly, the reaction of the toluenesulfonamide **50** with butyllithium and subsequent exposure to phenyl(*tert*-butyloxycarbonyl)ethynyl)iodonium trifluoromethanesulfonate leads to the ynesulfonamide **51** in a moderate yield (Scheme 29).^[46] This discovery can be adapted using phenyl(trimethylsilyl)ethynyl)iodonium trifluoromethanesulfonate to obtain trimethylsilyl-protected analogues, including the formation of the ynesulfonamide **53** from the sulfonamide **52**, in good to excellent yields.^[47] Similarly, ynamides, such as the cyclic carbamate **54**, can be accessed in moderate yields by deprotonating N-unsubstituted oxazolidinones with potassium hexamethyldisilazide (in these cases this base is more effective than butyllithium) and allowing the anions to react with the iodonium trifluoromethanesulfonate (Scheme 29).^[48]

Scheme 29 Synthesis of Ynamides by Nucleophilic Addition of Amides to Alkynyliodonium Trifluoromethanesulfonates^[46–48]



(4R)-4-Phenyl-3-[(trimethylsilyl)ethynyl]oxazolidin-2-one (54**); Typical Procedure:**^[48]

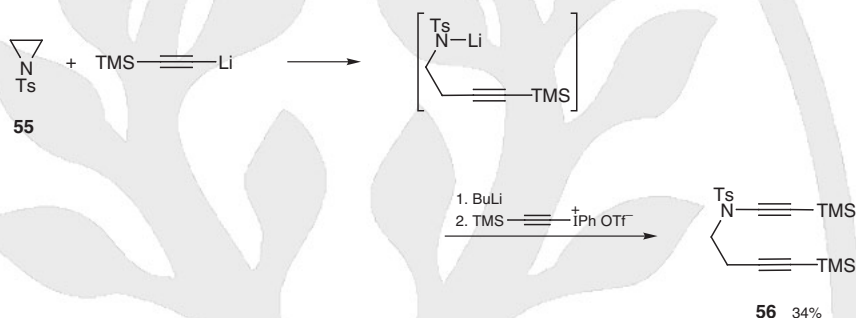
(4R)-4-Phenyloxazolidin-2-one (1.8 g, 11.5 mmol) was placed in a flame-dried flask (250 mL) under vacuum for 15 min. The flask was then flushed with dry N₂, and anhyd toluene (125 mL) was added. The resulting suspension was cooled to 0 °C and degassed twice by a freeze–thaw process, before 0.5 M KHMDS (1.2 equiv) in toluene (27.6 mL) was added dropwise under N₂. The resulting mixture was warmed to rt over 3 h, and phenyl(trimethylsilyl)ethynyl)iodonium trifluoromethanesulfonate (6.71 g, 1.3 equiv) was added in portions, then it was stirred at rt overnight, and the course of the reaction was monitored by TLC. The mixture was then filtered through a plug of silica gel (1 cm), rinsed with Et₂O (5 × 100 mL), and the combined filtrate and washings were concentrated to give a residue that was purified by chromatography (silica gel); yield: 1.85 g (63%).

21.4.2.1.1.1

Variation 1:**Ring-Opening of Aziridines with Lithium Alkynes, and Trapping with Alkynyliodonium Trifluoromethanesulfonates**

Alkynyliodonium trifluoromethanesulfonates are also used, in conjunction with the ring opening of *N*-tosylaziridine (**55**), to give (*N*-ethynyl)ynesulfonamides in moderate yields. In an example of this process ring opening of the aziridine occurs upon exposure to [(trimethylsilyl)ethynyl]lithium, and a subsequent reaction with butyllithium and phenyl(trimethylsilyl)ethynyl)iodonium trifluoromethanesulfonate gives the yne-ynamide **56** in 63% yield (Scheme 30). Such yneynamides can be used in Pauson–Khand cyclizations.^[53]

Scheme 30 Synthesis of an Yneynamide by Aziridine Ring-Opening with [(Trimethylsilyl)ethynyl]lithium and Treatment with an Alkynyliodonium Trifluoromethanesulfonate^[53]



***N*-[4-(Trimethylsilyl)but-3-yn-1-yl]-*N*-[(trimethylsilyl)ethynyl]-4-toluenesulfonamide (**56**);**

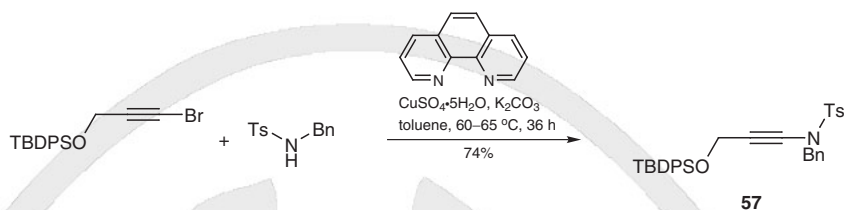
Typical Procedure:^[53]

1.6 M BuLi (15.1 mmol) in hexane (9.44 mL) was added dropwise to the lithium salt of *N*-[4-(trimethylsilyl)but-3-yn-1-yl]-4-toluenesulfonamide (9.0 mmol) (prepared in situ by the ring opening of the aziridine **55** with [(trimethylsilyl)ethynyl]lithium) in toluene (50 mL) at 0 °C. The mixture was allowed to warm to rt and was stirred for 1 h. Phenyl(trimethylsilyl)ethynyl)iodonium trifluoromethanesulfonate (5.5 g, 12.1 mmol) was then added in 6 portions over 1 h. The mixture was allowed to stir for an additional 12 h, and when the reaction was over (TLC), the mixture was concentrated, and the residue was purified by chromatography (silica gel, EtOAc/hexanes 1:8); yield: 2 g (34%).

21.4.2.1.2

Method 2:**Copper(II)-Catalyzed Coupling of Amides and Haloalkynes**

A generally applicable copper(II)-catalyzed coupling method for the *N*-alkynylation of carbamates, sulfonamides, oxazolidinones, imidazolidinones, lactams, pyrroles, and indoles has been developed.^[52] Utilizing a copper sulfate pentahydrate/1,10-phenanthroline catalyst system this represents a great improvement over an earlier approach based upon a copper(I)-catalytic system (see Section 21.4.2.1.2.1).^[50] The new route yields ynamides in moderate to excellent yields. It operates under mild conditions and is useful for many types of amidic starting materials; moreover, it works on a large scale, and tolerates a wide variety of functional groups on the electrophile (normally a bromoalkyne). One such synthesis is shown in Scheme 31 leading to the ynamide **57** from *N*-benzyl-4-toluenesulfonamide.^[52]

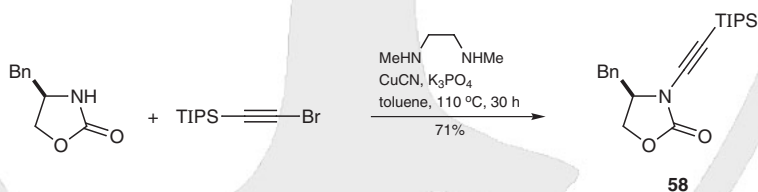
Scheme 31 Synthesis of an Ynamide by Copper(II)-Catalyzed Coupling of an Amide and a Bromoalkyne^[52]**N-Benzyl-N-[3-(tert-butyldiphenylsiloxy)prop-1-yn-1-yl]-4-toluenesulfonamide (57); Typical Procedure:**^[52]

N-Benzyl-4-toluenesulfonamide (2.00 mmol), K_2CO_3 (560 mg, 4.00 mmol), $CuSO_4 \cdot 5H_2O$ (50 mg, 0.20 mmol, 10 mol% Cu), and 1,10-phenanthroline (74 mg, 0.40 mmol) were added to 3-bromo-1-(tert-butyldiphenylsilyl)prop-2-yn-1-ol (2.20 mmol) in anhyd toluene (2 mL) contained in a vial. The vial was capped under a blanket of N_2 and heated in an oil bath at 60–65 °C for 32 h. The progress of the reaction was monitored using TLC and, when it was completed, the mixture was cooled to rt, and diluted with $CHCl_3$ (12 mL). After filtration through Celite, the filtrate was concentrated under reduced pressure, and the residue was purified by chromatography (silica gel, EtOAc/hexanes 0 to 10%); yield: 74%. In syntheses of this type K_3PO_4 can be used in place of K_2CO_3 .

21.4.2.1.2.1

Variation 1:**Copper(I)-Catalyzed Coupling of Amides and Haloalkynes**

Although a copper(I)-catalyzed method that can be used for the coupling of amides with alkynyl bromides, to give a range of ynamides with silyl-, alkyl-, and aryl-substituents is available, the route is not generally applicable and yields range from good to poor, with oxazolidinones giving the best results. For example, (4R)-4-benzylloxazolidin-2-one can be coupled with (triisopropylsilyl)ethynyl bromide to afford the ethynylated heterocycle **58** in 71% yield (Scheme 32).^[50]

Scheme 32 Synthesis of an Ynamide by Copper(I)-Catalyzed Coupling of an Amide and a Bromoalkyne^[50]**(4R)-4-Benzyl-3-[(triisopropylsilyl)ethynyl]oxazolidin-2-one (58):**^[50]

CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic.

(Triisopropylsilyl)ethynyl bromide (261.0 mg, 1.00 mmol, 1 equiv) in anhyd toluene (10 mL) and *N,N'*-dimethylethylenediamine (10.7 μ L) were added in succession to a vial containing (4R)-4-benzylloxazolidin-2-one (177.0 mg, 1.00 mmol), K_3PO_4 (424.0 mg, 2.00 mmol, 2 equiv), and CuCN (4.50 mg, 0.050 mmol, 5 mol% Cu). The vial was sealed and placed in an oil bath at 110 °C for 18–30 h. When the reaction was complete (TLC) the mixture was filtered through a small bed of silica gel, and the filtrate was concentrat-

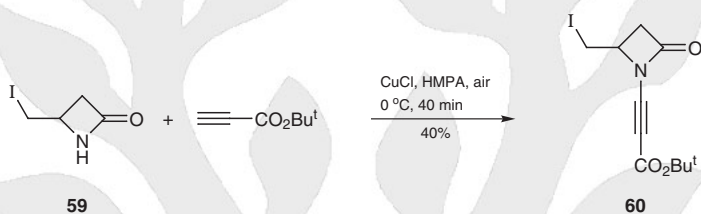
ed under reduced pressure. Purification of the residue by chromatography (silica gel, EtOAc/hexanes 0 to 50%) afforded the title compound; yield: 254.0 mg (71%).

21.4.2.1.2.2

Variation 2: Stoichiometric Copper(I) Coupling of Amides and Alkynes

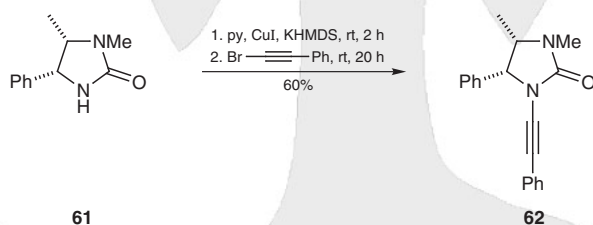
The first reported example of a copper(I)-mediated ynamide formation came about unexpectedly when an attempt was made to displace the iodine atom of 4-(iodomethyl)-azetidin-2-one **59** with *tert*-butyl propynoate in the presence of equimolar amounts of copper(I) chloride and oxygen in hexamethylphosphoric triamide solution at 0°C. The iodine remained in place and instead the ynamide **60** was isolated in up to 40% yield (Scheme 33).^[67]

Scheme 33 Synthesis of an Ynamide by Stoichiometric Copper(I) Coupling of an Amide and an Alkyne^[67]



Although this early approach may be limited, a general method for the N-alkynylation of carbamates, sulfonamides, oxazolidinones, and imidazolidinones has now been developed. It too is stoichiometric in copper(I) iodide and uses an excess of an alkynyl bromide, proceeding at room temperature to give ynamides in moderate to good yields. A broad range of alkynyl bromides is tolerated, and the procedure can be used on a large scale. An illustration of the technique is provided by the synthesis of the *N*-(ethynyl)imidazolidin-2-one **62** from the parent heterocycle **61** (Scheme 34).^[51]

Scheme 34 Synthesis of an Ynamide by the Stoichiometric Copper(I) Coupling of an Amide and a Bromoalkyne^[51]



(4*R*,5*S*)-1,5-Dimethyl-4-phenyl-3-(phenylethynyl)imidazolidin-2-one (**62**); Typical Procedure:^[51]

A two-necked, round-bottomed flask, equipped with an addition funnel and a rubber septum fitted with an argon inlet needle, was charged with the amide **61** (0.242 g, 1.27 mmol) and pyridine (5 mL). The soln was cooled to 0°C and 0.91 M KHMDS (1.3 mmol) in THF (1.4 mL) was added via a syringe over 4 min. The mixture was stirred at 0°C for 10 min, and a soln of CuI (0.243 g, 1.28 mmol) in pyridine (3.5 mL) was added via a cannula in one portion, and the cannula was rinsed through with more pyridine. The ice bath was removed, and the resulting soln was stirred at rt for 2 h. A soln of 0.6 M phenylethynyl bromide (2.5 mmol) in benzene (4.2 mL) (**CAUTION: carcinogen**) was then added over 1 h, and the mixture was stirred at rt for 20 h, before being diluted with Et₂O (30 mL), and

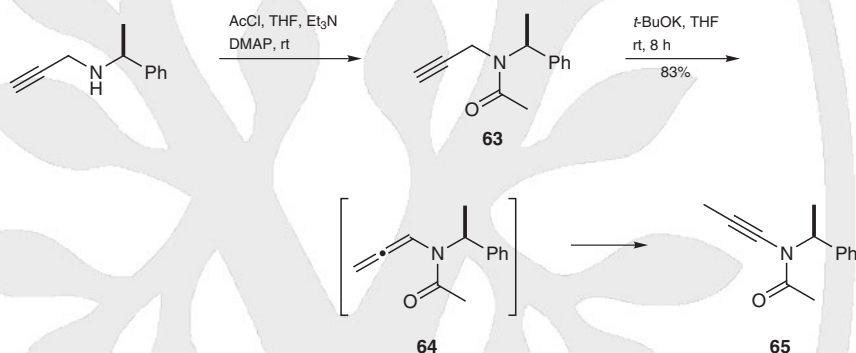
washed with 2:1 sat. aq NaCl/concd NH_4OH . The combined aqueous washings were extracted with Et_2O and the combined extracts and the organic layer were washed with a sat. aq NaCl (300 mL), dried (MgSO_4), filtered, and concentrated to give a red solid (0.56 g). Chromatography (silica gel, EtOAc /hexanes 0 to 30%) gave the title compound as a pale purple-colored solid; yield: 0.22 g (60%).

21.4.2.1.3

Method 3:**Base-Induced Isomerization of Prop-2-yn-1-ylated Amides**

Although initial efforts to synthesize ynamides from N-propargylimidazolidinone or oxazolidinones via a base-induced isomerization failed, the method can be applied successfully to acyclic prop-2-yn-1-ylated amides and carbamates such as N-[(1S)-1-phenylethyl]-N-prop-2-yn-1-ylacetamide (**63**). In this case the isomer **65** is formed via the intermediate allene **64** in 83% yield (Scheme 35). Dieneynamides, precursors for ring closing metathesis and tandem ring closing metathesis reactions, are also available by this approach.^[59]

Scheme 35 Synthesis of an Acyclic Ynamide by Base-Induced Isomerization of a Propargylated Amide^[59]



N-[(1S)-1-Phenylethyl]-N-prop-1-yn-1-ylacetamide (65**); Typical Procedure:**^[59]

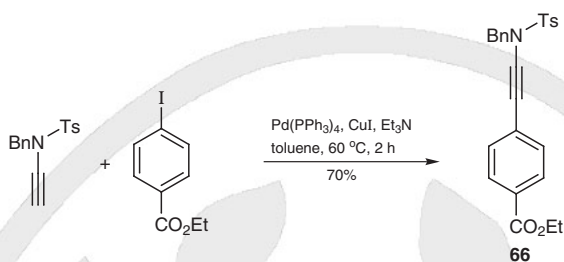
Et_3N (3 equiv), DMAP (8 mol%), and then AcCl (1.0 equiv) were added to 0.05 M [(1S)-phenylethyl]prop-2-yn-1-ylamine (1 equiv) in THF with stirring. After 10 h, the mixture was diluted with Et_2O and filtered. Concentration of the filtrate under reduced pressure yielded a residue that was purified by column chromatography (silica gel, EtOAc /hexanes) to give the amide **63** as a mobile oil. 20 mol% $t\text{-BuOK}$ was added with stirring to a 1.4 M soln of the amide in THF. When the reaction was complete (TLC), the soln was diluted with Et_2O and filtered through Celite. After concentration of the filtrate under reduced pressure, the residue was purified by chromatography (silica gel, EtOAc /hexanes) to give an oil; yield: 83% (for the isomerization step).

21.4.2.1.4

Method 4:**Sonogashira Coupling of Unsubstituted Ynamides**

Oxazolidinone- and sulfonamide-based ynamides with novel substitutions at the terminal alkyne carbon atom are accessible via Sonogashira cross-couplings of hydrogen-terminated ynamides with aryl or vinyl iodides. A variety of aryl-, hetaryl-, and vinyl-substituted ynamides including the ester **66** (Scheme 36) may be obtained by this method in moderate to excellent yields, without any homocoupling of the ynamide precursor.^[60]

Scheme 36 Synthesis of an Ynamide by Sonogashira Cross-Coupling of an Unsubstituted Ynamide with an Aryl Iodide^[60]



Ethyl 4-[[Benzyl(tosyl)amino]ethynyl]benzoate (66):^[60]

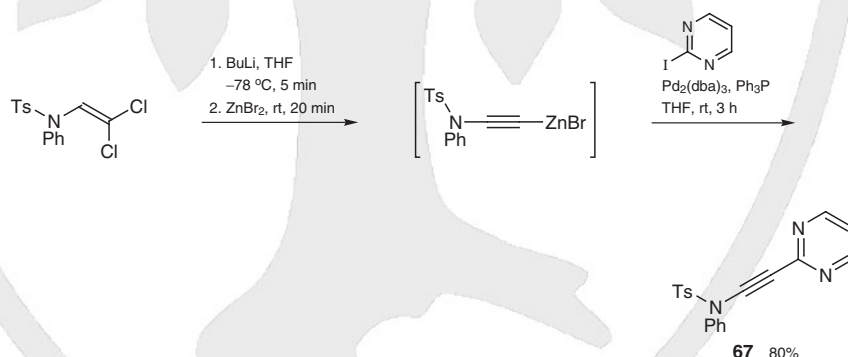
N-Benzyl-N-ethynyl-4-toluenesulfonamide (428 mg, 1.6 mmol), ethyl 4-iodobenzoate (497 mg, 1.6 mmol), $\text{Pd(PPh}_3)_4$ (86 mg, 0.075 mmol, 5 mol%), Et_3N (8 mL), and toluene (4 mL) were mixed together and the soln was stirred at rt for 10 min. CuI (4.3 mg, 1.5 mol% Cu) was then added to the soln, which was then heated at 60°C for 2 h. After cooling, the soln was diluted with EtOAc and filtered through Celite, the filtrate was concentrated under reduced pressure, and the residue was purified by chromatography (silica gel, EtOAc/hexanes 1:9 to 1:4); yield: 473 mg (70%).

21.4.2.1.4.1

**Variation 1:
Negishi Coupling of Unsubstituted Ynamides**

Aryl- and hetaryl-substituted ynamides, such as the pyrimidinyl derivative **67** (Scheme 37) can be obtained by the Negishi cross-coupling of dichlorovinylamides with aryl iodides. Arylated and heteroarylated ynamides are isolated in yields of 25–92%, with little formation of the corresponding ynamide homocoupled products.^[61]

Scheme 37 Synthesis of an Arylated Ynamide by Negishi Cross-Coupling of a Dichlorovinylamide with an Aryl Iodide^[61]



N-Phenyl-N-(pyrimidin-2-ylethynyl)-4-toluenesulfonamide (67):^[61]

1.6 M BuLi in hexanes (0.56 mL) was slowly added to N-(2,2-dichlorovinyl)-N-phenyl-4-toluenesulfonamide (0.15 g, 0.46 mmol) in anhyd THF (8 mL) at -78°C , and the mixture was stirred for 5 min. 1.5 M ZnBr_2 in THF (0.31 mL) was then added via a syringe and the stirring was continued for 20 min at rt. The whole mixture was transferred via a cannula into a soln of $\text{Pd}_2(\text{dba})_3$ (22 mg, 0.02 mmol), Ph_3P (22 mg, 0.09 mmol), and 2-iodopyrimidine (0.11 g, 0.53 mmol) in anhyd THF (4 mL). After 3 h, TLC showed complete consumption of the ethynylzinc intermediate. The volatiles were removed and the residue was dissolved

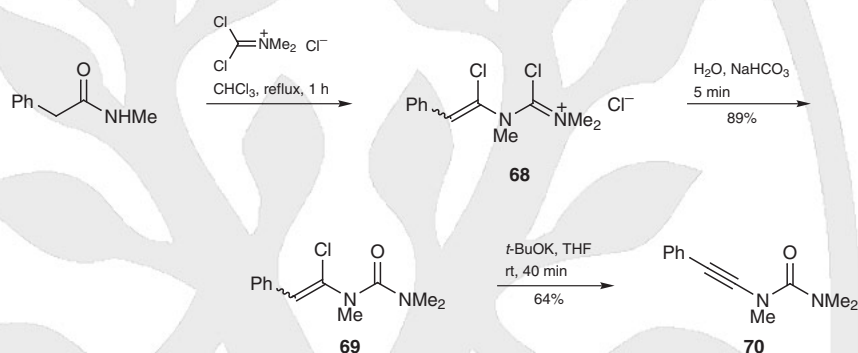
in EtOAc (20 mL) and washed with brine (2 × 20 mL). The organic layer was dried (Na₂SO₄) and evaporated to dryness. The residue was purified by chromatography (silica gel, EtOAc/hexanes 2:1) to give colorless prisms; yield: 0.12 g (80%).

21.4.2.1.5

Method 5: Elimination of Vinyl Chlorides

One of the earliest accounts of ynamide synthesis was reported in 1972.^[68] Using this approach the ynamide **70** (Scheme 38) is obtained by treating *N*-methylbenzamide with *N,N*-dimethyl dichloroformamidinium chloride. The initial product **68** is immediately hydrolyzed to afford a vinyl chloride **69**, which is then dehydrochlorinated with potassium *tert*-butoxide.^[69] Difficulties are noted in attempting to dehydrohalogenate the analogous vinyl bromides.

Scheme 38 Synthesis of an Ynamide by Elimination of a Vinyl Chloride^[69]



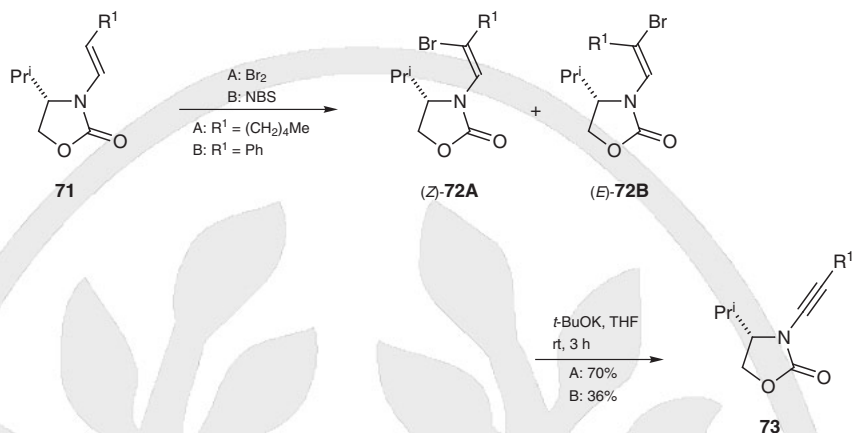
N,N,N'-Trimethyl-*N'*-phenylethynylurea (**70**):^[69]

N-methyl-2-phenylacetamide (1 mol) and *N,N*-dimethylchloroformamidinium chloride (2 mol) were refluxed in CHCl₃ for 30–60 min. The solvent was removed and the residue was extracted with anhyd Et₂O to remove byproducts. A portion of the initial product **68** (2.5 g, 8.5 mmol) was then added to a stirred suspension of NaHCO₃ in H₂O (10 mL) at neutral pH. After 5 min, the mixture was extracted with CH₂Cl₂. The extract was dried (K₂CO₃), filtered, and the solvent was removed to give the vinyl chloride **69**; yield: 1.8 g (89%). This compound (0.37 g, 1.55 mmol) in THF (2.5 mL) was stirred at rt and a soln of *t*-BuOK (0.176 g, 1.55 mmol) in anhyd THF (5 mL) was added, and after 10 min, anhyd Et₂O (10 mL) was introduced, and stirring was continued for 30 min. The precipitate that formed was removed by filtration, and the filtrate was evaporated to give an oily residue that was distilled (140 °C/0.4 Torr) to give a colorless stable oil; yield: 20 g (64%).

21.4.2.1.5.1

Variation 1: Elimination of Vinyl Bromides

Chiral ynamides **73** [R¹ = (CH₂)₄Me, Ph] can be prepared by the bromination/dehydrobromination of the corresponding *N*-ethenyloxazolidinones **71** (Scheme 39). The latter are obtained by 4-toluenesulfonic acid catalyzed condensations of the *N*-unsubstituted chiral oxazolidinones and an appropriate aldehyde (R¹CH₂CHO). The method of bromination depends upon the nature of the group R¹; bromine (Method A) is employed if R¹ is pentyl, or *N*-bromosuccinimide (Method B) if R¹ is phenyl. A mixture of *Z/E*-isomers, **72A** and **72B**, is formed in both cases, and when the *Z*-isomers are then separated (often with difficulty) and treated with potassium *tert*-butoxide the corresponding ynamides **73** are formed. The *E*-isomers are resistant to this form of base-promoted dehydrobromination.^[70]

Scheme 39 Synthesis of Ynamides by Elimination of Vinyl Bromides^[70]**3-[(E/Z)-2-Bromohept-1-en-1-yl]-(4S)-isopropylloxazolidin-2-one [72, R¹ = (CH₂)₄Me]:^[70]**

CAUTION: Bromine is a severe irritant of the eyes, mucous membranes, lungs, and skin. Liquid bromine causes severe and painful burns on contact with eyes and skin.

Method A: Br₂ (1.5 equiv) in 1,2-dichloroethane (5 mL) was added dropwise over 10 min under N₂ to the oxazolidinone **71** [R¹ = (CH₂)₄Me; 1.0 mmol] in anhyd 1,2-dichloroethane (20 mL) at –40 °C. The mixture was allowed to warm to rt and held at this temperature for 30 min, and then it was refluxed for 12 h. The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, EtOAc/hexanes 0 to 25%) to give a mixture of *E*- and *Z*-isomers.

3-[(E/Z)-2-Bromo-2-phenylvinyl]-(4S)-isopropylloxazolidin-2-one (72, R¹ = Ph):^[70]

Method B: NBS (1.5 equiv) in one portion was added to the oxazolidinone **71** (R¹ = Ph; 1.0 mmol) in anhyd 1,2-dichloroethane (20 mL) at rt. The mixture was refluxed for 1 h under N₂, and then the solvents was removed under reduced pressure. The residue was chromatographed (silica gel, EtOAc/hexanes 0 to 25%) to give a mixture of *E*- and *Z*-isomers.

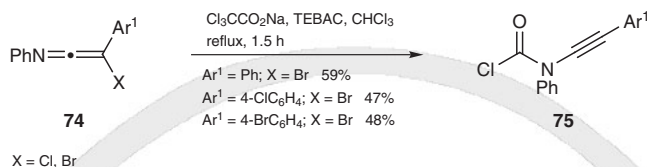
3-Hept-1-yn-1-yl-(4S)-isopropylloxazolidin-2-one [73, R¹ = (CH₂)₄Me]:^[70]

t-BuOK (1.5 - 3.0 equiv) in THF was added dropwise over 10 min under N₂ to a soln of (*Z*)-*N*-(2-bromohept-1-enyl)oxazolidin-2-one (1.0 mmol) in anhyd THF (50 mL) at –10 °C. The mixture was warmed to rt and stirred for 3 h, and then filtered through Celite, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes 0 to 25%); yield: 70%.

21.4.2.1.6

Method 6:**Acylation of C-Halogenated Ketenimines**

Halogenated arylketenimines **74** (X = Cl, Br) yield *N*-(arylethynyl)carbamoyl chlorides **75** when they are heated in chloroform in the presence of sodium trichloroacetate and benzyltriethylammonium chloride (Scheme 40). Yields are typically 47–61%.^[71]

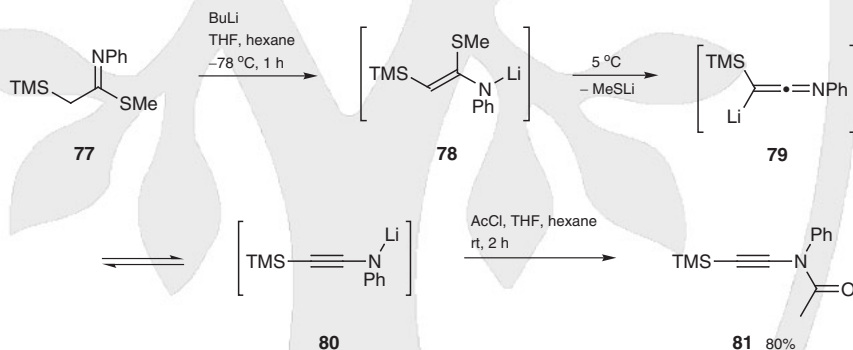
Scheme 40 Synthesis of Ynamides by Acylation of C-Halogenated Ketenimines^[71]**N-(Arylethynyl)-N-phenylcarbamoyl Chlorides 75; General Procedure:**^[71]

A mixture of the halogenated ketenimine **74** (3.2 mmol), TEBAc (0.25 g), and sodium trichloroacetate (4.0 g) in CHCl₃ (60 mL) was refluxed for 1.5 h. The mixture was cooled, filtered, washed with H₂O, dried (CaCl₂) and evaporated. Purification of the residue was achieved by chromatography (silica gel, CHCl₃/hexanes 1:4) and crystallization (hexanes).

21.4.2.1.6.1

Variation 1:**Acylation of β -Lithio- β -silyl Ketenimines**

The lithium salt **78** of the silylated ketenimine **77** ultimately reacts with acetyl chloride to give the ynamide **81**. This process occurs by elimination of methylsulfonyllithium from the initial salt to give the lithiated ketenimine **79**, which is in equilibrium with the lithiated ynamine **80**. Seemingly, it is this last salt that reacts with the electrophile (Scheme 41).^[72]

Scheme 41 Synthesis of an Ynamide by Acylation of a β -Lithio- β -silyl Ketenimine^[72]**N-Phenyl-N-(trimethylsilylethynyl)acetamide (81):**^[72]

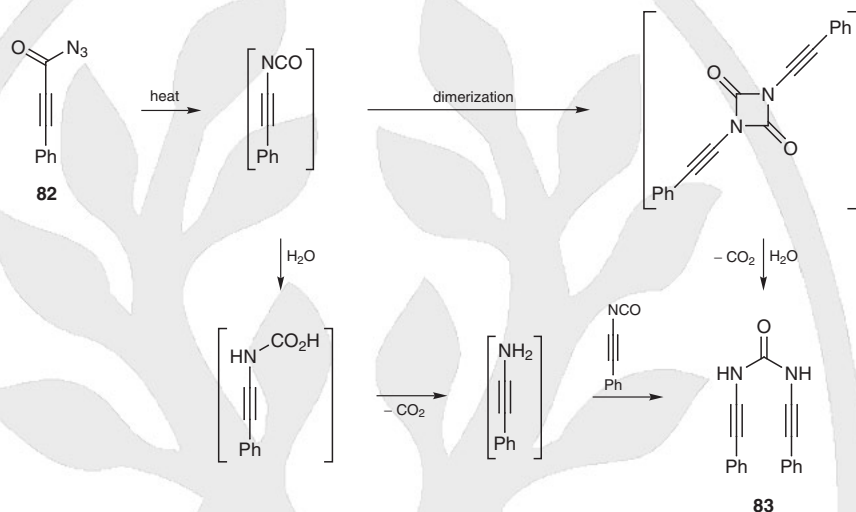
BuLi (8.3 mL, 13.26 mmol, 2.1 equiv) was added to a stirred soln of the imine **77** (1.5 g, 6.32 mmol) in THF (40 mL) and hexane (9 mL) cooled to -78°C . Stirring was maintained for 1 h at -78°C , and then the temperature was allowed to reach 5°C in order to induce an elimination of MeSLi and deprotonation. The product was treated with AcCl (3 equiv), which both trapped MeSLi and caused the acetylation of the ynamine salt **80**. The mixture was stirred at rt for 2 h, and then poured into sat. aq. NH₄Cl. The organic layer was removed, and the aqueous layer was extracted twice with petroleum ether. The organic layer and extracts were combined and washed with brine, dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by distillation ($125^\circ\text{C}/0.8$ Torr) as a colorless liquid; yield: 1.2 g (80%).

21.4.2.1.7

Method 7:
Pyrolysis of Alkynyl Azides

In another early, but in this case, inefficient ynamide synthesis, *N,N'*-bis(phenylethynyl)urea (**83**) was isolated in 4% yield when the azide **82** was pyrolyzed. The reaction may proceed as shown in Scheme 42.^[73]

Scheme 42 Synthesis of an Ynamide by Pyrolysis of an Alkynyl Azide^[73]

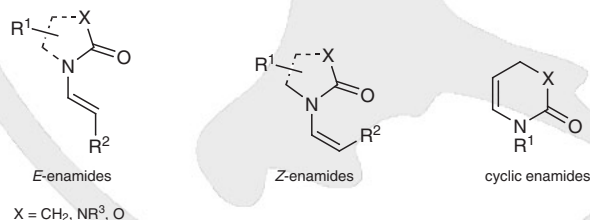


21.4.3

Product Subclass 3:
Enamides

The types of compounds discussed in this section are shown in Scheme 43, extending the coverage of simple enamides to include *N*-alkenylated imidazolidinones, oxazolidinones, and lactams. Although in some cyclic systems the enamide C=C bond is constrained within a heterocycle, in others, where there is a β -substituted *N*-alkenyl side chain, both *E*- and *Z*-isomers occur; indeed, the major problem associated with the early syntheses of many enamides was a lack of configurational control and, more generally, low yields.

Scheme 43 Structures of Enamides



The enamide unit is commonly present in natural products and in drug candidates. Enamides are very reactive and are used in the preparation of a wide variety of heterocyclic compounds. Although many enamide syntheses proceed under mild conditions this is not always necessary and other routes concentrate instead on efficiency and stereoselectivity. In the synthesis of enamides there are three major disconnections to consider. The first and easiest is through the carbonyl C—N bond, which in practice normally means the *N*-acylation of an enamine or its equivalent. The second point of disconnection is the C=C

bond. Formation of this bond can be accomplished in many ways including the elimination of various α - and β -substituents from saturated starting materials, the condensation of amides and aldehydes, and transition-metal-catalyzed isomerizations of the more readily available N-allylated amides. The final disconnection is that of the N—C bond. Syntheses where this last bond is formed by coupling reactions are often the most economical and efficient, using transition-metal chemistry similar to that employed in the formation of N-arylalkanamides and ynamides.

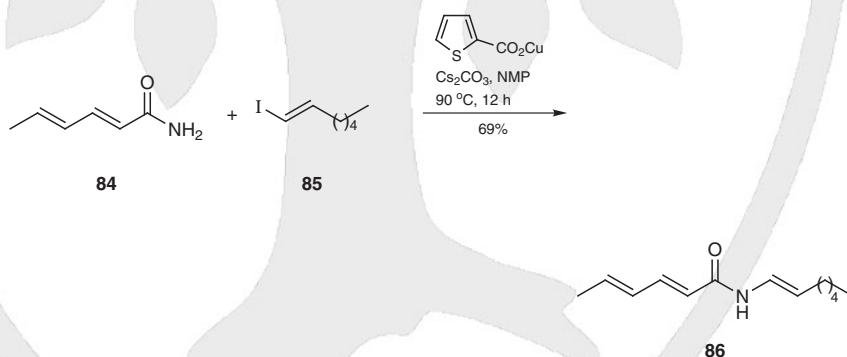
The ^1H NMR spectra of enamides containing an N-vinyl component with protons at the α and β -positions show the resonance of the α -proton at ca. δ 7.0 and that of the β -proton at ca. δ 5.0; the associated coupling constant can be used to determine the stereochemistry of the double bond, with a large J -value indicating an *E*-isomer and a smaller J -value indicating a *Z*-isomer. In the IR spectrum enamides exhibit a band at ca. $\tilde{\nu}_{\text{max}}$: 1560 cm^{-1} corresponding to the C=C bond stretching frequency, and *E*-enamides have a band at ca. $\tilde{\nu}_{\text{max}}$: 975 cm^{-1} that signifies the presence of the *trans* double bond.

21.4.3.1 Synthesis of Product Subclass 3

21.4.3.1.1 Method 1: Copper(I)-Catalyzed Coupling of Amides and Vinyl Iodides with Copper(I) Thiophenecarboxylate

The synthesis of enamides can be achieved via a copper(I)-catalyzed coupling of vinyl iodides and amides. In some cases the products are the starting materials for macrolides.^[74] An example of this type of coupling reaction is shown in Scheme 44 where (2*E*,4*E*)-*N*-[(1*E*)-hept-1-en-1-yl]hexa-2,4-dienamide (**86**), can be obtained from the amide **84** and the iodide **85** using copper(I) thiophene carboxylate (CuTC) as the coupling agent. This methodology is used in the syntheses of antitumor natural products bearing an enamide side chain, such as the lobatamides A–F,^[75,76] oximidines I–III,^[77,78] and CJ-12,950.^[79]

Scheme 44 Synthesis of an Enamide by Copper(I)-Catalyzed Coupling of an Amide and a Vinyl Iodide with Copper(I) Thiophenecarboxylate^[74]



(2*E*,4*E*)-*N*-[(1*E*)-Hept-1-en-1-yl]hexa-2,4-dienamide (**86**):^[74]

(2*E*,4*E*)-Hexa-2,4-dienamide (**84**; 83 mg, 0.75 mmol), copper(I) thiophenecarboxylate (CuTC; 28.6 mg, 0.15 mmol), and Cs₂CO₃ (245 mg, 0.75 mmol) were placed in an oven-dried Schlenk flask (10 mL) equipped with a stirrer bar. Anhyd NMP (2 mL) was added via a syringe. The suspension was held under high vacuum until the evolution of gas had ceased. (*E*)-1-Iodoheptene (**85**; 112 mg, 0.5 mmol, 79 μL) was added using a microliter syringe. The mixture was degassed again at high vacuum until no further gas was evolved. The suspension was stirred at 90 °C for 12 h under argon. The red slurry was cooled to rt, and washed with Et₂O. The Et₂O layers were combined and washed with a pH 7 buffer. The

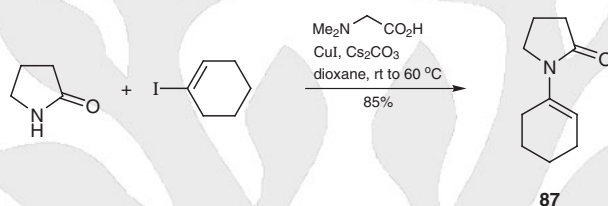
aqueous layer was extracted twice more with Et₂O and all the organic layers and extracts were combined, dried (Na₂SO₄), and concentrated to give a colorless solid, which was chromatographed (silica gel, 1% Et₃N/EtOAc/hexane); yield: 71 mg (69%).

21.4.3.1.1.1

Variation 1:**Copper(I)-Catalyzed Coupling of Amides and Vinyl Iodides with Copper(I) iodide**

The synthesis of enamides by the copper(I)-catalyzed coupling of vinyl halides and amides or carbamates provides useful substrates that can be used in the total synthesis of some natural products. In the formation of the enamide **87** (Scheme 45) coupling in the presence of *N,N*-dimethylglycine in 1,4-dioxane gives better results^[80] than *N,N'*-dimethylethylenediamine in toluene.^[81]

Scheme 45 Synthesis of an Enamide by Copper(I)-Catalyzed Coupling of an Amide and a Vinyl Iodide with Copper(I) iodide^[80]

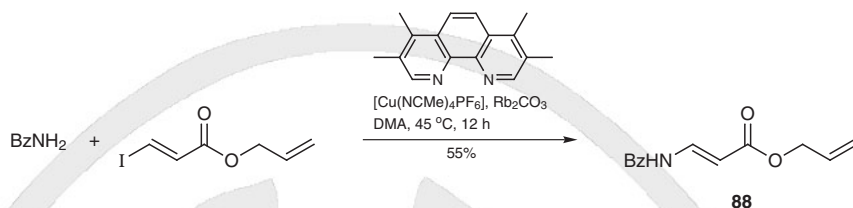
**1-Cyclohex-1-en-1-ylpyrrolidin-2-one (87):**^[80]

A Schlenk tube was charged with pyrrolidin-2-one (116 mg, 1.2 mmol), iodocyclohexene (208 mg, 1 mmol), CuI (20 mg, 0.1 mmol), *N,N*-dimethylglycine (28 mg, 0.2 mmol), and Cs₂CO₃ (659 mg, 2 mmol), evacuated, and backfilled with argon at low temperature. 1,4-Dioxane (2 mL) was then added under argon. The Schlenk tube was immersed in a preheated oil bath and the mixture was stirred at 60 °C for 12 h. It was then cooled to rt, and the resulting suspension was diluted with EtOAc (10 mL), and filtered through a plug of silica gel (EtOAc). The filtrate was concentrated and the residue was purified by chromatography (silica gel, EtOAc/hexane 1:4 to 1:2); yield: 180 mg (85%).

21.4.3.1.1.2

Variation 2:**Copper(I)-Catalyzed Coupling of Amides and Vinyl Iodides with (Acetonitrile)copper(1⁺) Phosphorus Hexafluoride(1⁻)/Rubidium Carbonate**

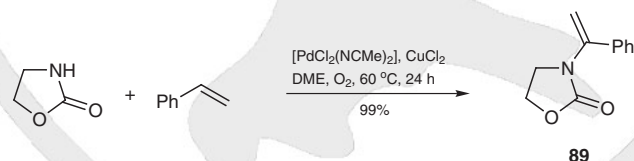
The synthesis of *N*-acylated vinylogous carbamic acids and ureas through (acetonitrile)-copper(1⁺) phosphorus hexafluoride(1⁻)/rubidium carbonate-catalyzed coupling of amides with 2-iodopropenates and propanamides can be applied in the syntheses of biologically active natural products that include palytoxin, enamidonin, cyclic lipopeptides K97-0239A and B, and CJ-15,801.^[49] An example of such a coupling procedure is shown in Scheme 46 leading to allyl (2*E*)-3-(benzoylamino)propenoate (**88**). In this synthesis the use of 1,2-dimethoxyethane as a solvent, instead of dimethylacetamide, provides better yields (71 versus 55%). The use of other copper(I) salts such as copper(I) thiophenecarboxylate (CuTC) and copper(I) iodide are of little value in such coupling reactions.

Scheme 46 Synthesis of an Enamide by Copper(I)-Catalyzed Coupling of an Amide and a Vinyl Iodide with (Acetonitrile)copper(1+) Phosphorus Hexafluoride(1–)^[49]**Allyl (2E)-3-(Benzoylamino)propenoate (88):^[49]**

Benzamide (90.9 mg, 0.85 mmol), Rb_2CO_3 (173.2 mg, 0.75 mmol), $\text{Cu}(\text{NCMe})_4\text{PF}_6$ (9.3 mg, 0.025 mmol), and 3,4,7,8-tetramethyl-1,10-phenanthroline (11.8 mg, 0.05 mmol) were placed in a flame-dried, 10-mL Schlenk tube equipped with a stirrer bar. Allyl (2E)-3-iodopropenoate (59.5 mg, 0.25 mmol, 36 μL) and anhyd DMA (1 mL) were added to the Schlenk tube. The mixture was degassed under high vacuum until no further gas evolution was observed. The suspension was stirred at 45 $^\circ\text{C}$ for 12 h under argon. The brown slurry was cooled to rt and diluted with EtOAc (4 mL) and pH 7 buffer (1 mL). The EtOAc extract was then filtered through neutral alumina. The aqueous layer was further extracted with EtOAc (20 mL) until the entire product had been removed (TLC). The EtOAc extracts were washed with pH 7 buffer, and brine to remove DMA, and the aqueous layer was extracted twice more with EtOAc (this step is not necessary when using DME as solvent). The organic layers were combined, dried (Na_2SO_4), and concentrated to afford a colorless solid; yield: 32.0 mg (55%). This yield was increased to 41.2 mg (71%) using DME as solvent rather than DMA. The product was purified by chromatography (silica gel, EtOAc/hexane 1:3).

21.4.3.1.2**Method 2:****Palladium(II)-Catalyzed Amidation of Alkenes**

The first general method for the intermolecular oxidative amination of styrenes, with molecular oxygen as the stoichiometric oxidant,^[82] is a palladium(II)-catalyzed coupling that is compatible with several different nitrogen nucleophiles, including oxazolidin-2-one, phthalimide, pyrrolidinone, and 4-toluenesulfonamide. The presence of a catalytic quantity of a Brønsted base in the reaction increases the catalytic activity but switches the regioselectivity. A simple illustration of the technique, giving 3-(1-phenylvinyl)oxazolidin-2-one (**89**), is shown in Scheme 47.

Scheme 47 Synthesis of an Enamide by Palladium(II)-Catalyzed Amidation of an Alkene^[82]**3-(1-Phenylvinyl)oxazolidin-2-one (89):^[82]**

$\text{PdCl}_2(\text{NCMe})_2$ (6.5 mg, 0.025 mmol), CuCl_2 (3.4 mg, 0.025 mmol), Et_3N (7.0 μL , 0.05 mmol), and oxazolidin-2-one (43.6 mg, 0.501 mmol) in DME (2 mL) were suspended in a disposable culture tube (13 \times 100 mm). The tube was placed in a custom 48-well parallel reactor, mounted in a Large Capacity Mixer (Glas-Col), and the headspace was purged with molecular O_2 for ca. 30 min. After warming to 60 $^\circ\text{C}$, styrene (0.34 mL, 3.0 mmol) was added to initiate the reaction, which was then allowed to proceed for 24 h under an O_2 atmosphere

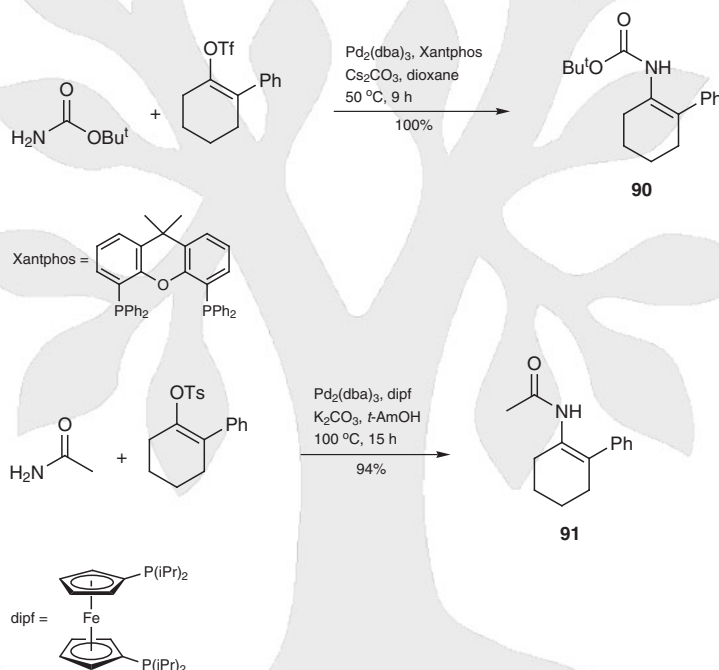
(1.1 atm). Purification by chromatography (silica gel, EtOAc/hexanes 1:4) gave the title compound; yield: 93.5 mg (99%). Similar syntheses can also be performed in flasks equipped with magnetic stirrer bars, but here O₂ must be vigorously bubbled through the soln in order that comparable yields of products are obtained.

21.4.3.1.2.1

Variation 1:**Palladium(0)-Catalyzed Amidation of Enol Trifluoromethanesulfonates and 4-Toluenesulfonates**

The synthesis of enamides through a mild palladium(0)-catalyzed coupling of enol trifluoromethanesulfonates with amides, carbamates, and sulfonamides may be achieved with minimal isomerization of the enol trifluoromethanesulfonate. A representative synthesis (that of the amide **90**) is shown in Scheme 48. Selective couplings of enol trifluoromethanesulfonates can also be achieved in the presence of aryl bromides.^[83] The related enamide **91** may also be obtained by coupling with an enol 4-toluenesulfonate.^[84]

Scheme 48 Synthesis of an Enamide by Palladium(0)-Catalyzed Amidation of an Enol Trifluoromethanesulfonate and a 4-Toluenesulfonate^[83,84]

***N*-tert-Butoxycarbonyl-2-phenylcyclohex-1-en-1-amine (90):^[83]**

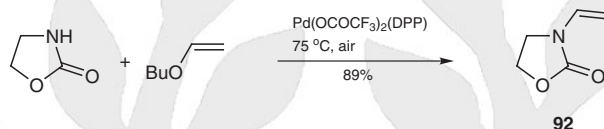
Cs₂CO₃ (379 mg, 1.16 mmol), pivalamide (109 mg, 1.08 mmol), Xantphos (43.6 mg, 0.075 mmol), and Pd₂(dba)₃ (23.0 mg, 0.025 mmol) were added to 2-phenylcyclohex-1-en-1-yl trifluoromethanesulfonate (255 mg, 0.832 mmol) in 1,4-dioxane (5.0 mL) at rt. The mixture was degassed and stirred at 50 °C for 9 h. The mixture was filtered, concentrated, and purified by chromatography (silica gel, toluene) to give a solid; yield: 214 mg (100%).

21.4.3.1.2.2

Variation 2:**Palladium(II)-Catalyzed Amidation of Enol Ethers**

Syntheses of enamides, through a formal palladium(II)-catalyzed cross-coupling of enol ethers with amides, carbamates, and sulfonamides, proceed in good yields in the presence of air. Thus, 3-vinyloxazolidin-2-one (**92**) is obtained from the oxazolidin-2-one and butyl vinyl ether in 89% yield using a palladium(II) catalyst [Pd(OCOCF₃)₂(DPP) (DPP = 4,7-diphenyl-1,10-phenanthroline)], as shown in Scheme 49.^[85]

Scheme 49 Synthesis of an Enamide by Palladium(II)-Catalyzed Amidation of an Enol Ether^[85]

**3-Vinyloxazolidin-2-one (**92**):**^[85]

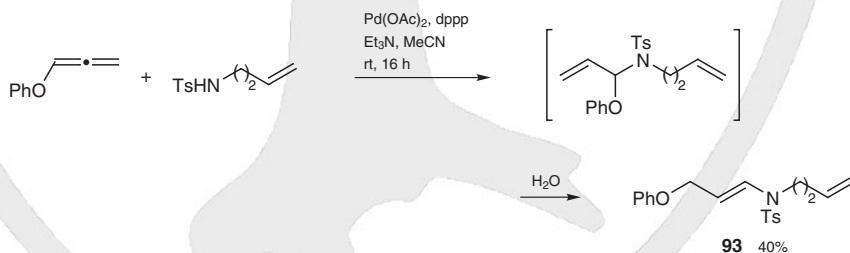
Oxazolidin-2-one (5.8 mmol, 500 mg), butyl vinyl ether (57.4 mmol, 7.43 mL), and [Pd(OCOCF₃)₂(DPP)] (0.28 mmol, 189 mg) were placed in a round-bottomed flask equipped with a magnetic stirrer bar. The flask was capped by a rubber septum with an 18-gauge needle punctured through it and its contents were stirred at 75 °C in an oil bath. The course of the reaction was monitored by ¹H NMR. When it was completed the mixture was allowed to cool and it was loaded directly onto a chromatography column (silica gel). Elution (Et₂O/hexanes 9:1) gave a light yellow oil; yield: 574 mg (89%).

21.4.3.1.2.3

Variation 3:**Palladium(II)-Catalyzed *N,O*-Acetal Formation and Isomerization**

A palladium(II)-catalyzed *N,O*-acetal formation between *N*-but-3-enyl-4-toluenesulfonamide and phenyl propadienyl ether, followed by isomerization, gives the ene-enamide **93** (Scheme 50). This type of product can be subjected to ring-closing metathesis.^[86]

Scheme 50 Synthesis of an Enamide by Palladium(II)-Catalyzed *N,O*-Acetal Formation and Isomerization^[86]

***N*-But-3-enyl-*N*-(3-phenoxypropenyl)-4-toluenesulfonamide (**93**):**^[86]

Et₃N (0.93 mL, 6.7 mmol, 1.5 equiv), phenyl propadienyl ether (0.65 g, 4.9 mmol, 1.1 equiv), dppp (91 mg, 5 mol%), and Pd(OAc)₂ (50 mg, 5 mol% Pd) were added to *N*-but-3-enyl-4-toluenesulfonamide (1.0 g, 4.5 mmol) in anhyd MeCN (15 mL) under N₂. The mixture was stirred at rt for 24 h, when TLC (silica gel, pentane/petroleum ether 1:1, anisaldehyde, R_f 0.52) indicated complete conversion into the product. H₂O (25 mL) and Et₂O (25 mL) were added, and the layers were separated. The aqueous layer was extracted with Et₂O (3 × 20 mL) and the combined organic layer and extracts were washed with brine

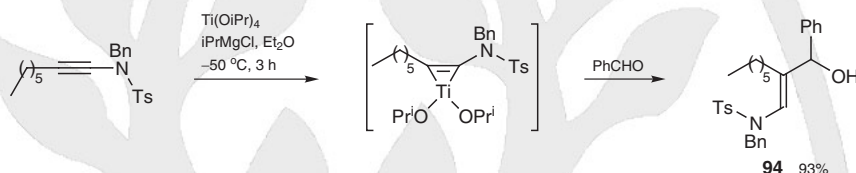
(25 mL), dried (Na_2SO_4), and concentrated. Chromatography (silica gel, 0.1% $\text{Et}_3\text{N}/\text{Et}_2\text{O}/\text{pentane}$ 1:8 to 1:4) afforded a colorless oil; yield: 0.64 g (40%).

21.4.3.1.3

Method 3:**Titanium(II)-Mediated Coupling of Ynamides and Aldehydes**

The synthesis of enamides and dienamides can be accomplished through titanium(II)-mediated coupling of ynamides and yne-sulfonamides with carbonyl compounds or alkynes. Stereoselectivity is induced by virtue of an intermediate ynamide–titanium complex, as in the formation of the enesulfonamide **94** from *N*-benzyl-*N*-(octyn-1-yl)-4-toluenesulfonamide shown in Scheme 51.^[66]

Scheme 51 Synthesis of an Enamide by Titanium(II)-Mediated Coupling of an Ynamide and an Aldehyde^[66]

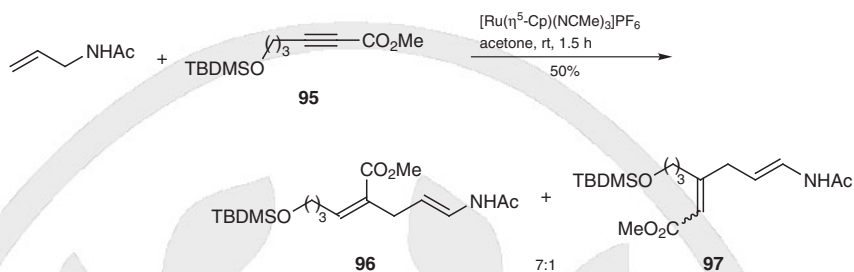
**(*E*)-3-[Benzyl(tosyl)amino]-2-hexyl-1-phenyl-2-propen-1-ol (**94**).^[66]**

1.48 M $i\text{PrMgCl}$ (0.49 mmol) in Et_2O (0.332 mL) was added at -78°C to *N*-benzyl-*N*-(octyn-1-yl)-4-toluenesulfonamide (45.5 mg, 0.123 mmol) and $\text{Ti}(\text{OiPr})_4$ (0.073 mL, 0.23 mmol) in Et_2O (3 mL) under argon. The yellow colored soln was warmed to -50°C over 30 min, during which time it turned black. After stirring at -50°C for 3 h, PhCHO (0.010 mL, 0.098 mmol) was added at -50°C and the soln was stirred for another 2 h. Then, the reaction was terminated by the addition of H_2O (0.3 mL) and the mixture was allowed to warm to rt. It was stirred for 30 min, and then filtered through Celite (Et_2O). The filtrate was concentrated under reduced pressure to give the title compound as an oil, it consisted of only one isomer (^1H NMR). This product was purified by chromatography (silica gel, $\text{Et}_2\text{O}/\text{hexane}$); yield: 42.7 mg (93%).

21.4.3.1.3.1

Variation 1:**Ruthenium(II)-Mediated Coupling of Alkynes and *N*-Allylated Amides**

The regio- and chemoselective synthesis of enamides by the ruthenium(II)-mediated coupling of alkynes and amides affords chain-extended products in an economical manner.^[87] In the procedure illustrated in Scheme 52 the major isomer of the reaction between *N*-allylacetamide and the alkyne **95** is the “linear” product **96**, whereas the “branched” isomer **97** is a byproduct. However, the balance between the isomers in other examples is quite subtle and the ratio of products is determined by the nature of the substitution on the alkyne; terminal alkynes typically give ratios of 2.5:1 in favor of the linear vinylsilanes, whereas reactions with trimethylsilylated alkynes take place under thermodynamic control to give only branched vinylsilanes. Further substitution may favor linear products to the extent of 7:1.

Scheme 52 Synthesis of an Enamide by Ruthenium(II)-Mediated Coupling of an Alkyne and an N-Allylated Amide^[87]

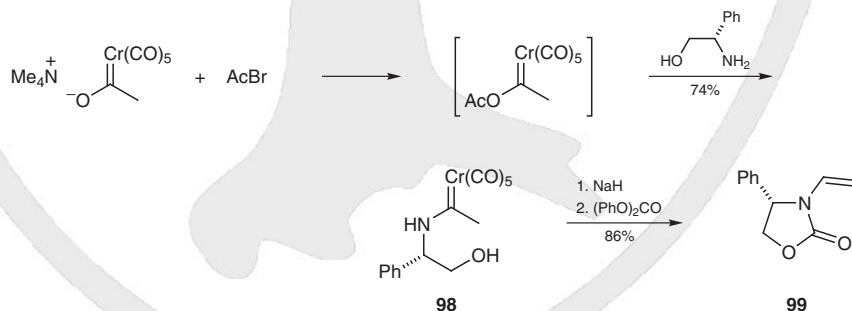
Methyl (2Z)-2-[(2E)-3-(Acetylamino)prop-2-en-1-yl]-6-(*tert*-butyldimethylsiloxy)hex-2-enoate (96)/Methyl (2E,5E)-6-(Acetylamino)-3-[3-(*tert*-butyldimethylsiloxy)propyl]hexa-2,5-dienoate (97); Typical Procedure:^[87]

Methyl 6-(*tert*-butyldimethylsiloxy)hex-2-ynoate (46 mg, 0.18 mmol) and *N*-allylacetamide (18 mg, 0.18 mmol) in acetone (1.8 mL) were added under argon to [RuCp(NCMe)₃]PF₆ (8.0 mg, 0.018 mmol). The mixture was stirred at rt for 1 h, and then evaporation of the solvent under reduced pressure, and purification of the residue by chromatography (silica gel, Et₂O/petroleum ether 7:1) gave a 7:1 mixture of the title compounds; yield: 21 mg (50%).

21.4.3.1.3.2

Variation 2:**Chromium(0)-Mediated Coupling of Amino Alcohols and Chromium Carbene Complexes**

Attempts to prepare optically active chromium carbene complexes containing an oxazolidinone heterocycle failed and led instead to an efficient and general synthesis of optically active ene-carbamates such as the *N*-allyloxazolidinone **99**, which was generated from the chiral pentacarbonylchromium compound **98** (Scheme 53); this methodology was applied in the total synthesis of (+)-thienamycin. The corresponding tungsten complex also gives ene-carbamates, albeit in slightly lower yields.^[88]

Scheme 53 Synthesis of an Enamide by Chromium(0)-Mediated Coupling of an Amino Alcohol and a Chromium Carbene Complex^[88]

3-Ethenyl-(4S)-phenyloxazolidin-2-one (99); Typical Procedure:^[88]

An Airless-ware flask was fitted with a stirrer bar, rubber septum, and argon-filled balloon. The apparatus was charged with the chromium complex **98** (50.0 mg, 0.141 mmol) and NaH (7.0 mg, 0.29, 82 mmol), and the system was kept under argon. Sufficient dry THF was added by syringe to form a 3 M soln of the carbene complex, H₂ was evolved for about 5 min, and the yellow-orange soln was stirred at rt for 1 h. Diphenyl carbonate

(151 mg, 0.706 mmol) was added as a solid under a gentle flow of argon. More H_2 was evolved and the color turned deep red. Stirring was continued at rt for 3 h. The solvent was evaporated, and the residue was taken up in 1:1 EtOAc/hexane. This soln was saturated with air and was oxidized in a light box equipped with six 20-W Vitalite fluorescent lamps. Eventually, the soln became light yellow in color and contained a dark brown precipitate, which was removed by filtration through Celite. Purification was achieved by radial chromatography (silica gel, EtOAc/hexane 1:4); yield: 23.0 mg (86%).

The corresponding tungsten complex (150 mg, 0.308 mmol), NaH (15.0 mg, 0.308 mmol), and diphenyl carbonate (198 mg, 0.925 mmol) can also be used to prepare the chiral oxazolidin-2-one **99**; yield: 47.0 mg (81%).

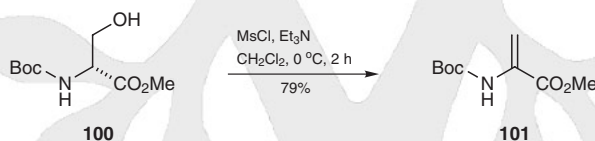
Note: Depending upon the substrates used in reactions of this type the time for the irradiation step ranged from a few hours up to 2 d and, in some cases, it was necessary to filter the soln through silica gel at the end of this procedure to remove any remaining soluble chromium-containing species.

21.4.3.1.4

Method 4:**Base-Promoted Elimination of Substituted Alcohols**

The synthesis of the enamide **101** can be accomplished via base-elimination of a mesylated intermediate generated in situ from the chiral alcohol **100** (Scheme 54).^[89] Similar eliminations are also documented including the dehydration of free alcohols,^[90] and eliminations involving glycosides, esters, and various other derivatives.^[91–94]

Scheme 54 Synthesis of an Enamide by Base-Promoted Elimination of a Substituted Alcohol^[89]

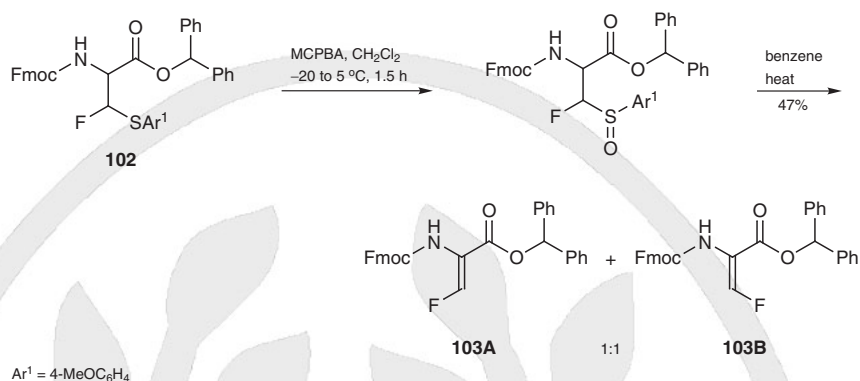
**Methyl 2-[(*tert*-Butoxycarbonyl)amino]-2-propenoate (**101**):^[89]**

Et_3N (4.12 g, 40.7 mmol) was added with stirring to the amino ester **100** (2.97 g, 11.7 mmol) and $MsCl$ (2.33 g, 20.3 mmol) in CH_2Cl_2 (40 mL) at $0\text{ }^\circ\text{C}$ under N_2 . The mixture was stirred at rt for 2 h, and then it was washed with sat. aq $NaHCO_3$ (40 mL), dried, filtered, and concentrated under reduced pressure. Purification of the residue by chromatography (silica gel, EtOAc/petroleum 1:6) gave a colorless oil; yield: 2.18 g (79%).

21.4.3.1.4.1

Variation 1:**Thermal Elimination of Sulfoxides**

The oxidation and thermolysis of the sulfide **102** generates a 1:1 mixture of the *E*- and *Z*-enamides **103** (Scheme 55).^[95]

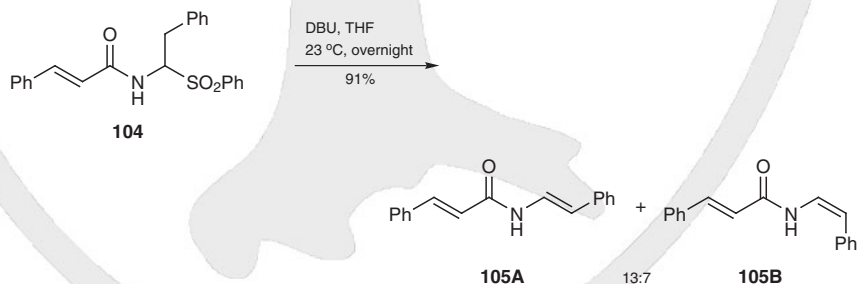
Scheme 55 Synthesis of Enamides by Thermal Elimination of Sulfoxides^[95]**Diphenylmethyl 2-(*E/Z*)-[(9H-Fluoren-9-ylcarbonyl)amino]-3-fluoropropenate (103A/B):**^[95]

The sulfide **102** (0.126 g, 0.199 mmol) was dissolved in CH₂Cl₂ (5 mL) and the soln was cooled to –20 °C. A soln of MCPBA (peracid content 57%; 0.066 g, 0.219 mmol) in CH₂Cl₂ (2 mL) was added, and the mixture was stirred at –20 to –5 °C for 1.5 h. It was then diluted with CH₂Cl₂ (80 mL), and washed with 10% aq Na₂S₂O₃ (30 mL), and brine (30 mL). The organic layer was dried and concentrated to give a product containing 4 diastereomers. The crude mixture was placed in a flask (10 mL) and anhyd benzene (5 mL) (**CAUTION: carcinogen**) was added. The soln was refluxed overnight. The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, EtOAc/hexane 1:5) to afford a 1:1 mixture of the *E*- and *Z*-isomers **103A/B**; yield: 0.046 g (47%).

21.4.3.1.4.2

**Variation 2:
Base-Promoted Elimination of Sulfones**

The formation of the enamides **105A/B** via the base-promoted elimination of the sulfone **104** (Scheme 56) is employed in total syntheses of the lansiumamides A, B, and I.^[96] Presumably the elimination occurs under thermodynamic control as the all-*trans* isomer **105A** is the major product.

Scheme 56 Synthesis of Enamides by Base-Promoted Elimination of a Sulfone^[96]**(2*E*)-3-Phenyl-N-[2-phenylvinyl]propenamides (105A/B):**^[96]

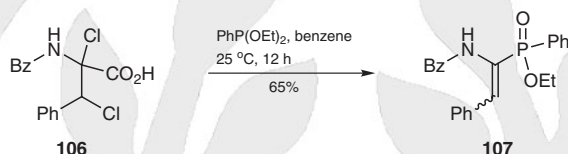
A soln of the sulfone **104** (0.059 g, 0.15 mmol) and anhyd DBU (0.024 mL, 0.16 mmol) in anhyd THF (5 mL) was stirred at rt overnight. The mixture was diluted with H₂O (15 mL) and extracted with Et₂O (3 × 15 mL). The combined organic layers were washed with brine (3 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. Purification of the residue by chromatography (silica gel, EtOAc/petroleum ether 1:4) gave yellow crystals; yield: 0.034 g (91%).

21.4.3.1.4.3

Variation 3:**Thermal Elimination of Hydrogen Chloride and Carbon Dioxide**

The synthesis of the enamide **107** is accomplished by the addition of diethyl phenylphosphonate to the acid **106** in an Arbuzov reaction, followed by decarboxylation and elimination of hydrogen chloride (Scheme 57).^[97] The geometry of the double bond in the product is unknown.

Scheme 57 Synthesis of an Enamide by Thermal Elimination of Hydrogen Chloride and Carbon Dioxide^[97]

**Ethyl [(1-Benzoylamino)-2-phenylethenyl]phenylphosphinate (107):^[97]**

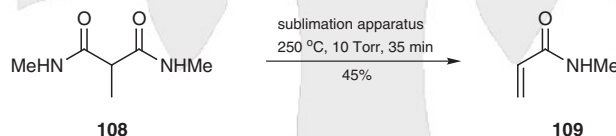
Diethyl phenylphosphonate (0.058 mol) was added to a suspension of the acid **106** (16.9 g, 0.05 mol) in benzene (20 mL) (**CAUTION: carcinogen**). The mixture was kept at rt for 12 h, a small amount of a precipitate was filtered off, and the solvent was removed under reduced pressure. The residue was treated with Et_2O , and then purified by crystallization (EtOAc); yield: 12.7 g (65%).

21.4.3.1.4.4

Variation 4:**Thermal Elimination of Amides**

The thermal decomposition of the bisamide **108** under reduced pressure in a sublimation apparatus produces the enamide **109** in a low yield (Scheme 58). In other cases, when the substrates are suitably substituted, Z-configured products predominate.^[98]

Scheme 58 Synthesis of an Enamide by Thermal Elimination of an Amide^[98]

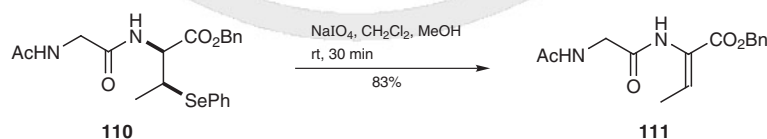


21.4.3.1.4.5

Variation 5:**Oxidative Elimination of Selenides**

The synthesis of enamides via oxidative-elimination of selenides allows the synthesis of dehydrobutyrine (Dhb)-containing peptides.^[99] The use of stereodefined selenides provides geometrically pure enamides; thus, the selenide **110** gives the Z-enamide **111** (Scheme 59).

Scheme 59 Synthesis of an Enamide by Oxidative Elimination of a Selenide^[99]



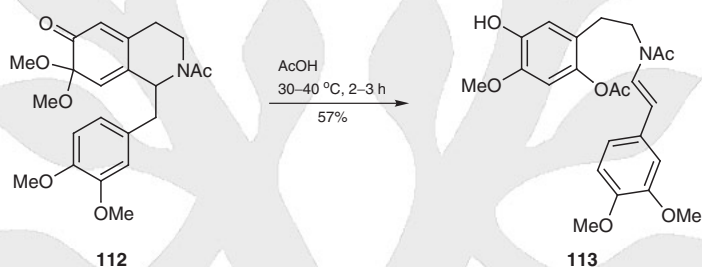
Benzyl (2Z)-2-[(N-Acetylglycyl)amino]but-2-enoate (111):^[99]

The selenide **110** (52.0 mg, 0.116 mmol) was dissolved in CH₂Cl₂ (6 mL) and MeOH (6 mL), and then NaIO₄ (120 mg, 0.560 mmol) in H₂O (3 mL) was added at rt. The mixture was stirred for 0.5 h, then H₂O (10 mL) was added, and the mixture was extracted with CH₂Cl₂ (80 mL). The organic layer was washed with H₂O (30 mL), brine (30 mL), and dried (MgSO₄). After filtration, the filtrate was evaporated under reduced pressure and the residue was chromatographed (silica gel, MeOH/CH₂Cl₂ 1:20); yield: 67 mg (83%).

21.4.3.1.4.6

Variation 6:**Base-Promoted Elimination of a Benzylic Proton**

The elimination of a benzylic proton from the *N*-acetylisquinoline **112** leads to subsequent cleavage of a C—C bond and affords the ring cleaved and rearranged isomer **113** (Scheme 60).^[100] This process is dependent upon the nature of the *N*-substituent; thus, while related carbamates and sulfonyl derivatives react in a similar fashion, the *N*-tri-fluoroacetyl and *N*-formyl compounds do not.

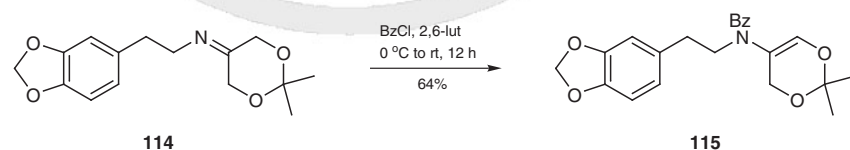
Scheme 60 Synthesis of an Enamide by Base-Promoted Elimination of a Benzylic Proton^[100]**2-(2-{Acetyl[(*E*)-2-(3,4-dimethoxyphenyl)vinyl]amino}ethyl)-4-hydroxy-5-methoxyphenyl Acetate (113):**^[100]

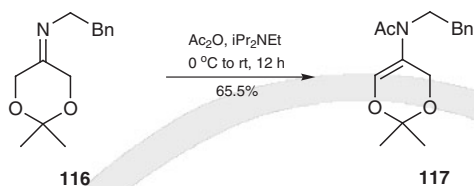
The *N*-acetylated amine **112** (100 mg, 233 mmol) in AcOH (5 mL) was stirred at 30–40 °C for 2 h. The mixture was diluted with H₂O and basified with 10% aq Na₂CO₃. A precipitate that formed was taken up in CH₂Cl₂ and, after aqueous workup, this was refined by TLC (silica gel, EtOAc/hexane 2:1) to afford an oil; yield: 66.3 mg (57%).

21.4.3.1.5

Method 5:**Acylation of Imines**

N-Acylation of the imine **114** with benzoyl chloride and 2,6-lutidine gives the enamide **115** in 64% yield (Scheme 61).^[101] In this and related examples the use of a catalytic amount of titanium(IV) chloride allows shorter reaction times (a reduction from 12 h to 1–2 h).^[102] In some cases anhydrides can be used in place of acid chlorides; thus, the imine **116** reacts with acetic anhydride in the presence of diisopropylethylamine to provide the enamide **117** (Scheme 61).^[101]

Scheme 61 Synthesis of Enamides by Acylation of Imines with Acid Chlorides and Anhydrides^[101]



***N*-[2-(1,3-Benzodioxol-5-yl)-*N*-(2,2-dimethyl-4*H*-1,3-dioxin-5-yl)benzamide (115):**^[101]

2,6-Lutidine (820 μL , 7.1 mmol) and BzCl (330 μL , 2.8 mmol), were added in succession to the *N*-acetylated isoquinoline **114** (665 mg, 2.4 mmol) in toluene (14 mL) and 4-Å molecular sieves (400 mg) at 0 °C. The mixture was allowed to warm to rt over 12 h, and then it was filtered through Celite, and washed with aq NaHCO₃. The aqueous layer was extracted three times with EtOAc, and the combined organic layer and extracts were dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, EtOAc/hexanes 1:3) to afford a colorless solid; yield: 590 mg (64%).

***N*-(2,2-Dimethyl-4*H*-1,3-dioxin-5-yl)-*N*-(2-phenylethyl)acetamide (117):**^[101]

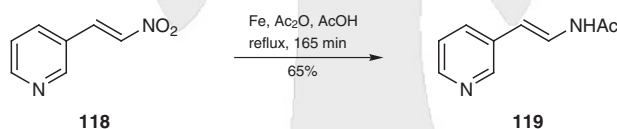
iPr₂NEt (1.05 mL, 6.0 mmol) and Ac₂O (380 μL , 4.0 mmol) were added in succession to the imine **116** (466 mg, 2.0 mmol) in toluene (10 mL) and 4-Å molecular sieves (250 mg) at 0 °C. The mixture was allowed to warm to rt over 12 h, and then worked up in the same way as detailed in the previous experimental procedure to give the title compound as a colorless oil; yield: 360 mg (65.5%).

21.4.3.1.5.1

**Variation 1:
Reductive Acylation of Nitroalkenes**

The synthesis of *N*-[(*E*)-2-pyridin-3-ylvinyl]acetamide (**119**) is achieved by the reduction of the nitroalkene **118**, followed by direct treatment of the product with acetic anhydride (Scheme 62). This preparation is representative of a simple and inexpensive approach to both aromatic and aliphatic enamides.^[103]

Scheme 62 Synthesis of an Enamide by the Reductive Acylation of a Nitroalkene^[103]



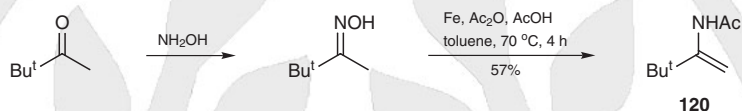
***N*-[(*E*)-2-Pyridin-3-ylvinyl]acetamide (119); Typical Procedure:**^[103]

A suspension of Fe powder (60 mmol) in Ac₂O (6 mL) and AcOH (0.3 mL) was refluxed under argon for 30 min and 3-(2-nitrovinyl)pyridine (**118**; 450 mg, 3 mmol) was then added in portions over 1 h. The mixture was heated for a further 2.75 h, and then it was cooled, diluted carefully with MeOH, and filtered. The filtrate was evaporated, and the residue taken up in a little MeOH, and the pH adjusted to about 12–14 (pH indicator paper) using methanolic KOH. Filtration through Celite, followed by removal of the solvent and purification of the residue by chromatography (silica gel) finally afforded the title compound; yield: 316 mg (65%).

21.4.3.1.5.2

**Variation 2:
Reductive Acylation of Oximes**

In a related reaction methyl ketones can be converted into their oximes and reduced with iron powder in the presence of acetic acid and acetic anhydride to afford *N*-vinylacetamides; for example, using this methodology 3,3-dimethylbutan-2-one affords *N*-(1-*tert*-butylvinyl)acetamide (**120**) in a modest yield (Scheme 63).^[104] Chromium(II) and titanium(III) compounds can be used to catalyze such processes.^[105]

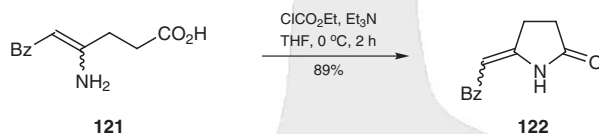
Scheme 63 Synthesis of an Enamide by the Reductive Acylation of an Oxime^[104]***N*-(1-*tert*-Butylvinyl)acetamide (**120**):^[104]**

Ac₂O (398 g, 3.9 mol) was added, in portions, to the oxime (150 g, 1.3 mol) of 3,3-dimethylbutan-2-one dissolved in toluene (1 L) under N₂. AcOH (234 g, 3.9 mmol) was then added, followed by Fe powder (Aldrich; 325 mesh; 145.2 g, 2.6 mol). The mixture was heated to 70 °C for 4 h, and then it cooled to rt, and filtered through Celite to remove a solid residue. This material was washed with toluene (2 × 100 mL), and the combined filtrate and washings were cooled in an ice bath, and washed with 2 M NaOH (2 × 1 L). The organic phase was separated, dried (MgSO₄), and evaporated to afford a colorless solid; yield: 104 g (57%).

21.4.3.1.5.3

**Variation 3:
Acylation of Enamines with Acid Chlorides**

The intramolecular cyclization of certain amino acids can be achieved through treatment with ethyl chloroformate and triethylamine; thus the enamine **121** can be converted into the 5-methylenepyrrolidin-2-one **122** in 89% yield, by acylation and subsequent ring closure (Scheme 64). This mild approach has been used to synthesize prostaglandin analogues,^[106] utilizing methyleneaziridines as the starting materials for the enamines.^[107]

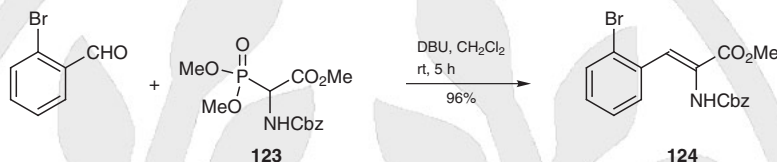
Scheme 64 Synthesis of an Enamide by Acylation/Intramolecular Cyclization^[106]**5-(2-Oxo-2-phenylethylidene)pyrrolidin-2-one (**122**):^[106]**

ClCO₂Et (1.95 g, 18 mmol) in THF (10 mL) was added dropwise to an ice-cooled soln of the enamine **121** (3.94 g, 18 mmol) in anhyd THF (40 mL) containing Et₃N (2.1 g, 20 mmol). Stirring was continued at 0 °C for 2 h, then the mixture was allowed to warm to rt, and stirring was continued for another 3 h. Et₃N•HCl, which had precipitated, was then removed by filtration and the filtrate was concentrated under reduced pressure; yield: 3.25 g (89%).

21.4.3.1.6

Method 6:
Alkenation Using Horner–Wadsworth–Emmons Conditions

The Horner–Wadsworth–Emmons alkenation of 2-bromobenzaldehyde with the phosphorylacetate **123** provides the enamide **124** in a high yield (Scheme 65). In related examples the stereoselectivity *Z/E* of the products range from 60:40 to 95:5.^[108] This type of preparation is used in the total syntheses of (+)-sinefungin^[109] and azinomyzin A.^[110]

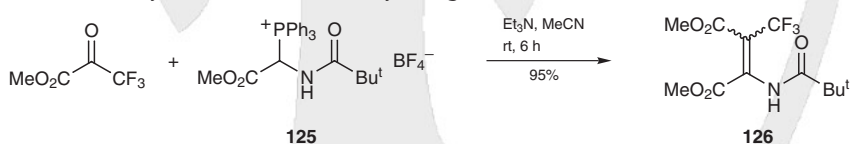
Scheme 65 Synthesis of an Enamide by Horner–Wadsworth–Emmons Alkenation^[108]

Methyl (2*Z*)-2-[(Benzyloxycarbonyl)amino]-3-(2-bromophenyl)propenoate (124**):**^[108]

DBU (1.2 mL, 7.88 mmol) was added slowly with stirring to the phosphorylacetate **123** (2.73 g, 8.24 mmol) in anhyd CH₂Cl₂ (20 mL) under argon. After ca. 10 min, 2-bromobenzaldehyde (1.39 g, 7.5 mmol) was added slowly, and then, 5 h later, the solvent was evaporated. The residue was redissolved in EtOAc (150 mL) and the soln was washed with 1 M HCl (2 × 30 mL), and brine (30 mL), dried (MgSO₄), and evaporated. The crude product was purified by chromatography (silica gel, EtOAc/CH₂Cl₂/hexanes 1:1:5) to give a colorless solid; yield: 2.81 g (96%).

21.4.3.1.6.1

Variation 1:
Alkenation Using Wittig Conditions

Wittig alkenation of methyl trifluoropyruvate with the α-amido phosphonium salt **125** provides the functionalized enamide **126** in high yield, but as a 1:1 mixture of *E*- and *Z*-isomers (Scheme 66).^[111]

Scheme 66 Synthesis of an Enamide by Wittig Alkenation^[111]

Dimethyl 2-[(2,2-dimethylpropanoyl)amino]-3-(trifluoromethyl)but-2-enedioate (126**):**^[111]

Methyl trifluoropyruvate (0.17 mL, 1.5 mmol) in MeCN (1.5 mL) and Et₃N (0.17 mL, 1.25 mmol) was added at rt to a stirred suspension of the tetrafluoroborate **125** (520 mg, 1.0 mmol) in MeCN (2.5 mL). After 6 h, the solvent was evaporated, and the residue was purified by chromatography [silica gel, EtOAc/benzene (**CAUTION: carcinogen**) 1:5]. The crude product was crystallized (benzene/hexane) to afford a 1:1 mixture of *E*- and *Z*-isomers; yield: 295 mg (95%).

21.4.3.1.6.2

**Variation 2:
Alkenation Using Thio-Wittig Conditions**

The enamide **128** is formed by a regioselective alkenation of *N*-thioformylacetamide with the ylide **127** (Scheme 67). A synthesis of iturinic acid has been described in which this methodology is used to generate a key intermediate.^[112]

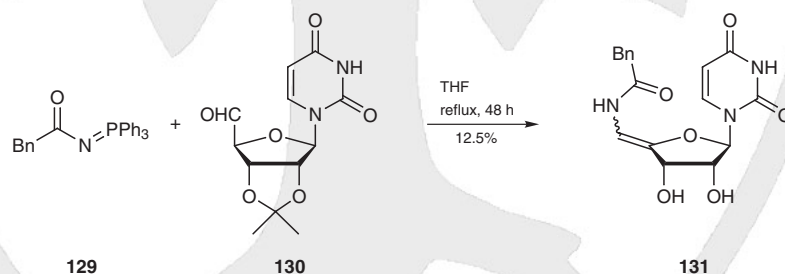
Scheme 67 Synthesis of an Enamide by Thio-Wittig Alkenation^[112]**Methyl (2*Z*)-3-(Acetylamino)propenoate (128):**^[112]

N-Thioformylacetamide (3.12 g 0.03 mol) was added to the ylide **127** (10.1 g, 0.03 mol) in benzene (100 mL) (**CAUTION: carcinogen**) and the mixture was refluxed for 16 h. The soln was concentrated under reduced pressure to yield an oil, which was redissolved in hexane and gently heated. The hexane layer was decanted off and this procedure was repeated several times, warming the mixture in each case, prior to separation. The combined hexane layers were filtered, concentrated under reduced pressure, and purified by chromatography (silica gel, Et₂O/hexane 1:1); yield: 3.3 g (70%).

21.4.3.1.6.3

**Variation 3:
Alkenation Using Aza-Wittig Conditions**

Aza-Wittig coupling between the iminophosphorane **129** and the aldehyde **130** proceeds very slowly, failing to reach completion after 6 days (Scheme 68). As a result the isolation of the pure enamide **131** is difficult and requires repeated chromatography; the yield is only 12.5%. This product is used in modeling studies to mimic the enzymatic binding activity of mureidomycin A.^[94]

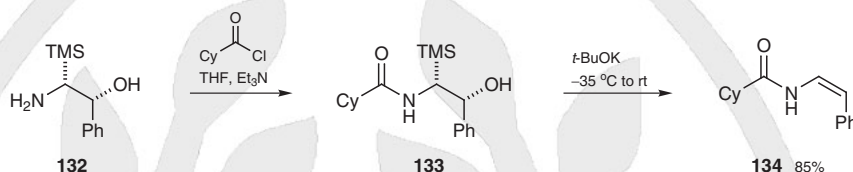
Scheme 68 Synthesis of an Enamide by Aza-Wittig Alkenation^[94]**5'-(*N*-Phenylacetyl)amino-5'-deoxy-4',5'-didehydro-2',3'-*O*-(isopropylidene)uridine (131):**^[94]

The iminophosphorane **129** (250 mg, 0.6 mmol, 1 equiv) in anhyd toluene (10 mL) was treated with a soln of the aldehyde **130** (178 mg, 0.6 mmol, 1 equiv) in anhyd THF (1 mL). After 48 h at reflux, the mixture was cooled, and the solvent removed under reduced pressure. Repeated column chromatography [silica gel, EtOAc/cyclohexane 2:1 (*R_f* 0.31) or MeOH/CH₂Cl₂ 1:25 (*R_f* 0.10)] gave a colorless solid; yield: 30 mg (12.5%).

21.4.3.1.6.4

Variation 4:
Alkenation Using Peterson Conditions

The enamide **134** is synthesized by the Peterson alkenation of the amide **133**, itself made by N-acylation of the amine **132** (Scheme 69).^[113] This methodology is utilized in the syntheses of (+)-crocin A^[114] and D.^[115]

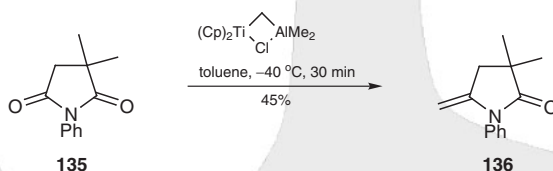
Scheme 69 Synthesis of an Enamide by Peterson Alkenation^[113]***N*-(*Z*)-2-Phenylvinyl]cyclohexanecarboxamide (**134**):^[113]**

Et₃N (0.27 mL, 1.91 mmol) and cyclohexanecarbonyl chloride (0.26 mL, 1.91 mmol) were added to the amine **132** (400 mg, 1.91 mmol) in THF (30 mL) at 0 °C. After 2 h of stirring at 0 °C, and 15 h at rt, the temperature of the mixture was reduced to –35 °C, and *t*-BuOK (0.47 g, 4.20 mmol) in THF (20 mL) was added, and then the mixture allowed to warm to rt. A pH 7 phosphate buffer (30 mL) was added to quench the reaction and the aqueous phase was extracted with Et₂O (3 × 50 mL). The combined organic layer and extracts were washed with sat. aq NaHCO₃, dried (Na₂SO₄), and concentrated to give a residue, which was purified by chromatography (alumina, EtOAc/hexane 1:15) to give a colorless solid; yield: 370 mg (85%).

21.4.3.1.6.5

Variation 5:
Alkenation Using Tebbe Conditions

Exposure of the pyrrolidinedione **135** to Tebbe's methylenation reagent provides the cyclic enamide **136** by attack at the less sterically encumbered carbonyl group (Scheme 70).^[116]

Scheme 70 Synthesis of an Enamide by Tebbe Alkenation^[116]**3,3-Dimethyl-5-methylene-1-phenylpyrrolidin-2-one (**136**):^[116]**

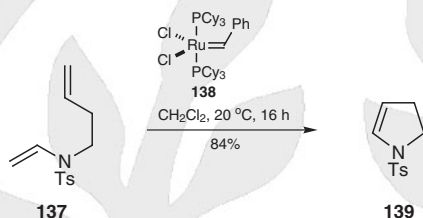
The pyrrolidinedione **135** (0.203 g, 1.00 mmol) was dissolved in THF (2 mL) and cooled to –40 °C, and then Tebbe's methylenation reagent (0.313 g, 1.10 mmol) in toluene (3.5 mL) was added dropwise over several min. The mixture was stirred for 0.5 h at –40 °C and allowed to warm to rt during the next 15 min. Workup gave a crude product [0.195 g (97%)], which crystallized (EtOH); yield: 0.09 g (45%).

21.4.3.1.6.6

Variation 6:
Alkenation by Ring-Closing Metathesis

Ring-closing metathesis (RCM) of acyclic enamides can be applied to the synthesis of five- and six-membered cyclic enamides using Grubb's first-generation catalyst **138**. For example, the sulfonamide **137** affords the corresponding dihydropyrrole **139** in 84% yield (Scheme 71).^[86] This method has been applied to the total synthesis of palau'amine.^[117]

Scheme 71 Synthesis of an Enamide by Ring-Closing Metathesis^[86]


1-Tosyl-2,3-dihydropyrrole (139):^[86]

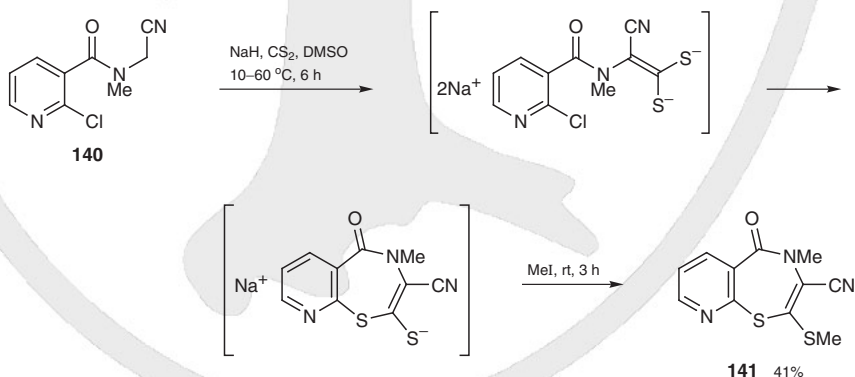
The sulfonamide **137** (80 mg, 0.319 mmol) in freshly distilled and degassed CH_2Cl_2 (20 mL) under argon was further degassed using argon, and then the Grubbs' catalyst **138** (13 mg, 0.016 mmol) was added. After 16 h at 20°C , the formation of the product was complete [TLC, Et_2O /pentane 1:4 (anisaldehyde, R_f 0.14)]. The solvent was removed under reduced pressure to give an oil that was purified by chromatography (silica gel, 0.1% Et_3N in Et_2O /pentane 1:4); yield: 60.0 mg (84%).

21.4.3.1.6.7

Variation 7:
Alkenation by Dithiocarboxylation

The nicotinamide **140** reacts with carbon disulfide in the presence of sodium hydride and undergoes intramolecular aromatic nucleophilic substitution. The initially formed thiolate is trapped by S-methylation to give a pyrido[3,2-*f*][1,4]thiazepine **141** (Scheme 72).^[118]

Scheme 72 Synthesis of an Enamide by Dithiocarboxylation^[118]



4-Methyl-2-(methylsulfanyl)-5(4H)-oxopyrido[3,2-f][1,4]thiazepine-3-carbonitrile (141):^[118]

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

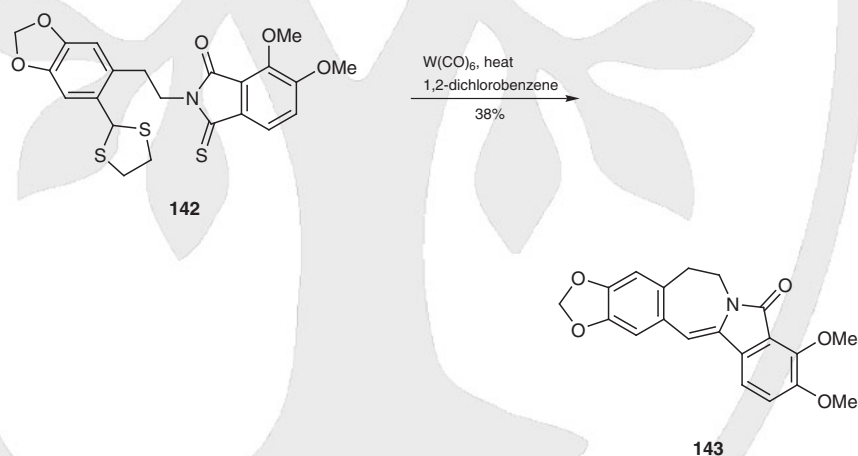
NaH as an 80% suspension in paraffin oil (0.5 g, 10 mmol) was added to the nicotinamide **140** (1.05 g, 5.1 mmol) and CS₂ (0.38 g, 0.3 mL, 5 mmol) in anhyd DMSO (20 mL) at 10 °C. After the addition, the mixture was warmed to 50–60 °C and stirred for 6 h. MeI (1.53 g, 0.66 mL, 10 mmol) was then added, and the mixture was stirred at rt for 3 h. The soln was poured into ice water, and the precipitate that formed was filtered, and dried. This yellow solid (1.76 g) was then heated with MeOH and filtered off. The filtrate was cooled and a pale yellow substance precipitated. Crystallization (MeOH) gave colorless needles; yield: 0.55 g (41%).

21.4.3.1.6.8

Variation 8:
Tungsten(0)-Mediated Coupling of Thiocarbonyl and Thioacetal Groups

The pentacyclic enamide **143** is formed by the reductive intramolecular cyclization of the thioxoisindolone **142** utilizing tungsten hexacarbonyl in chlorobenzene at reflux as the reducing agent (Scheme 73). The enamide is used as a key intermediate in a total synthesis of chilenine.^[92,119]

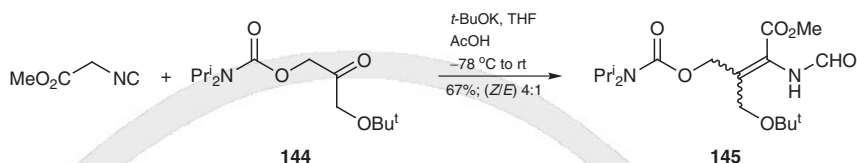
Scheme 73 Synthesis of an Enamide by Tungsten(0)-Mediated Coupling of Thiocarbonyl and Thioacetal Groups^[92]



21.4.3.1.6.9

Variation 9:
Schöllkopf Formylamino-Methylenation

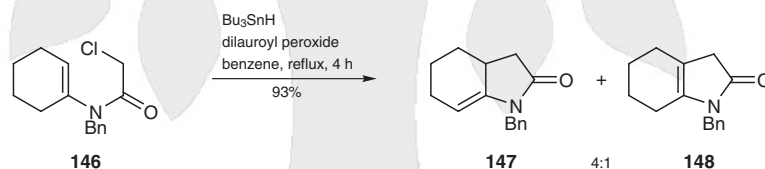
The reaction of the ketone **144** with methyl isocyanoacetate gives the α -aminopropenoate **145** as a 4:1 mixture *E*- and *Z*-isomers (Scheme 74).^[120] The rotameric nature of the formamide unit complicates still further the ¹H NMR spectrum of the mixture.

Scheme 74 Synthesis of an Enamide by Schöllkopf Formylamino-Methylenation^[120]**Methyl (*E/Z*)-3-*tert*-Butoxymethyl-4-(*N,N*-diisopropylcarbamoyloxy)-2-(formylamino)but-2-enoate (**145**):^[120]**

Methyl isocynoacetate (6.71 g, 67.7 mmol) was added dropwise to a soln of $t\text{-BuOK}$ (8.35 g, 74.4 mmol) in THF (150 mL) at -78°C , and the mixture was stirred for 30 min. Then, while stirring at the same temperature, it was treated with the ketone **144** (18.51 g, 67.7 mmol) in THF (40 mL). After 3 h, the mixture was allowed to warm to rt and glacial AcOH (5 mL) was added. The solvent was removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (1 L), washed with a phosphate buffer (100 mL), and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified by filtration through silica gel (300 g, Et_2O); yield: 17.7 g (67%).

21.4.3.1.7**Method 3:****Tributyltin Hydride Mediated Radical Cyclization of Enamides**

Efficient *endo-trig* oxidative radical cyclizations leading to enamides use tributyltin hydride and dilauroyl peroxide as both an initiator and an oxidant; thus, *N*-benzyl-2-chloro-*N*-cyclohex-1-en-1-ylacetamide (**146**) can be ring closed to a 4:1 mixture of the hexahydroindolones **147** and **148** (Scheme 75). Dibenzoyl peroxide or dicumyl peroxide may be used in place of dilauroyl peroxide. The ring system of certain Erythrina alkaloids can be constructed using this approach.^[121]

Scheme 75 Synthesis of an Enamide by Radical Cyclization with Tributyltin Hydride^[121]**1-Benzyl-1,3,3a,4,5,6-hexahydroindol-2(2H)-one (**147**) and 1-Benzyl-1,3,4,5,6,7-hexahydroindol-2(2H)-one (**148**); Typical Procedure:^[121]**

A soln containing dilauroyl peroxide (2.0 equiv, $0.038\text{ mmol}\cdot\text{mL}^{-1}$) in benzene (**CAUTION: carcinogen**) and Bu_3SnH (1.1 equiv) in benzene was added dropwise (syringe pump) to a degassed soln of the chloride **146** (1 equiv, $0.025\text{ mmol}\cdot\text{mL}^{-1}$) in boiling benzene over 4 h. The mixture was cooled, and the solvent was removed under reduced pressure. The residue was partitioned between hexane (10 mL) and MeCN (15 mL). The more polar layer was washed with hexane ($4 \times 10\text{ mL}$), and then the solvent was removed to afford a residue that was purified by chromatography (silica gel, EtOAc/hexanes) to give a 4:1 mixture of indoles **147** and **148**; yield: (93%).

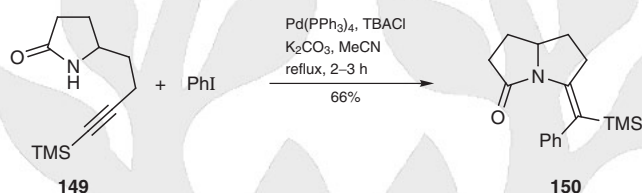
Similar procedures may be conducted using dibenzoyl peroxide in toluene soln at 95°C , or dicumyl peroxide in refluxing chlorobenzene, instead of dilauroyl peroxide in boiling benzene.

21.4.3.1.7.1

Variation 1:**Palladium(0)-Catalyzed Cyclization of Amides Bearing a But-3-yn-1-yl Side Chain**

The treatment of pyrrolidin-2-ones and oxazolidinones having a suitably located but-3-yn-1-yl side chain with aryl halides or vinyl bromides and a catalytic amount of tetrakis(triphenylphosphine)palladium gives rise to the corresponding bicyclic enamides. For example, the pyrrolidinone **149** undergoes intramolecular coupling to afford the pyrrolizinone **150** (Scheme 76).^[122] The aryl or vinyl group is incorporated with *cis*-selectivity with respect to the nitrogen ring atom.

Scheme 76 Synthesis of an Enamide by Palladium(0)-Catalyzed Cyclization of an Alkynylated Amide^[122]



(5E)-5-[Phenyl(trimethylsilyl)methylene]hexahydropyrrolizin-3(3H)-one (150**):**^[122]

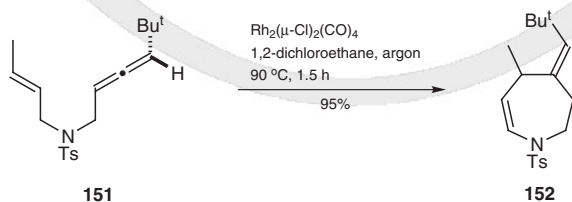
Benzene (7.5 mL) (**CAUTION: carcinogen**) was added to a mixture of K_2CO_3 (830 mg, 6 mmol), Bu_4NCl (624 mg, 2.25 mmol), and the solvent was removed under reduced pressure. After repeated azeotropic removal of H_2O , $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) was added and the flask was purged with argon. MeCN (30 mL) was added, followed by iodobenzene (1.22 g, 6.0 mmol) and the pyrrolidinone **149** (312 mg, 1.50 mmol) in MeCN (1.5 mL). The resulting yellow mixture was refluxed for 2–3 h, and then cooled, diluted with H_2O (75 mL), and extracted with Et_2O (3×75 mL). The combined Et_2O extracts were washed with H_2O (75 mL), brine (75 mL), dried (Na_2SO_4), and concentrated. Chromatography (silica gel, $EtOAc$ /pentane 1:1) gave an almost colorless solid; yield: 283 mg (66%).

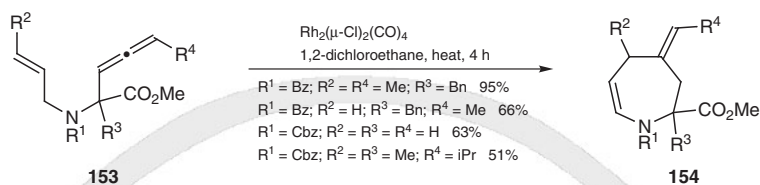
21.4.3.1.7.2

Variation 2:**Rhodium(I)-Catalyzed Cyclization of Ene-Allen**

In a novel strategy for the preparation of seven-membered heterocycles an ene-allene precursor is treated with a catalytic quantity of tetracarbonyldichlorodirhodium(I). In the case of the starting sulfonamide **151** the product is the azepine **152**, which is obtained in a very high yield. Similar reactions occur with amides and carbamates **153** giving the azepine esters **154** (Scheme 77). Here, however, the yields are variable and the products can be difficult to purify; not least because when $R^1 \neq H$ diastereomers can form. All these reactions proceed through an Alder-ene-type mechanism.^[123]

Scheme 77 Synthesis of Enamides by Rhodium(I)-Catalyzed Alder–Ene Carbocyclizations^[123]





(4Z)-4-(2,2-Dimethylpropylidene)-5-methyl-1-tosyl-2,3,4,5-tetrahydro-1H-azepine (152**):**^[123]

The sulfonamide **151** (29.9 mg, 0.009 mmol) and 1,2-dichloroethane (0.5 mL) were added to a flame-dried test tube equipped with a magnetic stirring bar. The test tube was evacuated and charged with argon (three cycles), and then $[\text{Rh}_2(\mu\text{-Cl})_2(\text{CO})_4]$ (1.7 mg, 0.00045 mmol) was added in 1,2-dichloroethane. The mixture was heated at 90 °C for 1.5 h. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, EtOAc/hexanes 1:9) to give an oil; yield: 28.4 mg (95%).

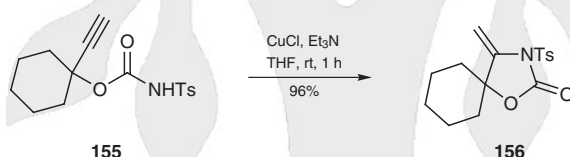
21.4.3.1.7.3

Variation 3:

Copper(I)-Catalyzed Cyclization of Prop-2-ynyl Carbamates

An intramolecular cyclization of the carbamate **155** to afford the spiro compound **156** is accomplished by the action of 10 mol% copper(I) chloride and 10 mol% triethylamine (Scheme 78). In related cyclizations, where the nitrogen atom is substituted with an acyl group, a stronger base (potassium *tert*-butoxide) is necessary and silver salts enhance the reactions better than copper(I) salts. However, with an aryl or an alkyl group bonded to the nitrogen atom only potassium *tert*-butoxide is needed and, in such cases, the addition of copper(I) chloride inhibits the reaction.^[124]

Scheme 78 Synthesis of an Enamide by Copper(I)-Catalyzed Intramolecular Cyclization^[124]



4-Methylene-3-tosyl-1-oxa-3-azaspiro[4.5]decan-2-one (156**):**^[124]

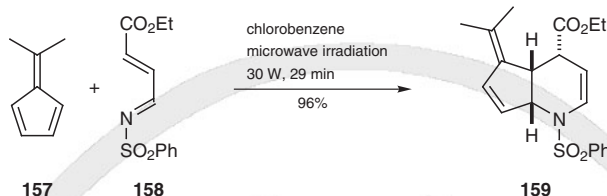
A flask containing the alkyne **155** (321 mg, 1.0 mmol) and CuCl (10 mg, 0.1 mmol) was purged with N_2 and then anhyd THF (5 mL) and Et_3N (14 μL , 0.1 mmol) was introduced via syringe. The mixture was stirred at rt for 1 h, and then diluted with EtOAc (50 mL), and washed with aq NaHCO_3 . The progress of the reaction was monitored [TLC silica gel, EtOAc/benzene (**CAUTION: carcinogen**) 1:16]. The organic phase was dried (MgSO_4) and condensed to give a waxy solid, which was purified by chromatography (silica gel, EtOAc/benzene) to give a colorless solid; yield: 308 g (96%).

21.4.3.1.8

Method 8:

Hetero [4 + 2] Cycloaddition

The inverse-electron-demand hetero-Diels–Alder reaction of the *N*-sulfonyl-1-azabuta-1,3-diene **158** with dimethylfulvene (**157**) is both regio and stereoselective and provides an efficient route to the cyclopenta[*b*]pyridine **159**.^[125] The cycloaddition occurs via a head-to-head *endo*-transition state. Several techniques can be used to effect this reaction, of which the highest yielding is promoted by microwave irradiation (Scheme 79).

Scheme 79 Synthesis of an Enamide by Hetero [4 + 2] Cycloaddition^[125]

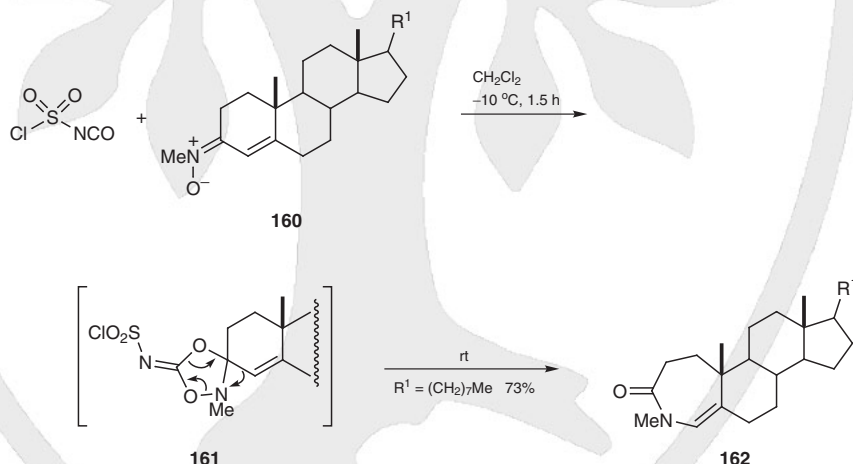
Ethyl (4R,4aS,7aR)-5-Isopropylidene-1-(phenylsulfonyl)-4,4a,5,7a-tetrahydro-1H-cyclopenta[b]pyridine-4-carboxylate (159**):**^[125]

A mixture of dimethylfulvene (**157**; 66 mg, 0.62 mmol) and the azabutadiene **158** (134 mg, 0.5 mmol) in 2-chlorobenzene (3 mL) were placed in a quartz vial (10 mL) and subjected to microwave irradiation at 30 W. After a period of 2–3 min, the temperature of the mixture reached a plateau of 125 °C where it remained throughout the reaction. After irradiation for 29 min and cooling, the soln was concentrated and the residue was purified by chromatography (silica gel, EtOAc/hexane 1:6) to give a yellow oil; yield: 179 mg (96%).

21.4.3.1.8.1

Variation 1:**[3 + 2] Cycloaddition and Rearrangement**

The reaction of the steroidal nitronone **160** [$R^1 = (CH_2)_7Me$] with chlorosulfonyl isocyanate gives the corresponding enamide **162** [$R^1 = (CH_2)_7Me$] in 73% yield. The reaction mechanism is thought to involve a [3 + 2] cycloaddition, followed by a ring expansion/rearrangement within the adduct **161** (Scheme 80).^[126]

Scheme 80 Synthesis of an Enamide by [3 + 2] Cycloaddition and Rearrangement^[126]

Tetracyclic Azepinones **162 by Ring Expansion of Steroidal Nitronones; General Procedure:**^[126]

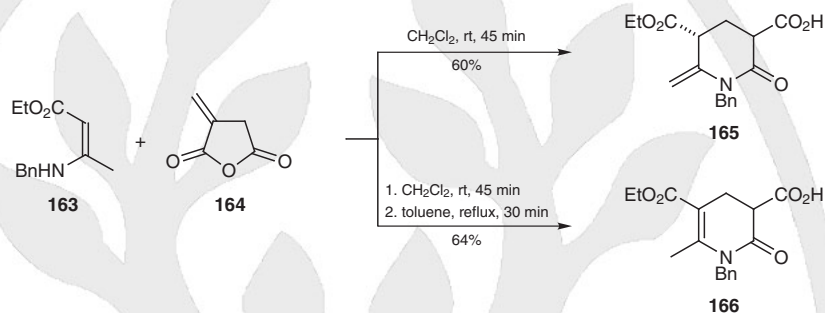
CSI (0.09 mL, 10 mmol) in CH_2Cl_2 (5 mL) was added dropwise at $-15\text{ }^\circ\text{C}$ to a stirred soln of the nitronone **160** (10 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 1.5 h. The mixture was poured directly onto a column of silica gel, which was then eluted [$CHCl_3$ /benzene (**CAUTION: carcinogen**) 2:3].

21.4.3.1.8.2

Variation 2:**Aza-Annulation of Enaminones with Itaconic Anhydride**

The enamino ester **163** reacts with itaconic anhydride (**164**) in dichloromethane at room temperature to give mainly the enamide **165**, but when the reaction mixture is refluxed in toluene only the more thermodynamically stable acid **166** with an endocyclic double bond is isolated (Scheme 81).^[127]

Scheme 81 Synthesis of Enamides by Aza-Annulation of Enaminones with Itaconic Anhydride^[127]



(5R)-1-Benzyl-5-(ethoxycarbonyl)-6-methylene-2-oxopiperidine-3-carboxylic Acid (165):^[127] Itaconic anhydride (**164**) (500 mg, 4.5 mmol) was added to a soln of the enamino ester **163** (4.5 mmol) in CH_2Cl_2 (25 mL) and the mixture was stirred at rt for 45 min. Concentration under reduced pressure, followed by chromatography [silica gel, EtOAc (R_f 0.66)], gave the enamide **165**; yield: 880 mg (60%).

1-Benzyl-5-(ethoxycarbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carboxylic Acid (166):^[127]

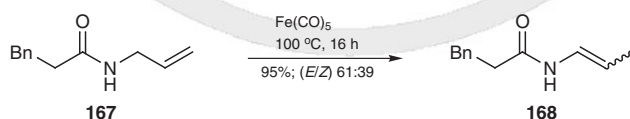
The crude product **165** was refluxed in toluene (20 mL) for 30 min, and then the solvent was concentrated under reduced pressure. Chromatography (silica gel, EtOAc) of the residue gave only the acid **166** with an endocyclic double bond (R_f 0.66); yield: 950 mg (64%).

21.4.3.1.9

Method 9:**Isomerization of N-Allyl Amides with Pentacarbonyliron**

The isomerization of various N-allylated amides in the presence of iron pentacarbonyl smoothly affords the corresponding enamides. For example, the amide **167** gives the enamine **168** in 95% yield as a mixture of geometrical isomers (Scheme 82).^[128] The methodology is compatible with various functional groups, including amino and hydroxy groups, and the products are shown to arise from the *cis*-elimination of a metal hydrido species. When the nitrogen atom of the starting amide is substituted by a second group only the *E*-isomer of the product is obtained.

Scheme 82 Synthesis of an Enamide by Iron(0)-Catalyzed Isomerization of an N-Allylated Amide^[128]



3-Phenyl-*N*-prop-1-enylpropanamide (168):^[128]

CAUTION: Pentacarbonyliron is a pulmonary irritant. Handling requires care because the heavy vapor released into the air following a spillage is hard to contain in standard extraction facilities.

A mixture of the amide **167** (945 mg, 5 mmol) and $\text{Fe}(\text{CO})_5$ (0.2 mL, 1 mmol) was stirred under argon for 16 h at 100 °C. The mixture was allowed to reach rt, and then the catalyst was removed under reduced pressure, and collected in a trap cooled by liq N_2 . The contents of the trap were treated with a 5% alcoholic FeCl_3 soln to destroy $\text{Fe}(\text{CO})_5$. The residue was redissolved in CHCl_3 and filtered through Celite. Evaporation of the solvent under reduced pressure and chromatography of the residue (silica gel, $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ 1:10) afforded a 61:39 mixture of *E*- and *Z*-isomers; yield: 898 mg (95%).

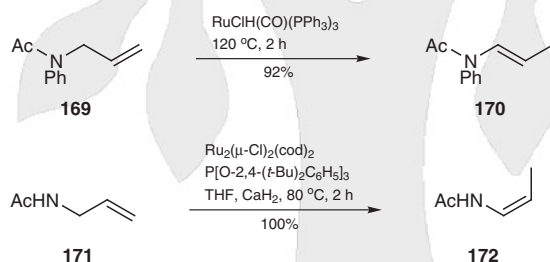
21.4.3.1.9.1

Variation 1:

Isomerization of *N*-Allyl Amides with Carbonyl(hydrido)tris(triphenylphosphine)ruthenium(II)

The isomerization of various *N*-allyl-*N*-arylethanamides in the presence of carbonyl(chloro)hydridotris(triphenylphosphine)ruthenium(II) mainly affords the corresponding *E*-enamides; thus, the phenylated amide **169** gives its isomer **170** in 92% yield (Scheme 83). The aryl group is thought to direct the isomerization through ruthenium coordination within the transition state.^[129] By changing the ligands of the ruthenium complex, removing the coordinating phenyl group, and adding calcium hydride, the reaction reverses its selectivity and, for example, the amide **171** then gives the *Z*-enamide **172** in a quantitative yield (Scheme 83).^[130]

Scheme 83 Synthesis of Enamides by Ruthenium(II)-Catalyzed Isomerization of *N*-Allyl Amides^[129,130]



(*E*)-*N*-Phenyl-*N*-(prop-1-en-1-yl)acetamide (170); Typical Procedure:^[130]

A mixture of the amide **169** (1.75 mg 0.1 mmol) and $[\text{RuClH}(\text{CO})(\text{PPh}_3)_3]$ (0.5 mol% Ru) was heated at 120 °C for 2 h under argon. After cooling to rt, hexane (300 mL) was added and the mixture was cooled to 0 °C. The precipitated ruthenium complex and Ph_3P were removed by filtration. The filtrate was concentrated under reduced pressure and purified by chromatography [silica gel (5 g), hexanes] to yield the *E*-enamide **170** as a single isomer; yield: 1.6 mg (92%).

(*Z*)-*N*-(Prop-1-en-1-yl)acetamide (172):^[130]

A mixture of the amide **171** (10 mg 0.01 mmol) and $[\text{Ru}_2(\mu\text{-Cl})_2(\text{cod})_2]$ (1 mol% Ru), tris(2,4-di-*tert*-butylphenyl) phosphite (1 mol%), and CaH_2 (10 mol%) were heated at 80 °C for 2 h under argon. After cooling to rt, benzene/hexane (1:3, 10 mL) (**CAUTION:** carcinogen) was added and the precipitate filtered off. The filtrate was concentrated under reduced pressure and purified by chromatography [siliceous mesoporous cellular foam (0.6 g), hex-

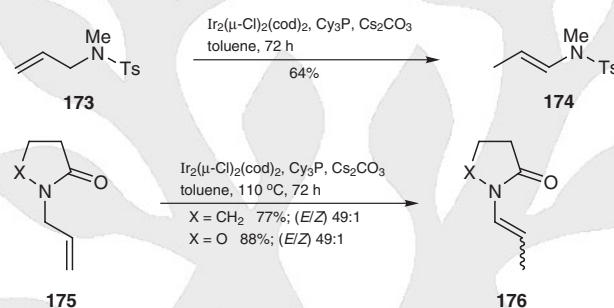
anes] to yield the crude enamide. The product was distilled under reduced pressure (90 °C, 10 Torr) and the solid that formed was crystallized (MeOH); yield: 10 mg (100%).

21.4.3.1.9.2

Variation 2:
Isomerization of *N*-Allyl Amides with
Dichlorobis(cyclooctadiene)diiridium(I)

Another catalyst that can be used to isomerize various *N*-allylated amides and related compounds to afford mainly the *E*-configured products is di- μ -chlorobis(cyclooctadiene)-diiridium(I). Examples include the sulfonamide **173**, the cyclic amide **175** (X = CH₂) and the related carbamate **175** (X = O) which smoothly afford the corresponding (*E*)-enamides **174**, **176** (X = CH₂) and **176** (X = O), respectively (Scheme 84).^[131] *N*-But-2-enylamides do not isomerize under these conditions.

Scheme 84 Synthesis of Enamides by Iridium(I)-Catalyzed Isomerization of *N*-Allyl Amides^[131]



***N*-Methyl-*N*-(*E*)-prop-1-enyl-4-toluenesulfonamide (**174**):**^[131]

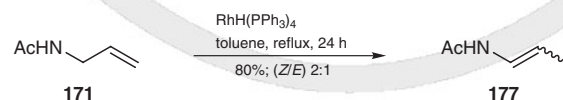
The *N*-allylated amide **173** (563 mg, 0.25 mmol), anhyd toluene (0.5 mL), Cs₂CO₃ (4.0 mg, 0.0125 mmol), tricyclohexylphosphine (7.0 mg, 0.025 mmol) and [Ir₂(μ -Cl)₂(cod)₂] (9.0 mg, 0.0125 mmol) were placed in a 1-mL vial. The orange mixture was degassed, placed under a positive pressure of N₂, the vial was sealed and heated at 110 °C for 72 h. The mixture was then cooled to rt, the toluene was removed under reduced pressure and the residue was purified by chromatography (silica gel, Et₂O/pentane 1:4); yield: 359 mg (64%).

21.4.3.1.9.3

Variation 3:
Isomerization of *N*-Allyl Amides with
Hydrotetrakis(triphenylphosphine)rhodium

The isomeric enamides **177** are synthesized from the *N*-allylacetamide **171** by a double bond migration induced by a rhodium(I) catalyst (Scheme 85). A ruthenium catalyst induces the same rearrangement and again the *Z/E*-product ratio obtained is 2:1.^[132]

Scheme 85 Synthesis of an Enamide by Rhodium(I)-Catalyzed Isomerization of an *N*-Allyl Amide^[132]



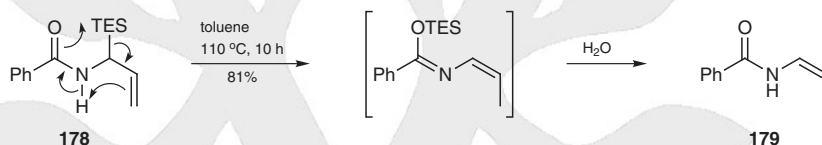
(*E/Z*)-*N*-Prop-1-enylacetamide (177):^[132]

N-Allylacetamide (**171**; 1.0 g, 1.0 mmol) in degassed toluene (5 mL) containing RhH(PPh₃)₄ (56 mg, 0.05 mmol) was stirred and refluxed for 24 h. The reaction was monitored by TLC, and ¹H NMR analysis of the mixture indicated a 80% conversion with a *Z/E*-product ratio of about 2:1. The mixture was cooled to rt, and concentrated under reduced pressure, the oily residue was distilled in a Kugelrohr apparatus (100 °C, 20 μm) to yield a colorless crystalline solid; yield: 80% (*Z/E* 2:1). The solid was recrystallized twice (Et₂O/hexane) to afford the *Z*-isomer with a trace of the *E*-form. The mixture was completely separated by MPLC (silica gel, acetone/hexane 3:7, 2.7 atm; 100 × 2 cm glass column). Each isomer was sublimed at 40 °C (0.01 Torr).

21.4.3.1.10

**Method 10:
Dyotropic Rearrangement**

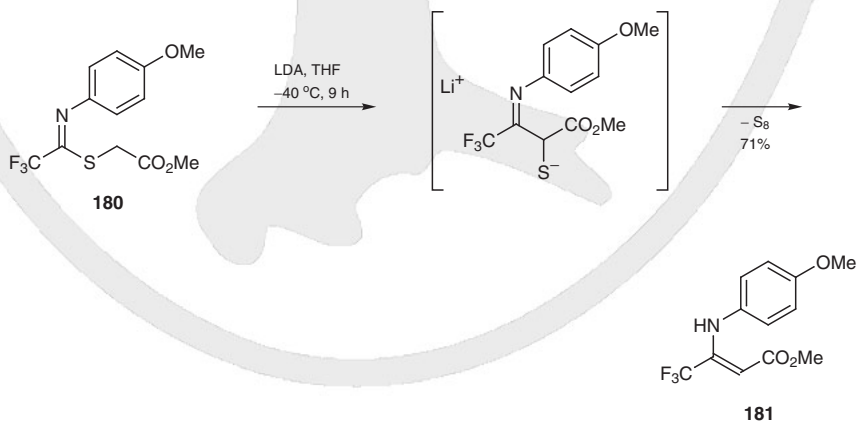
A novel transformation of the silylated amide **178** into the *Z*-enamide **179** (Scheme 86) embodies a formal stepwise 10-electron double-sigmatropic, or dyotropic, rearrangement, which occurs when the starting material is heated in toluene at 110 °C for 10 h. This method is used in the total syntheses of the proteasome inhibitors TMC-95A and TMC-95B.^[133] Computational studies have been carried out to provide support for the proposed reaction mechanism.^[134]

Scheme 86 Synthesis of an Enamide by Dyotropic Rearrangement^[133]

21.4.3.1.10.1

**Variation 1:
1,2-Thio-Wittig-Type Rearrangement Reactions**

A base-catalyzed 1,2-thio-Wittig-type rearrangement of the methyl [(iminomethyl)sulfonyl]acetate **180** gives the enamide **181** through a desulfurization process (Scheme 87).^[135]

Scheme 87 Synthesis of an Enamide by a 1,2-Thio-Wittig-Type Rearrangement^[135]

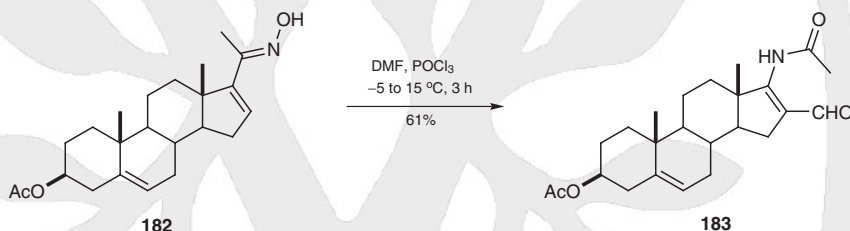
Methyl 3-[(4-Methoxyphenyl)amino]-4,4,4-trifluorobut-2-enoate (181):^[135]

LDA was prepared by adding BuLi in hexane (0.75 mmol) dropwise to $i\text{Pr}_2\text{NH}$ (0.75 mmol) in freshly distilled anhyd THF (3 mL) precooled to -40°C under argon, and the mixture was stirred for 30 min at this temperature. The methyl [(iminomethyl)sulfanyl]acetate **180** (156 mg, 0.5 mmol) was added dropwise to the LDA soln over 10 min, and the mixture was then stirred for 9 h. After almost all the starting material had disappeared (TLC), Et_2O (10 mL) was added and the reaction was quenched by the addition of aq NH_4Cl (10 mL). The organic layer was then separated, washed with H_2O , and dried (MgSO_4). Purification by chromatography (silica gel, EtOAc /hexane 1:10) gave a yellowish solid; yield: 98 mg (71%).

21.4.3.1.10.2

Variation 2:**Beckmann Rearrangement and α -Formylation**

A preparation of a novel class of steroidal 16-formyl-17-enamides involves a Beckmann rearrangement of the corresponding oximes, with concomitant formylation at an α -carbon atom. This takes place when the substrates are subjected to Vilsmeier conditions; thus, the oxime **182** affords the enamide **183** when it is treated with phosphoryl chloride and dimethylformamide (Scheme 88).^[136]

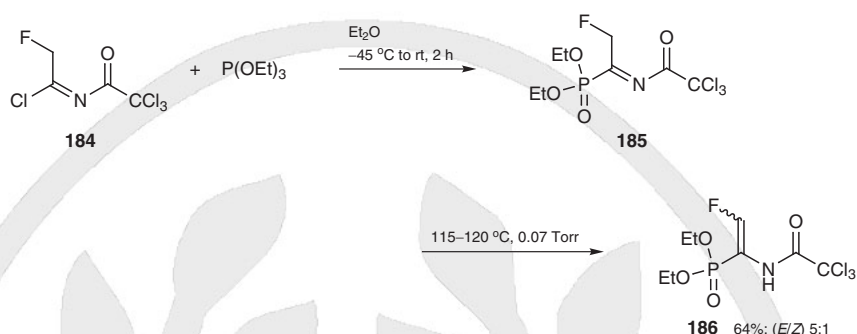
Scheme 88 Synthesis of an Enamide by Beckmann Rearrangement^[136]**(3 β)-17-(Acetyl-amino)-16-formylandrosta-5,16-dien-3-yl Acetate (183):**^[136]

POCl_3 (11.2 mL, 12 mmol) and DMF (10 mL, 13 mmol) 0°C were added to an oven-dried flask flushed with N_2 . The mixture was stirred vigorously until a colorless salt separated out. A cold soln of the oxime **182** (1.16 g, 3.13 mmol) in CHCl_3 (100 mL) was prepared and was added to the salt at -5°C under N_2 . Stirring was continued for 3 h, during which time the temperature gradually rose to 15°C . The mixture was immediately poured into ice-cold H_2O and stirred vigorously. Removal of some solvent under reduced pressure at 20°C gave an aqueous mixture, which was basified with powdered KOH to pH 10, and then warmed on a water bath at 60°C for 2 h. Extraction of the mixture with CH_2Cl_2 (3×20 mL) and washing with H_2O (2×50 mL) gave a light yellow-colored soln that was dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a colorless solid; yield: 760 mg (61%).

21.4.3.1.10.3

Variation 3:**Imine/Enamide Rearrangement**

The imidoyl chloride **184** undergoes an Arbuzov reaction with triethyl phosphite to form an imidoylphosphonate intermediate **185** that through a 1,3-hydrogen transfer yields the corresponding enamide **186** in a *E/Z*-product ratio of 5:1 (Scheme 89).^[137]

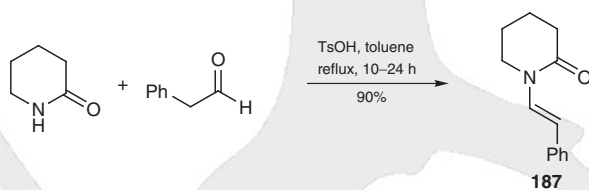
Scheme 89 Synthesis of a Phosphorylated Fluorenamide by Imine/Enamide Rearrangement^[137]**(E/Z)-1-(Diethoxyphosphoryl)-2-fluoro-1-(trichloroacetyl)ethene (186):**^[137]

A soln of the imidoyl chloride **184** (12 mmol) in Et₂O (10 mL) was cooled to –45 °C and P(OEt)₃ (12 mmol) was added dropwise with vigorous stirring. The mixture was gradually warmed to rt over 2 h and concentrated under reduced pressure at rt to yield a residue containing a 1:1 mixture of the imine **185** and the enamides **186**. Vacuum distillation of the residue led to complete conversion of the imine **185** into an oil that contained a 5:1 mixture of the *E*- and *Z*-isomers of the title compound; yield: 64%. The pure *E*-enamide was obtained by fractional crystallization of the mixed isomers (Et₂O/petroleum ether 1:1).

21.4.3.1.11

Method 11:**Condensation of Amides and Aldehydes**

A simple synthesis of *E*-enamides is accomplished by treating lactams with aldehydes under mild conditions. A wide variety of solvents, acids and conditions can be used, but toluene and a catalytic amount of 4-toluenesulfonic acid (with azeotropic removal of the water formed) is a good choice. Both aryl and alkyl aldehydes undergo the condensation. Scheme 90 illustrates a typical procedure in which piperidin-2-one is condensed with phenylacetaldehyde to afford the enamide **187**.^[138]

Scheme 90 Synthesis of an Enamide by the Condensation of an Amine with an Aldehyde^[138]**N-[(E)-2-Phenyleth-1-en-1-yl]piperidin-2-one (187):**^[138]

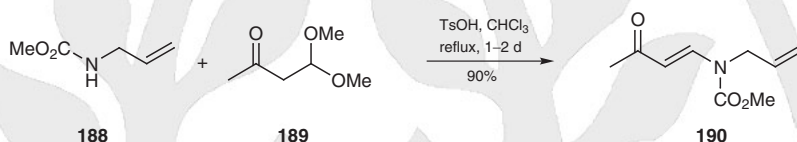
A mixture of piperidin-2-one (9.9 g, 0.1 mol) and phenylacetaldehyde (12.0 g, 0.1 mol) were dissolved in anhyd toluene (200 mL) and treated with TsOH (50 mg). The flask was fitted with a Dean–Stark trap and condenser and the soln was refluxed until the maximum amount of H₂O was collected (10–24 h). The soln was then cooled to rt, washed with sat. aq NaHCO₃ (100 mL), and then the combined aqueous layers were extracted with Et₂O (100 mL). The organic phases were combined, dried (MgSO₄), and concentrated

under reduced pressure. The residue was then purified by chromatography (silica gel); yield: 18 g (90%).

21.4.3.1.11.1 Variation 1: Amide Addition to Acetals

The enecarbamate **190** is prepared by an acid-catalyzed condensation of the carbamate **188** with the commercially available acetal **189** (Scheme 91).^[139] On a small scale, the product can be isolated by column chromatography to give the desired enamide in 90% yield, but on a larger scale purification by vacuum distillation (unoptimized) gives only half that amount.

Scheme 91 Synthesis of an Enamide by the Addition of an Amide to an Acetal^[139]



Methyl Allyl[(1E)-3-oxobut-1-en-1-yl]carbamate (**190**):^[139]

Small scale: A soln of the carbamate **188** (230 mg, 2.0 mmol) and the acetal **189** (0.57 mL, 4.3 mmol) in CHCl_3 (5 mL) containing TsOH (20 mg) was gently refluxed for 27 h. Concentration of the mixture, followed by chromatography (silica gel, EtOAc/hexane 1:1) gave a colorless oil; yield: 330 mg (90%).

Larger scale: A soln of the carbamate **188** (44.1 g, 383 mmol) and the acetal **189** (52 mL, 392 mmol) in CHCl_3 (1 L) containing TsOH (2 g) was gently refluxed for 44 h, during which time MeOH was removed using a Soxhlet apparatus packed with 4-Å molecular sieves. The mixture was washed with a sat. aq NaHCO_3 (200 mL), and brine (200 mL), dried (MgSO_4), and concentrated under reduced pressure. The residue was distilled twice to give a yellow oil; yield: 31.3 g (45%).

21.4.3.1.12 Method 12: Addition of Alcohols to Isocyanates

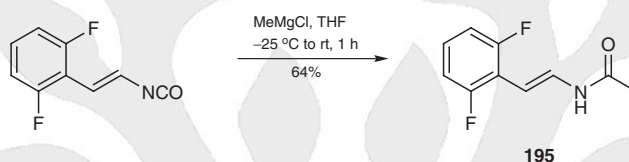
The enecarbamate **193** is synthesized from the corresponding vinyl isocyanate **192** by the addition of 2-(trimethylsilyl)ethanol, the isocyanate being generated by a Curtius rearrangement of the acyl azide **191** (Scheme 92). This methodology is employed in the total synthesis of (+)-crocin D,^[140] but a drawback is the difficulty in controlling the geometry of the vinyl isocyanate before the addition of the nucleophile. In another example of this general procedure the ene-carbamate **43** is obtained by the addition of prop-2-yn-1-ol to phenyl isocyanate under basic conditions.^[40]

vial. To this residue was added an aliquot of a soln prepared from HF•pyridine (0.5 g) in pyridine (1.25 mL) and THF (6.75 mL, 100 μ L·mg⁻¹). After stirring at rt for 6–12 h, the reaction was quenched by the addition of a pH 7.0 phosphate buffer, followed by extraction (EtOAc), drying (Na₂SO₄), and concentration. The residue was purified by semi-preparative HPLC (5 μ Luna silica gel, 250 \times 10-mm column).

21.4.3.1.12.2 Variation 2: Addition of Alkyl Anions to Isocyanates

In related chemistry isocyanates, generated by the Curtius rearrangement, are reacted with Grignard reagents to give enamides. In a specific case 2,6-difluorocinnamic acid is converted into its acyl azide and combined with methylmagnesium chloride to yield the enamide **195** (Scheme 94).^[146]

Scheme 94 Synthesis of an Aryl Enamide by the Addition of a Grignard Reagent to an Isocyanate^[146]



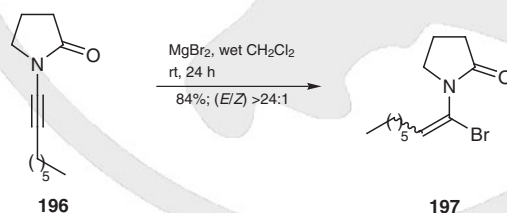
N-[(E)-2-(2,6-Difluorophenyl)vinyl]acetamide (195):^[146]

A soln of 2,6-difluorostyryl isocyanate (345 mg, 1.91 mmol) in THF (7 mL) was added dropwise with stirring to 3 M MeMgCl (2.10 mmol) in THF, precooled to -25 °C and protected by an atmosphere of N₂. After stirring for 30 min at -25 °C, then for another 30 min at rt, the product was hydrolyzed with 10% aq NH₄Cl, and extracted with CH₂Cl₂. The extract was dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by radial TLC (CH₂Cl₂/petroleum ether); yield: 241 mg (64%).

21.4.3.1.13 Method 13: Hydrohalogenation of Ynamides

Highly stereoselective syntheses of α -halogenated enamides from the reactions of magnesium salts and ynamides in wet solvents at ambient temperature have been accomplished. Scheme 95 illustrates the procedure by summarizing the synthesis of the bromo enamide **197** from 1-oct-1-yn-1-ylpyrrolidin-2-one (**196**); the *E/Z* ratio is 24:1.^[57]

Scheme 95 Synthesis of a Halogenated Enamide by Hydrohalogenation of an Ynamide^[57]



1-(1-Bromooct-1-en-1-yl)pyrrolidin-2-one (197); Typical Procedure:^[57]

MgBr₂ (0.1 mmol) was added to the ynamide **196** (19.3 mg, 0.1 mmol) in wet CH₂Cl₂ (2 mL). The vessel containing the heterogeneous mixture was capped and its contents were stirred vigorously at rt for 24 h. The mixture was washed with a sat. aq Na₂S₂O₃ (2 \times 2 mL)

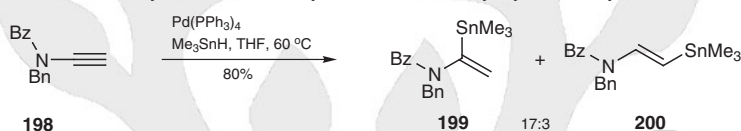
and the organic layer was then dried (Na_2SO_4), and filtered through a short column of alumina. The solvent was removed from the filtrate under reduced pressure and the residue was purified by chromatography (silica gel, EtOAc/hexanes 0 to 25%) to give an orange oil; yield: 23.0 mg (84%).

21.4.3.1.13.1

Variation 1: Hydrostannylation of Ynamides

A palladium(0)-catalyzed stannylation of ynamides has been developed for the efficient preparation of a wide range of enamides that are useful in organic synthesis. In a typical example the stannylated enamides **199** and **200** are formed by the reaction of the ynamide **198** with trimethylstannane in the presence of tetrakis(triphenylphosphine)palladium; here the attack of the stannane occurs preferentially at the α -carbon atom of the *N*-alkynyl group (Scheme 96).^[48]

Scheme 96 Synthesis of Stannylated Enamides by Hydrostannylation of an Ynamide^[48]



N-Benzyl-N-[1-(trimethylstannyl)vinyl]benzamide (**199**):^[48]

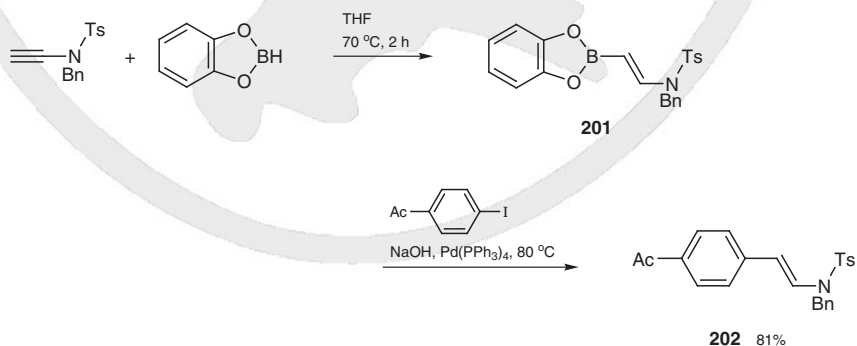
$\text{Pd(PPh}_3)_4$ (0.6 mg, 0.1 mol% Pd) was added to a soln of the ynamide **198** (117 mg, 0.5 mmol) and Bu_3SnH (0.55 mmol) in anhyd and degassed THF (25 mL) in a flame-dried flask (100 mL). The mixture was degassed, protected under N_2 , and warmed to 60 °C. Upon completion of the reaction (TLC), the mixture was concentrated under reduced pressure, and the residue was purified by chromatography (silica gel, Et₂O/pentane); yield: 160 mg (80%).

21.4.3.1.13.2

Variation 2: Hydroboration/Suzuki–Miyaura Cross-Coupling of Ynamides

The sulfonamide **202** is synthesized from *N*-benzyl-*N*-ethynyl-4-toluenesulfonamide by hydroboration with catecholborane and subsequent Suzuki–Miyaura cross-coupling of the product **201** with 4-iodoacetophenone (Scheme 97). Although this was the first reaction of its kind, it has wider application and other aryl iodides or bromides can be used affording a number of *E*- β -arylenamides and 3-(2'-amidovinyl)indoles.^[56]

Scheme 97 Synthesis of an Enamide by the Hydroboration/Suzuki–Miyaura Cross-Coupling of an Ynamide^[56]



N-[(E)-2-(4-Acetylphenyl)ethenyl]-N-benzyl-4-toluenesulfonamide (202):^[56]

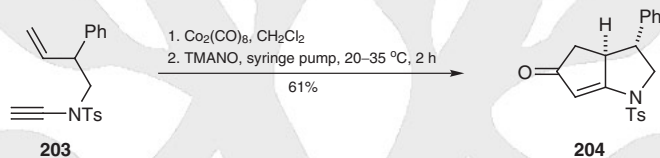
N-Benzyl-N-ethynyl-4-toluenesulfonamide (63 mg, 0.22 mmol) was placed in a Schlenk tube with a screw cap, and THF (2 mL) was added, and the contents were protected under N₂. 1 M Catecholborane in THF (0.33 mL) was introduced via a syringe and the sealed tube was kept at 70–80 °C for 2 h. Thereafter, NaOH (17.6 mg, 0.44 mmol), Pd(PPh₃)₄ (17 mg, 0.02 mmol), 4-iodoacetophenone (37 mg, 0.15 mmol) and additional THF (3 mL) were added in succession, and the mixture was kept at 80 °C for additional 4 h. After cooling, Et₂O (20 mL) and 3 M NaOH (20 mL) were added, and the mixture was washed with brine. The organics were dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by chromatography [silica gel, Et₂O/hexanes 1:19; TLC, EtOAc/hexanes 1:4 (*R_f* 0.21)] to give a colorless solid; yield: 49 mg (81%).

21.4.3.113.3

**Variation 3:
Pauson–Khand Reactions of Ynamides**

Certain eneynamides undergo inter- and intramolecular Pauson–Khand reactions. In the case shown in Scheme 98 the tetrahydrocyclopenta[*b*]pyrrolone **204** can be constructed from the sulfonamide **203** in a regioselective manner.^[47] This reaction is one of the first in which a ynamide was subjected to a transition-metal-mediated ring closure.

Scheme 98 Synthesis of an Enamide by Pauson–Khand Reaction of an Ynamide^[47]

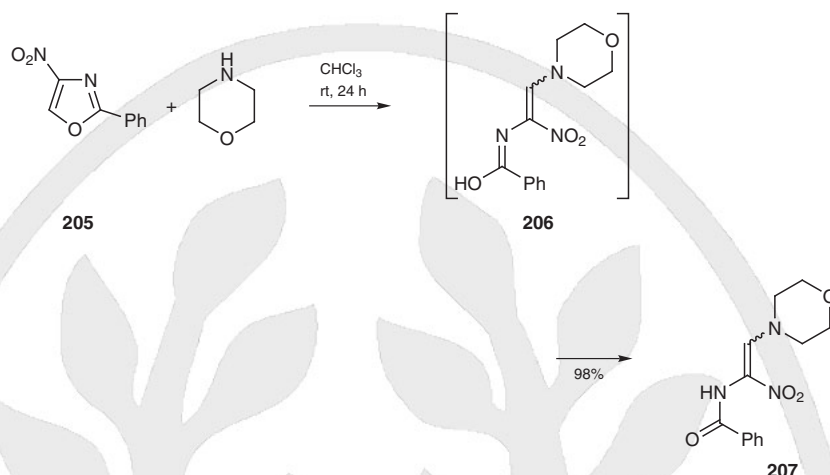
**(3*R*,3*aS*)-3-Phenyl-1-tosyl-2,3,3*a*,4-tetrahydrocyclopenta[*b*]pyrrol-5(1*H*)-one (204):**^[47]

The ene-ynamide **203** (92 mg, 0.28 mmol) was added to a suspension of Co₂(CO)₈ (116 mg, 0.34 mmol) in CH₂Cl₂ at 20–35 °C. The formation of the cobalt complex was monitored by TLC [silica gel, Et₂O/petroleum ether 1:4 (*R_f* 0.48)]. After the reaction was complete, a soln of TMANO (115 mg, 1.53 mmol) in CH₂Cl₂ (8 mL) was added by a syringe pump over 2 h. The mixture was then filtered through a plug of Alox III/N (CH₂Cl₂/EtOAc). Purification by chromatography (Alox III/N, Et₂O/petroleum ether 1:1) gave the title compound; yield: 60 mg (61%).

21.4.3.114

**Method 14:
Oxazole Ring Opening with Amines**

Ring opening of the nitrooxazole **205** with morpholine gives the enamide **207** (Scheme 99). This is an example of a more general reaction in which a diverse group of amino nucleophiles can be used to cleave the heterocycle.^[147] In the case illustrated subsequent cycloaddition reactions may proceed through the tautomer **206** of the ring-opened product.

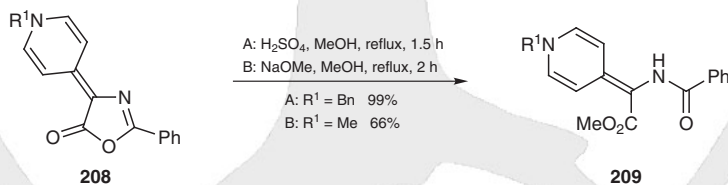
Scheme 99 Synthesis of a Nitroenamide by the Ring Opening of a Nitrooxazole with an Amine^[147]**N-[(E)-2-Morpholino-1-nitrovinyl]benzamide (207):**^[147]

Morpholine (44 mg, 0.51 mmol) was added to the nitrooxazole **205** (95 mg, 0.5 mmol) in CHCl_3 (1.5 mL) and the mixture was stirred at rt for 24 h. The solvent was then removed under reduced pressure. The residue was taken up in pentane (2–3 mL), and the soln was filtered, dried, and concentrated to give the title compound; yield: 136 mg (98%). Crystallization (EtOAc) gave a pale yellow solid.

21.4.3.1.14.1

Variation 1:**Methanolysis of a 4-Methyleneoxazol-5(4H)-one under Acid or Base Catalysis**

The oxazolones **208** are cleaved when they are treated with methanol at reflux in the presence of sulfuric acid (Method A) or sodium methoxide (Method B) to give methyl (benzoylamino)[1-benzylpyridin-4(1H)-ylidene]acetate (**209**, $\text{R}^1 = \text{Bn}$) of methyl-substituted acetate **209** ($\text{R}^1 = \text{Me}$), respectively (Scheme 100).^[148]

Scheme 100 Synthesis of an Enamide by the Methanolysis of an Oxazolone^[148]**Methyl (Benzoylamino)[1-benzylpyridin-4(1H)-ylidene]acetate (209, $\text{R}^1 = \text{Bn}$):**^[148]

Method A: A mixture of the oxazolone **208** (328 mg 1.00 mmol) and 96% H_2SO_4 (0.3 mL) in MeOH (2 mL) was refluxed for 1–1.5 h, cooled, neutralized with 5% aq NaHCO_3 , and the product extracted with CHCl_3 (5 mL). The organic phase was collected, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The oily residue was triturated with an appropriate solvent and the product was collected by vacuum filtration; yield: 99%.

Methyl (Benzoylamino)[1-methylpyridin-4-ylidene]acetate (209, R¹ = Me):^[148]

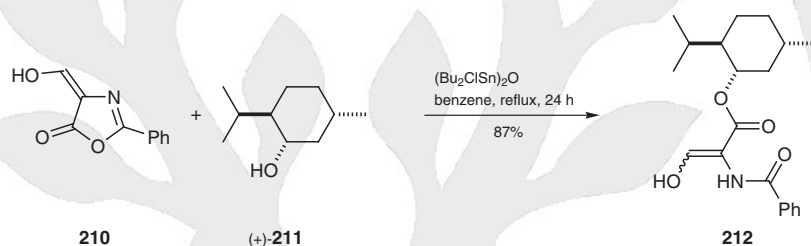
Method B: A mixture containing the oxazolone **208** (328 mg, 1.00 mmol) and NaOMe, previously obtained from Na metal (92 mg, 4.00 mmol) and MeOH (5 mL), was refluxed for 2 h. After cooling the mixture, the solid that had formed was collected; yield: 66%.

21.4.3.1.14.2

Variation 2:**Ring Opening of a 4-Methyleneoxazol-5(4H)-one by an Alcohol/Lewis Acid**

An essentially similar reaction can be carried out in which the oxazolone **210** is cleaved with (+)-menthol (**211**), in the presence of catalytic amount of 1,1,3,3-dibutyl-1,3-dichlorodistannoxane in benzene, to give the enamide **212** (Scheme 101). (–)-Menthol is equally effective and each enamide product can then be used as a chiral dieneophile in stereoselective [4 + 2] cycloadditions; with an appropriate diene the formation of the *exo*-cycloadduct is favored.^[149]

Scheme 101 Synthesis of an Enamide by the Ring Opening of an Oxazolone with an Alcohol and a Lewis Acid^[149]

**(1R,2R,5S)-2-Isopropyl-5-methylcyclohexyl-2-(benzoylamino)-3-hydroxyacrylate (212):**^[149]

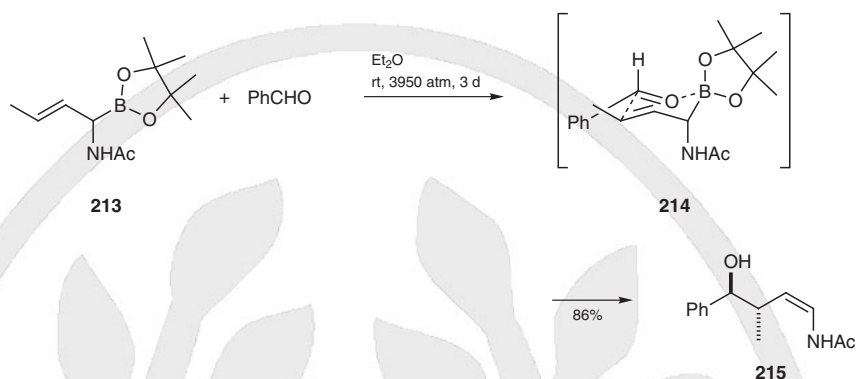
The anhyd oxazolone **210** (756 mg, 4.0 mmol) was suspended in anhyd benzene (30 mL) (**CAUTION: carcinogen**) under a N₂ atmosphere. (+)-Menthol (**211**; 416 mg, 2.67 mmol) and bis(dibutylchlorotin)oxide (243 mg, 0.44 mmol) were added, and the mixture was refluxed for 24 h. This gave a clear soln, which was then evaporated to dryness, and the residue was purified by chromatography (silica gel, CH₂Cl₂) to give an oil; yield: 800 mg (87%).

21.4.3.1.15

Method 15:**Condensation of α -Acetamidobutenyl Boronates and Aldehydes**

α -Sulfonamido- and α -(acylamino)butenyl boronates react with aldehydes under high pressure affording *Z*-enamides; for example, the acetamide **213** reacts selectively with benzaldehyde to give the enamide **215** with *anti* relative stereochemistry, probably through the participation of a six-membered cyclic transition state **214** in which the amide unit assumes a pseudo axial position (Scheme 102).^[150]

Scheme 102 Synthesis of an Enamide by the Reaction of an α -(Acylamino)butenyl Boronate and an Aldehyde^[150]



N-[(1Z,3S,4S)-4-Hydroxy-3-methyl-4-phenylbut-1-en-1-yl]acetamide (215):^[150]

The boronate **213** (190 mg, 0.83 mmol) and PhCHO (96 mg, 0.91 mmol) in Et₂O (2 mL) were pressurized to 3950 atm for 3 d. Triethanolamine (127 mg, 0.85 mmol) was then added and the mixture was stirred at rt for 3 h. The mixture was filtered and the filtrate was concentrated. The residue was purified by chromatography (EtOAc) to yield a colorless solid; yield: 149 mg (86%).

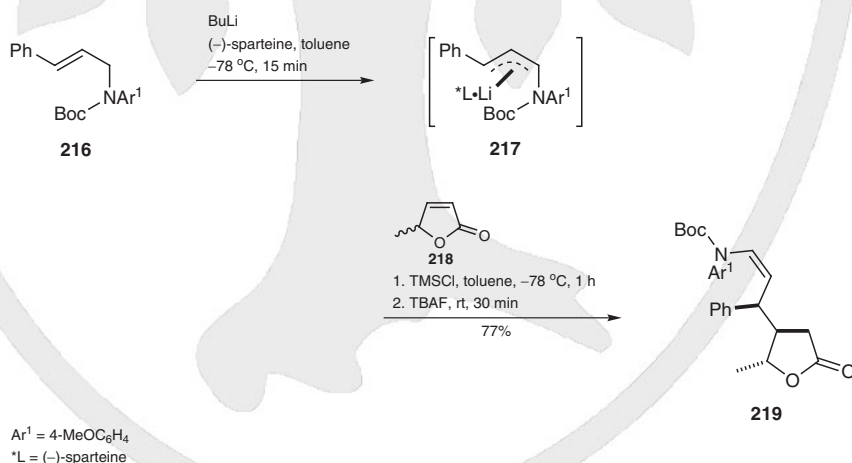
21.4.3.1.16

Method 16:

1,4-Addition of Allyl Anions to Furanones

The complex allyl anion **217**, generated in situ by the treatment of the carbamate **216** with butyllithium in the presence of (–)-sparteine, combines with the furanone **218** to give a chiral 1,4-addition product **219** in 77% yield (Scheme 103).^[151]

Scheme 103 Synthesis of an Enamide by 1,4-Addition of an Allyl Anion to a Furanone^[151,152]



There are other related examples in which dilithiated *N*-allylamides are trapped with various electrophiles to generate substituted enamides.^[152]

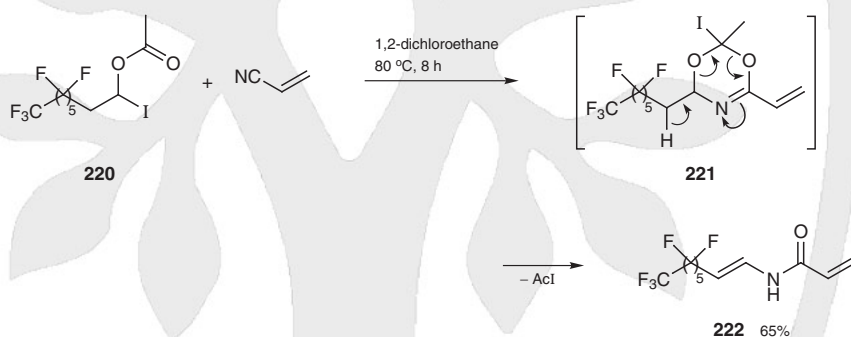
(4R,5R)-4-[(1S,2Z)-3-[(*tert*-Butoxycarbonyl)(4-methoxyphenyl)amino]-1-phenylprop-2-en-1-yl]-5-methyldihydrofuran-2(3H)-one (219):^[152]

(–)-Sparteine (0.19 mL, 0.80 mmol) was added with stirring to *tert*-butyl(4-methoxyphenyl)[(2*E*)-3-phenylprop-2-en-1-yl]carbamate (**216**; 230 mg, 0.73 mmol) in toluene (10 mL) under N₂. The mixture was cooled to 78 °C, and BuLi (0.51 mL, 0.80 mmol) was added. The mixture was stirred for 15 min, and then it was added slowly to a cooled soln of 5-methylfuran-2(5*H*)-one (**218**; 0.17 mL, 1.83 mmol) and TMSCl (0.47 mL, 3.7 mmol) in toluene (5 mL). After stirring the mixture for 1 h, MeOH was added to quench the reaction, and the mixture was then warmed to rt. TBAF (3.7 mmol) was added, and the soln was stirred for an additional 30 min, before Et₂O was introduced. The layers were separated and the aqueous layer was extracted with Et₂O. The organic layer and the extracts were combined, dried (MgSO₄), and evaporated under reduced pressure to give a yellow oil, which was purified by chromatography (silica gel, EtOAc/hexanes 1:3) to give a clear oil; yield: 246 mg (77%).

21.4.3.1.17

Method 17:**Addition of Nitriles to Geminal Haloacylated Compounds**

The addition of propenenitrile to the iodoalkyl ester **220** gives the *E*-enamide **222** in 65% yield.^[153] Acetyl iodide is eliminated, perhaps as shown in Scheme 104, through the cleavage of a 1,3,5-dioxazine intermediate **221**.

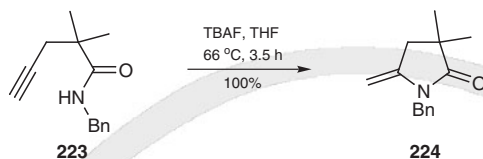
Scheme 104 Synthesis of an Enamide by the Addition of a Nitrile to an Iodoalkyl Ester^[153]**N-[(1*E*)-3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooct-1-en-1-yl]propenamide (222):**^[153]

A conical flask was equipped with a condenser and charged with the 1-iodooctyl acetate **220** (10.64 g, 20.0 mmol), propenenitrile (2.82 g, 60.0 mmol), and 1,2-dichloroethane (15 mL). The mixture was heated to 80 °C for 8 h and then left to stand at 0 °C for 3 h. The solid, which had formed, was collected, washed, and crystallized (1,2-dichloroethane); yield: 5.40 g (65%).

21.4.3.1.18

Method 18:**Amide Additions to Alkynes**

A 5-*exo-dig* cyclization of the alkynylated amide **223** is catalyzed by tetrabutylammonium fluoride to afford the 5-methylenepyrrolidone **224** (Scheme 105). Related cyclizations are promoted by lithium aluminum tetrabenzylamide [LiAl(NHBn)₄] in place of tetrabutylammonium fluoride. This methodology is used in the syntheses of naturally occurring chlorins, isobacteriochlorins, and corrins.^[154]

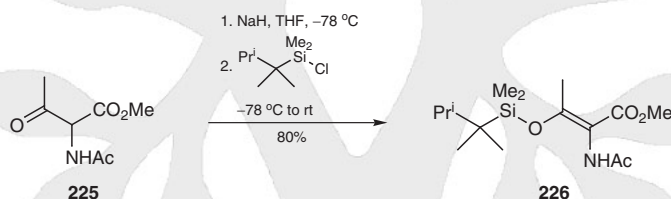
Scheme 105 Synthesis of an Enamide by the Cycloaddition of an Amide to an Alkyne^[154]**1-Benzyl-3,3-dimethyl-5-methylenepyrrolidin-2-one (224):**^[154]

Freshly prepared 1.0 M TBAF in THF (0.57 mL) was added dropwise with vigorous stirring to *N*-benzyl-2,2-dimethylpent-4-ynamide (127 mg, 0.59 mmol) in anhyd THF (5.9 mL). Then the mixture was refluxed under argon for 3.5 h, cooled, and concentrated under reduced pressure. The residue was purified by chromatography [silica gel, EtOAc/hexanes 1:9 (*R_f* 0.25)] to give an oil that crystallized on standing; yield: 133 mg (100%).

21.4.3.1.19

**Method 19:
Enol Ether Formation**

The silyl enol ether **226** is obtained from the parent amino ketone **225** with high degree of stereoselectivity and in 80% yield by the action of sodium hydride and (chloro)dimethyl(1,1,2-trimethylpropyl)silane (Scheme 106).^[155]

Scheme 106 Synthesis of an Enamide by Silyl Enol Ether Formation^[155]**Methyl (Z)-2-(Acetylamino)-3-[dimethyl(1,2,2-trimethylpropyl)siloxy]but-2-enoate (226):**^[155]

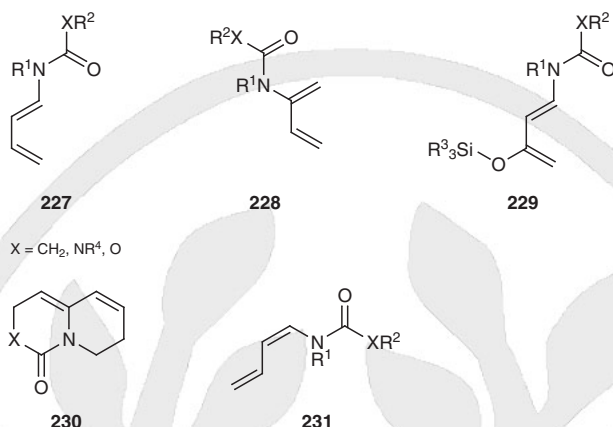
A soln of methyl 2-(acetylamino)-3-oxobutanoate (**225**; 346 mg, 2.0 mmol) in THF (3 mL) was added to a suspension of NaH (52.8 mg, 2.2 mmol) in THF (4 mL) at -78 °C. After 1 h of stirring at 0 °C, (chloro)dimethyl(1,1,2-trimethylpropyl)silane (395 mg, 2.2 mmol) was added to the mixture that had been precooled to -78 °C. The temperature of the mixture was allowed to rise and, after stirring at rt for 1 h, the suspension was filtered through Celite, and the solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, EtOAc/hexane 1:1), giving a colorless solid; yield: 461 mg (80%).

21.4.4

**Product Subclass 4:
Dienamides**

Dienamides **227–229** (Scheme 107) can act as either electron-poor or electron-rich dienes, depending upon the substituents; their behavior in Diels–Alder reactions has been reviewed.^[156] Other types of dienamides, such as the bicyclic **230** and the *E/Z*-acyclic forms **231**, are also well known although their constitutions may preclude them from entering into cycloadditions with dieneophiles.

Scheme 107 Structures of Dienamides



Despite their synthesis and use in [4 + 2] cycloadditions in the 1970s,^[157,158] the Diels–Alder reactions of dienamides received little further interest until such a reaction was used as a key step in a synthesis of strychnine.^[159] This and related Diels–Alder reactions are completely regioselective;^[160,161] and they may be highly *endo*-selective. The first asymmetric version of the cycloaddition employs chiral dienophiles,^[162] but more recently, chiral sulfoxides are incorporated as auxiliaries into dienamides.^[163] Diels–Alder reactions using dienamides derived from lactams are known,^[164] and this chemistry can be extended to chiral dienamides derived from pyroglutamic acid.^[165] Although the asymmetric induction achieved in these latter cycloadditions is excellent, there is no possibility of removing the lactam unit while retaining the nitrogen functionality. However, if nitroso dienophiles are employed then the chiral pyroglutaminate can be readily removed after the cycloaddition.^[166,167] Both chiral and achiral, highly reactive siloxylated dienamides **229** (Scheme 107) show great promise as amino equivalents to Danishefsky's diene, and are used for the synthesis of cyclohexenes with densely packed functionality.^[168] These siloxylated dienamides are less reactive than their siloxylated diamine equivalents, but three times more reactive than a *tert*-butylsilylated version of Danishefsky's diene in both competitive and kinetic experiments.^[168] Recently, catalytic asymmetric Diels–Alder reactions of dienamides have been developed that use chiral transition-metal-based Lewis acid catalysts^[169,170] and monoclonal antibodies.^[171] Furthermore, the use of chiral dienamides in stereoselective vinylogous Mukaiyama aldol reactions has been reported.^[172]

Generally, dienamides are thermally stable and can be synthesized by the thermal rearrangement of prop-2-yn-1-yl trichloroacetimidates at temperatures as high as 143 °C; however, some are much more labile and the decomposition of some siloxylated dienamides occurs even when they are stored in a refrigerator.^[168] Recently a synthesis of dienamides by copper(I)-catalyzed N-allenylation of N-unsubstituted amides with allenyl iodides, coupled with in situ isomerization has been reported.^[173] Many dienamides are solids that can be purified by crystallization, but when they exist as oils, purification by distillation or silica gel chromatography is commonly used. Dienamides exhibit a signal at ca. δ 130 in their ¹³C NMR spectra corresponding to the resonance of the α -carbon atom of the N=C=C=C unit.

21.4.4.1 Synthesis of Product Subclass 4

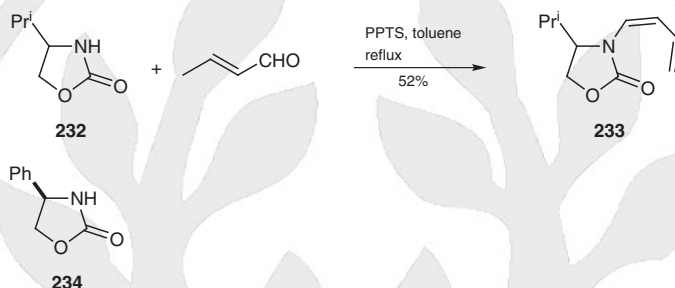
Many, although certainly not all, of the methods of synthesis used to form members of this subclass show very close resemblances to those used to prepare enamides.

21.4.4.1.1

Method 1:
Condensation of Amides and Aldehydes

The oxazolidinone **232** condenses easily with but-2-enal to give the dienamide **233** (Scheme 108). However, the chiral oxazolidinone **234** does not react satisfactorily with this aldehyde and other methods are required to form chiral dienamides based upon this heterocycle.^[156,174,175]

Scheme 108 Synthesis of a Dienamide by Condensation of an Amide and an Aldehyde^[156]


3-(1Z)-Buta-1,3-dien-1-yl-4-isopropyl-2-oxazolidinone (233):^[156]

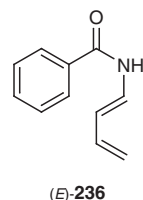
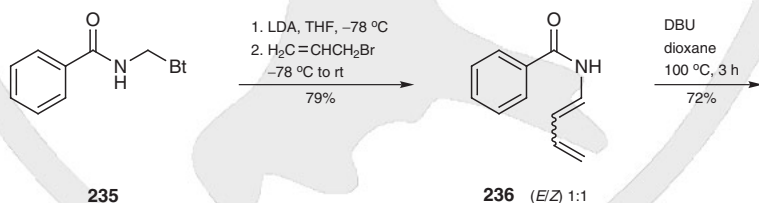
4-Isopropyl-2-oxazolidinone (**232**; 2.0 g, 16 mmol), freshly distilled (*E*)-but-2-enal (2.2 g, 31 mmol) and PPTS (0.1 g, 0.3 mmol) in toluene (100 mL) were heated for 5 h with azeotropic removal of H₂O using a Dean–Stark trap. The soln was concentrated and the residue was chromatographed (silica gel) to give a clear oil; yield: 1.5 g (52%).

21.4.4.1.1.1

Variation 1:
Addition of Amides to Allyl Bromide and Elimination of 1H-Benzotriazole

When the amide **235** is reacted with allyl bromide in the presence of excess lithium diisopropylamide an elimination of 1H-benzotriazole occurs to give the *E*- and *Z*-dienamides **236** in a 1:1 ratio (Scheme 109). If the mixed dienamides are heated with 1,8-diazabicyclo[5.4.0]undec-7-ene in dioxane isomerization to the thermodynamically favored *E*-isomer, (*E*)-**236**, occurs.^[176]

Scheme 109 Synthesis of a Dienamide by Addition of an Amide to Allyl Bromide and the Elimination of 1H-Benzotriazole^[176]



N-[(1E)-Buta-1,3-dien-1-yl]benzamide (236):^[176]

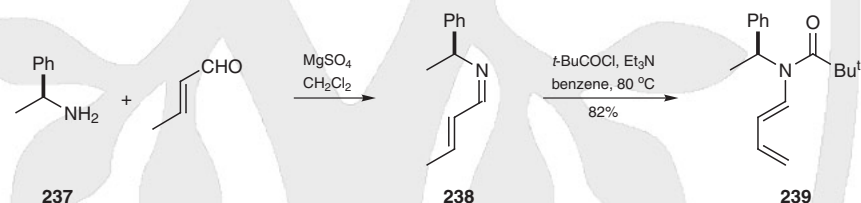
The amide **235** (13.9 g, 55.2 mmol) in THF (300 mL) was added slowly to freshly prepared LDA [from $i\text{Pr}_2\text{NH}$ (16.5 mL, 117 mmol) and 1.6 M BuLi (118 mmol) in hexanes (74.0 mL)] in THF (80 mL) kept at -78°C over 30 min. After the first drop, the soln became dark violet in color. After 2 h of stirring at -78°C , allyl bromide (4.70 mL, 672 mg, 55.5 mmol) was quickly added, and then 10 min later, the mixture was allowed to warm to rt and was stirred overnight. The orange-colored mixture was then diluted with EtOAc and washed three times with sat. aq NaCl. The combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (silica gel, EtOAc/hexane 1:12 to 1:7) gave a 1:1 mixture of *E*- and *Z*-isomers; yield: 7.58 g (79%). DBU (0.9 mL, 917 mg, 6.02 mmol) was added to a soln of the isomers (336 mg, 1.94 mmol) in degassed 1,4-dioxane (15 mL), and the mixture was refluxed for 4 h. After cooling, it was diluted with EtOAc, and washed with H_2O . The combined organic phases were dried (Na_2SO_4). The soln was concentrated, and chromatography of the residue (silica gel, 1:12 EtOAc/hexane) gave (*E*)-**236** as a pale yellow solid; yield: 242 mg (72%).

21.4.4.1.2

Method 2:**Acylation of Enamines with Acid Chlorides**

A condensation between the chiral primary amine **237** and (*E*)-but-2-enal, followed by *N*-acylation of the intermediate product **238** with pivaloyl chloride, gives the dienamide **239** (Scheme 110).^[156] This methodology is employed in a synthesis of pumiliotoxin C.^[177]

Scheme 110 Synthesis of a Dienamide by the Acylation of an Ene-Imine with an Acid Chloride^[156]

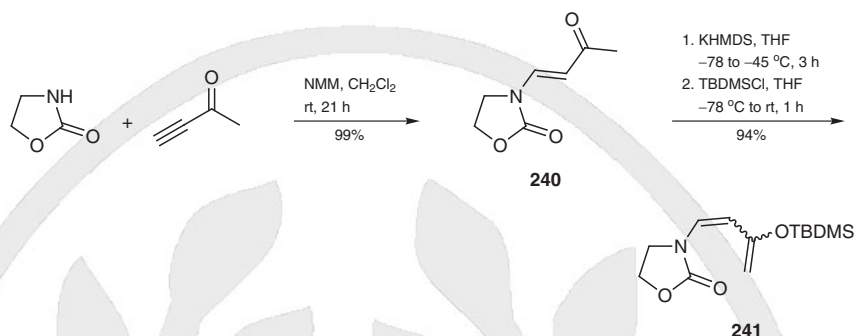
**N-[(1E)-Buta-1,3-dien-1-yl]-2,2-dimethyl-N-[(1S)-1-phenylethyl]propanamide (239):**^[156]

[(1S)-phenylethyl]amine (**237**; 4.7 g, 3.9 mmol) was added to (*E*)-but-2-enal (2.7 g, 3.9 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred at rt for 1 h. Then the aqueous layer was separated and MgSO_4 (2 g) was added to the organic phase. After stirring at rt for 1 h, MgSO_4 was removed by filtration and the filtrate was concentrated to give an oil. This oil was redissolved in benzene (45 mL) (**CAUTION: carcinogen**) containing Et_3N (4.6 g, 4.6 mmol) and pivaloyl chloride (5.5 g, 4.6 mmol) was added dropwise over 5 min. The soln was then refluxed for 2 h, cooled, washed with sat. aq Na_2SO_4 , and concentrated to give a red oil. Kugelrohr distillation gave the title compound as a pale yellow oil; yield: 8.2 g (82%).

21.4.4.1.3

Method 3:**From Vinylogous Amides by O-Silylation**

The addition of oxazolidin-2-one to but-3-yn-2-one in the presence of *N*-methylmorpholine yields the vinylogous amide **240**, which can be deprotonated with potassium hexamethyldisilazane and and trapped with *tert*-butyldimethylsilyl chloride to afford the *O*-silyl enol ether **241** (Scheme 111). On a larger scale potassium hexamethyldisilazanide can be replaced by sodium hexamethyldisilazane without loss of productivity. In either case the product is pure enough for subsequent reactions.^[168]

Scheme 111 Synthesis of a Dienamide by Enolization of a Vinylogous Amide and Trapping with *tert*-Butyldimethylsilyl Chloride^[168]

This methodology is used to prepare chiral amino equivalents of Danishefsky's diene, which are highly reactive in [4+2] cycloadditions employed in the total syntheses of (±)-tabersonine,^[178] (+)-tabersonine,^[139] (+)-aspidospermine,^[139] and quebrachamine.^[139]

3-[3-(*tert*-Butyldimethylsiloxy)buta-1,3-dien-1-yl]oxazolidin-2-one (241).^[168]

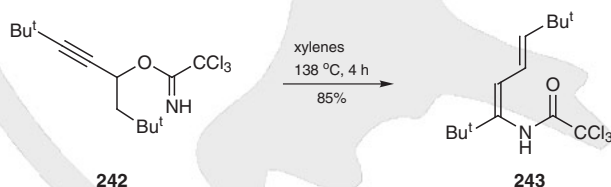
The vinylogous imide **240** (155 mg, 1.00 mmol) in THF (2.3 mL) was added dropwise to a stirred, chilled soln (−78 °C cold bath) of 0.5 M KHMDS (1.05 mmol) in toluene, 2.1 mL) and THF (2.1 mL). The mixture was warmed to −45 °C over 2.5 h, cooled to −78 °C, and treated with a soln of TBDMSCl (166 mg, 1.10 mmol) in THF (0.8 mL). The cold bath was removed, and the mixture was allowed to reach rt. Dilution with Et₂O (20 mL), followed by filtration through Celite and concentration of the filtrate under reduced pressure, gave a colorless solid; yield: 253 mg (94%). Purification of this material was accomplished by bulb-to-bulb distillation (200 °C, 0.15 Torr).

21.4.4.1.4

Method 4:

Thermal Rearrangement of Pent-2-yn-1-yl 2,2,2-Trichloroethanimidoates

The rearrangement of the pent-2-yn-1-yl 2,2,2-trichloroethanimidoate **242** occurs in xylene at reflux to give the dienamide **243** (Scheme 112). The trichloroacetyl group is easily removed from this product under dilute basic conditions.^[158] In related cases varying amounts of *E*- and *Z*-isomers are formed during the thermolysis.

Scheme 112 Synthesis of a Dienamide by Thermal Rearrangement of a Prop-2-yn-1-yl Trichloroacetimidate^[158]

21.4.4.1.4.1

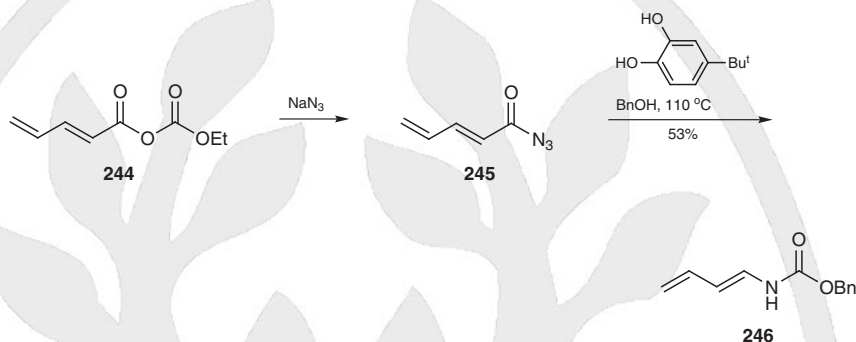
Variation 1:

Thermal Rearrangement of Acyl Azides (A Modified Curtius Rearrangement)

As for simple dienamides the Curtius rearrangement of suitable acyl azides can be used to form dienyl carbamates through the entrapment of the intermediate isocyanates by alcohols. In the example shown in Scheme 113 the acyl carbonate **244** is converted into the acyl azide **245** and reacted with benzyl alcohol, in the presence of 4-*tert*-butylcatechol and

N,N-diisopropylethylamine, to produce the carbamate **246**; however, as ethanol is a by-product in the formation of the acyl azide **245** care is need to ensure its complete removal by azeotropic distillation prior to the addition of benzyl alcohol. In other cases an alternative technique is to use a more reactive alcohol than ethanol.^[179] This procedure cannot be modified to give the analogous ureas probably because these products are too reactive.

Scheme 113 Synthesis of a Dienamide by Thermal Rearrangement of an Acyl Azide (A Modified Curtius Rearrangement)^[179]



Benzyl (1E)-Buta-1,3-dien-1-ylcarbamate (246):^[179]

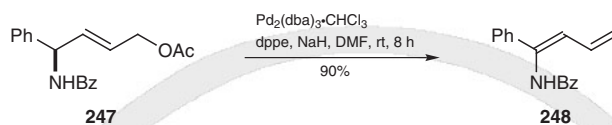
CAUTION: Contact of metal azides with acids liberates the highly toxic and explosive hydrazoic acid.

A 1-L, three-necked flask was fitted with a stirring bar, a thermometer, and a dropping funnel. The flask was flushed with N₂ and charged with *trans*-penta-2,4-dienoic acid (49.0 g, 0.50 mol), iPr₂NEt (80.0 g, 0.62 mol), acetone (300 mL), and the soln was cooled to 0 °C. A soln of ethyl chloroformate (55.0 g, 0.50 mol) and acetone (150 mL) was added over 30 min while maintaining the temperature of the soln below 0 °C. After stirring for an additional 30 min at 0 °C, a chilled soln of NaN₃ (65.0 g, 1.0 mol) and H₂O (150 mL) was added. The mixture was stirred for an additional 15 min at 0 °C and poured into ice water (500 mL). The acyl azide **245** was isolated by extraction with toluene (6 × 250 mL), dried (MgSO₄) for 20 min, and filtered, and any residual EtOH was removed by concentration (to ca. 300 mL) on a rotary evaporator. The acyl azide **245** soln was then added to a vigorously stirred soln of benzyl alcohol (43.0 g, 0.40 mol), 4-*tert*-butylcatechol (250 mg), and anhyd toluene (200 mL), while rapid reflux was maintained. Heating was continued for 10–30 min, by which time the bands in the IR spectrum due to the acyl azide ($\tilde{\nu}_{\text{max}}$: 2130 cm⁻¹) and the isocyanate ($\tilde{\nu}_{\text{max}}$: 2270 cm⁻¹) had disappeared. The mixture was rapidly cooled to rt and concentrated to afford a yellow semi-solid residue, which was purified immediately. Crystallization (95% EtOH, 50 mL) of this residue at rt gave an almost pure product; yield: 39–46 g (49–56%). An analytical sample was prepared by recrystallization (EtOAc/hexane).

21.4.4.1.5

Method 5:
Palladium(0)-Catalyzed Elimination of Allyl Acetate

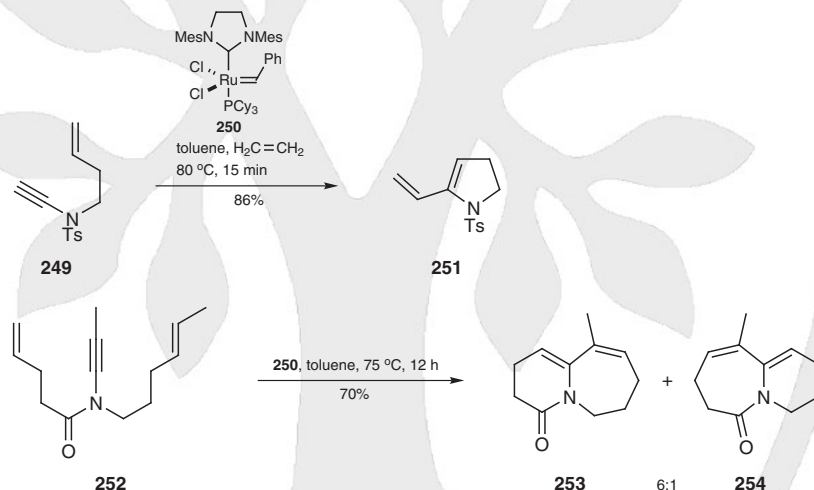
When the amino acetate **247** (1 equiv) in dimethylformamide is treated with 1 mol% tris(dibenzylideneacetone)dipalladium–chloroform, 1,2-bis(diphenylphosphine)ethane (4 mol%) and sodium hydride (1 equiv) at room temperature the expected palladium(0)-catalyzed dihydroxazole formation did not take place. Instead the dienamide **248** (90% yield) is the only product (Scheme 114); this compound originates through the elimination of allyl acetate from a π -allyl intermediate.^[180]

Scheme 114 Synthesis of a Dienamide by Palladium(0)-Catalyzed Elimination of an Allyl Acetate^[180]

21.4.4.1.6

Method 6:
Ring-Closing Metathesis of Eneynamides

Ring-closing metathesis of the enesulfonamide **249** using Grubbs' second-generation catalyst **250** under an ethene atmosphere provides the 2-vinyldihydropyrrole **251** in 86% yield (Scheme 115).^[58] Subsequent cycloadditions with various dieneophiles can be conducted upon this and related products; indeed, a tandem version of the ring closure incorporating an intramolecular cycloaddition can be carried out when the ynamide **252** is treated with the catalyst in toluene at 75°C . In this illustration (Scheme 115) the product is a mixture of the bicyclic heterocycles **253** and **254** in a ratio of 6:1. Chiral starting materials can also be used leading to bi- and tricyclic systems with some degree of stereochemical induction.^[59]

Scheme 115 Synthesis of a Dienamide by Ring-Closing Metathesis of an Eneynamide^[58,59]**1-Tosyl-5-vinyl-2,3-dihydro-1H-pyrrole (251); Typical Procedure:**^[58]

A soln of the sulfonamide **249** (91.5 mg, 0.37 mmol) and Grubbs' second-generation catalyst **250** (15.6 mg, 0.018 mmol) in degassed toluene (10 mL) was refluxed for 15 min under ethene gas (1 atm). Then the mixture was cooled to rt , and a few drops (excess) of ethyl vinyl ether were added, before the solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, $\text{Et}_3\text{N}/\text{Et}_2\text{O}/\text{hexane}$ 1:5:100) to give a colorless oil; yield: 76.2 mg (86%).

10-Methyl-2,6,7,8-tetrahydropyrido[1,2-a]azepin-4(3H)-one (253) and 10-Methyl-3,4,7,8-tetrahydropyrido[1,2-a]azepin-6(2H)-one (254); Typical Procedure:^[59]

Grubbs' second-generation catalyst **250** (5–10 mol% Ru) was added to 0.1 M soln of the amide **252** in toluene contained in a sealed tube in a dry box. The tube was then sealed and heated at 75°C for 5–10 h. After cooling to rt , the contents of the tube were removed,

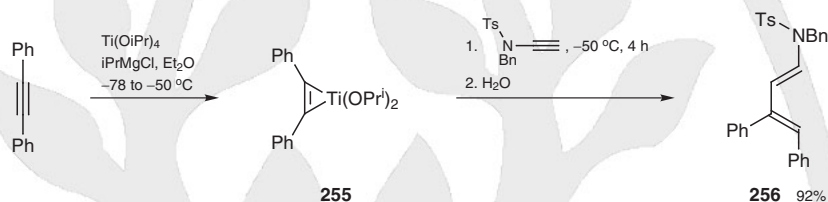
and purified by chromatography (silica gel, EtOAc/hexane) to give a mixture of **253** and **254** (6:1) as an oil; yield: 70%.

21.4.4.1.7

Method 7: Titanium(II)-Mediated Coupling of Ynamides and Alkynes

The titanium complex **255**, generated by the action of titanium(IV) isopropoxide and isopropylmagnesium chloride on diphenylacetylene, can be coupled with *N*-benzyl-*N*-ethynyl-4-toluenesulfonamide to afford the *N*-(1*E*,3*Z*)-buta-1,3-dienylated sulfonamide **256** in 92% yield (Scheme 116).^[66]

Scheme 116 Synthesis of a Dienamide by Titanium-Mediated Coupling of an Ynamide and an Alkyne^[66]



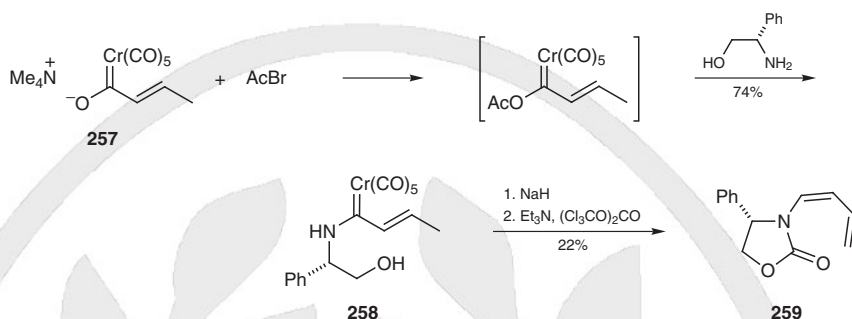
N-Benzyl-*N*-[(1*E*,3*Z*)-3,4-diphenylbuta-1,3-dienyl]-4-toluenesulfonamide (**256**):^[66]

1.41 M *i*PrMgCl (0.22 mmol) in Et₂O (0.16 mL) was added to a stirred soln of diphenylacetylene (16 mg, 0.09 mmol) and Ti(O*i*Pr)₄ (0.032 mL, 0.11 mmol) in Et₂O (2 mL) at -78 °C protected under argon. This gave a yellow colored soln, which turned black as it was warmed to -50 °C over 30 min. After stirring at -50 °C for 2 h, pulverized *N*-benzyl-*N*-ethynyl-4-toluenesulfonamide (20 mg, 0.070 mmol) was added in one portion at -50 °C. Then, after stirring for a further 4 h at the same temperature, the reaction was terminated by the addition of H₂O (0.2 mL), and the suspension that had formed was filtered through Celite with the aid of Et₂O. The organic phase was separated and concentrated under reduced pressure to give a crude oil which contained a single dienamide (¹H NMR). The title compound was isolated by chromatography (silica gel, EtOAc/hexane) as a colorless solid; yield: 30 mg (92%).

21.4.4.1.7.1

Variation 1: Chromium(0)-Mediated Coupling of Amino Alcohols and Chromium Carbene Complexes

Attempts to prepare optically active chromium(0) carbene complexes containing an oxazolidinone moiety led instead to a generally useful synthesis of optically active *N*-dienylated products. For example, when the chromium pentacarbonyl **257** is acetylated and the product treated in situ with (2*S*)-2-amino-2-phenylethanol a complex **258** is formed, which can be deprotonated and treated with bis(trichloromethyl) carbonate (triphosgene) to give the chiral *N*-butadienyloxazolidinone **259** (Scheme 117). This methodology is used in a total synthesis of (+)-thienamycin.^[88]

Scheme 117 Synthesis of a Dienamide by Chromium(0)-Mediated Coupling of an Amino Alcohol and a Chromium–Carbene Complex^[88]**(4S)-3-(1Z)-Buta-1,3-dien-1-yl-4-phenyloxazolidin-2-one (259):**^[88]

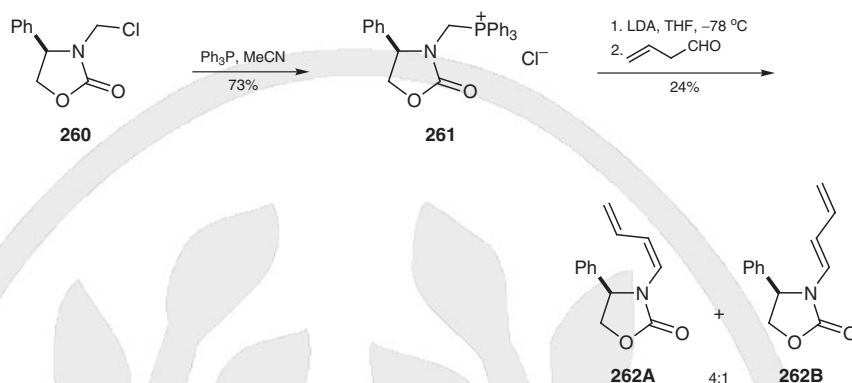
CAUTION: Bis(trichloromethyl) carbonate must be handled in an efficient hood; it should not be inhaled or allowed to come into contact with the skin

An Airless-ware flask (25-mL) was fitted with a magnetic stirrer bar, rubber septum, and an argon-filled balloon. The apparatus was charged with the chromium complex **258** (200 mg, 0.525 mmol) and NaH (25.0 mg, 1.1 mmol), and the system was protected under argon. THF (10 mL) was added by syringe and the orange-colored soln was stirred at rt for 1 h. The soln was cooled to -78°C and Et_3N (27.0 mg, 0.26 mmol) was added via a syringe, followed by a soln of $(\text{Cl}_3\text{CO})_2\text{CO}$ (57.0 mg, 0.19 mmol) in THF (3 mL) that was added by a cannula. The color turned deep red quickly, and after 5 min, the cooling bath was removed and stirring was continued for 3 h. The solvent was evaporated, and the residue was taken up in 1:1 hexane/EtOAc. This soln was saturated with air and was oxidized in a light box equipped with six 20-W Vitalite fluorescent lamps for only 3 h (as the title compound decomposes slowly under these conditions). The product was purified by radial chromatography (silica gel, EtOAc/hexane 1:4) to yield a clear oil; yield: 25.0 mg (22%). This solidified and was then crystallized (Et_2O /hexane).

21.4.4.1.8

Method 8:
Alkenation Using Wittig Conditions

The phosphonium salt **261** is readily prepared by addition of triphenylphosphine to the chloride **260**, but a reaction of the corresponding ylide with propenal gives a 4:1 mixture of the isomeric *Z/E*-dienes **262A** and **262B** in a disappointing 24% yield (Scheme 118).^[156]

Scheme 118 Synthesis of a Dienamide by Wittig Alkenation^[156]

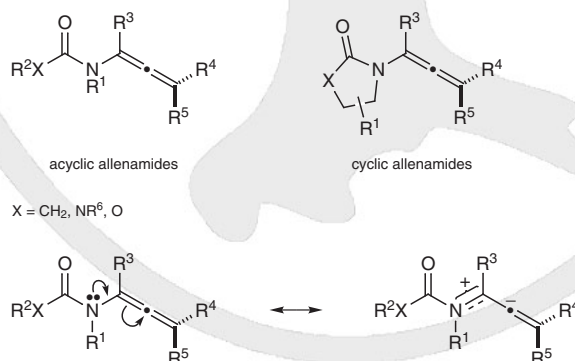
(4R)-3-(1Z)-Buta-1,3-dien-1-yl-4-phenyloxazolidin-2-one (262A) and (4R)-3-(1E)-Buta-1,3-dien-1-yl-4-phenyloxazolidin-2-one (262B):^[156]

1.5 M LDA (1.4 mmol) in hexane (0.9 mL) was added dropwise to the phosphonium chloride **261** (0.5 g, 1.1 mmol) in anhyd THF (20 mL) at -78°C under N_2 . The mixture was stirred for 15 min at this temperature and propenal (74 mg, 1.1 mmol) was then added dropwise. The mixture was allowed to warm to rt, H_2O (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (2×20 mL). The combined extracts were dried (MgSO_4), and concentrated, and the residue was chromatographed to give a *Z/E* mixture (4:1) of the title compounds as a yellow oil; yield: 58 mg (24%).

21.4.5

**Product Subclass 5:
Allenamides**

For the purposes of this review allenamides are electron-deficient compounds formed by the attachment of an allene unit to the nitrogen atom of an amide, lactam, oxazolidinone, or imidazolidinone thereby forming both acyclic and cyclic types (Scheme 119).^[181] The presence or introduction of chiral elements makes these compounds useful synthons in cycloaddition reactions.^[181] Resonance within the allenamine component dictates the electronic bias and potential stereoselectivity.

Scheme 119 Allenamides and the Regioselective Bias Imposed by the Nitrogen^[181]

Allenamides are more versatile compounds than allenamines and this has led to emerging interest in them; current studies relate to 'living' polymerization,^[182] α - and γ -deprotonation/addition reactions,^[183–185] cyclizations (anionic,^[186–189] palladium catalyzed,^[190–193] and iodine promoted^[194]), and various types of cycloaddition procedures,^[195–205] including

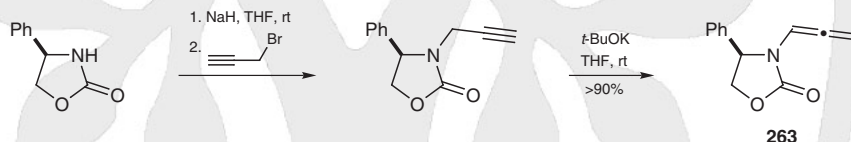
Pauson–Khand reactions.^[184] Most allenamides are oils that may crystallize in the freezer in the absence of solvent. Bulky substitution, such as that provided by Sibi's dibenzylidene oxazolidinone,^[71] can also provide crystalline allenamides. Frequently they are stable enough for purification by silica gel chromatography (except for those bearing an imidazolidinone component). Allenamides are usually stored under nitrogen in the freezer to prevent decomposition, which commonly occurs through polymerization. They exhibit a peak at ca. δ 202 in their ^{13}C NMR spectra, corresponding to the resonance of the central carbon of the allene unit. For unsubstituted allenamides the $\text{H}_2\text{C}=\text{C}=\text{CHN}$ unit gives rise to an A_2X spin-spin pattern in the ^1H NMR spectrum with the methine proton resonating at ca. δ 6.9 ($J_{\text{AB}} = 6\text{ Hz}$). A number of copper(I)-catalyzed syntheses of allenamides from amides and allenyl halides have been reported.^[173]

21.4.5.1 Synthesis of Product Subclass 5

21.4.5.1.1 Method 1: Base-Induced Isomerization of Cyclic Amides

The first preparation of an allenamide was reported in 1967 by a base-induced isomerization of a *N*-(prop-2-ynyl)oxazolidinone using sodium methoxide or sodium hydride.^[206] Other authors obtained a quinoxalinone-based allenamide using similar conditions; but the yield was only 50%.^[207] More recently both achiral^[71] and chiral^[199,208] allenamides, such as (4*R*)-4-phenyl-3-propa-1,2-dien-1-yloxazolidin-2-one (**263**) (Scheme 120), have been prepared from alkynylated precursors in high yields using 20 mol% potassium *tert*-butoxide in dry tetrahydrofuran as the base.

Scheme 120 Synthesis of an Allenamide by Base-Induced Isomerization of an *N*-Alkynylated Amide^[199]



(4*R*)-4-Phenyl-3-propa-1,2-dien-1-yloxazolidin-2-one (**263**); Typical Procedure:^[199]

t-BuOK (20 mol%) was added to (4*R*)-4-phenyl-3-prop-2-yn-1-yloxazolidin-2-one (1 g, 5.0 mmol) in anhyd THF (5.0 mL) under N_2 . The mixture was stirred at rt for 16–24 h, the progress of the reaction was monitored by TLC (silica gel, EtOAc/hexane) or by ^1H NMR. After removing the solvent under reduced pressure, the residue was redissolved in Et_2O (20–50 mL) and filtered through a small bed of Celite or basic alumina (EtOAc/hexane 1:4). The solvent was removed under reduced pressure to provide the product; yield: >90%

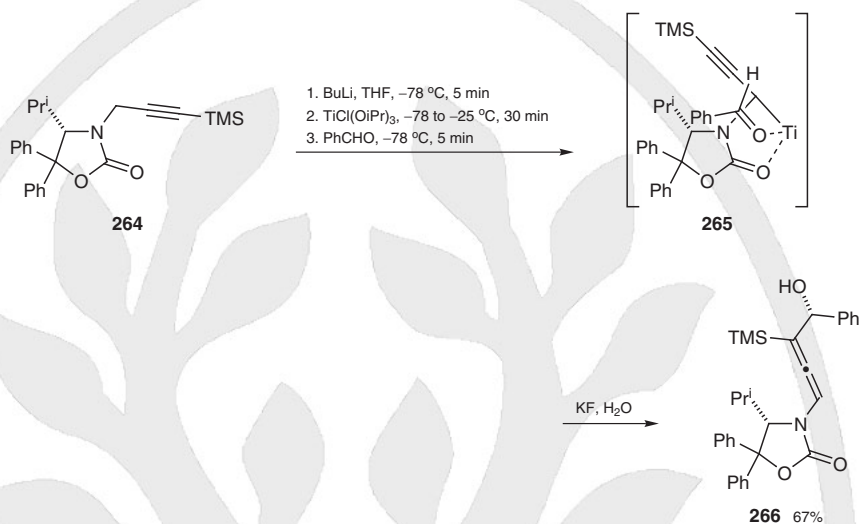
For all allenamides, except those based upon imidazolidinones, further purification can be achieved by chromatography (silica gel, EtOAc/hexane 0 to 50%). Imidazolidinone-based allenamides do not survive chromatography and are isolated by filtration and evaporation.

21.4.5.1.1.1 Variation 1: Base-Induced Isomerization/Addition to Aldehydes

The method just described can be adapted to provide a route to the chiral alcohol **266** from the *N*-propynyloxazolidinone **264**, first by deprotonation and then the capture of the intermediate anion with benzaldehyde in the presence of a titanium salt. A titanium complex **265** is considered to control the preferential addition of the aldehyde to its *si*-face (Scheme 121). This is a general process and related allenamides can be obtained in

yields ranging from 60 to 67% and, for chiral examples, diastereoselectivities up to 98% are noted for allenes with (*M*)-configurations.^[185]

Scheme 121 Synthesis of an Allenamide by Base-Induced Isomerization/Addition to an Aldehyde^[185]



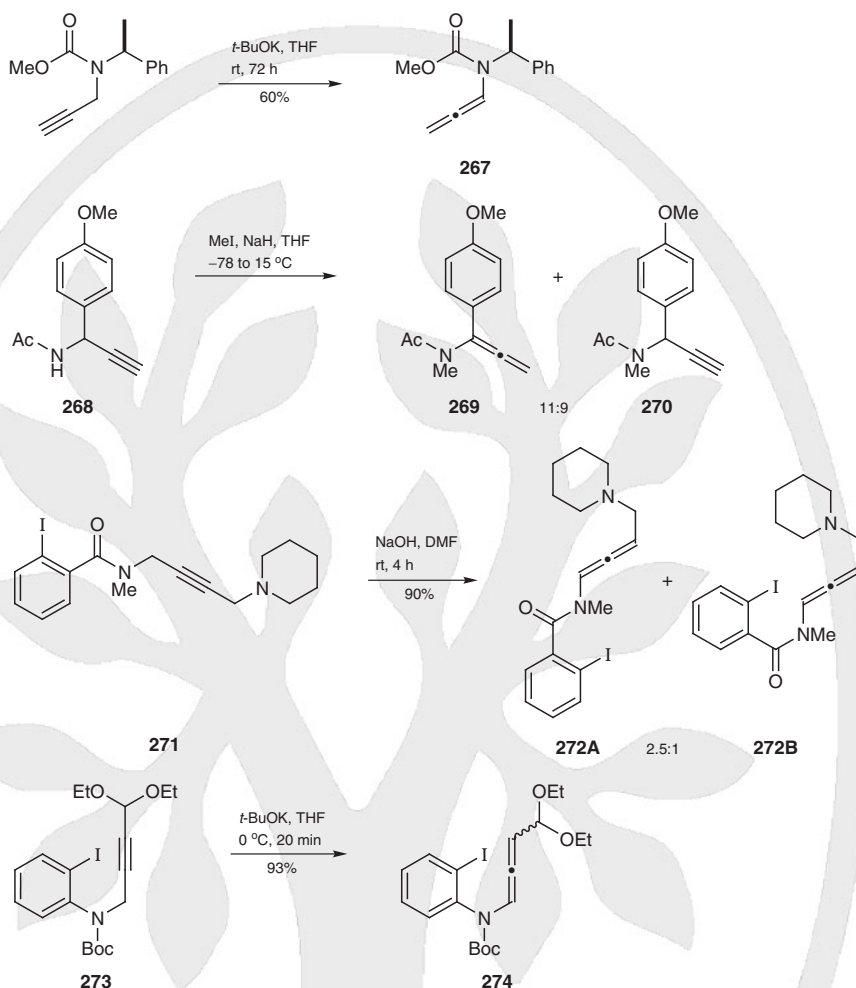
(4*S*)-3-[(4*S*)-4-Hydroxy-4-phenyl-3-(trimethylsilyl)buta-1,2-dien-1-yl]-4-isopropyl-5,5-diphenyloxazolidin-2-one (266); General Procedure:^[185]

BuLi (1.2 equiv) was added to a 0.25 M soln of the *N*-alkynyloxazolidinone **264** (1 equiv) in THF at -78°C . After stirring for 5 min at -78°C , $\text{TiCl}(\text{OiPr})_3$ (1.2 equiv) was added, and the mixture was warmed to -25°C . After stirring for 30 min at -25°C , the mixture was cooled to -78°C , and PhCHO (1.3 equiv) was added dropwise. The mixture was kept at -78°C for another 5 min, and then it was treated with sat. aq KF, and diluted with Et_2O . The organic layer was separated, and the aqueous layer was extracted three times with Et_2O . The combined organic layer and extracts were dried (MgSO_4) and concentrated under reduced pressure to give a residue that was purified by silica gel chromatography; yield: 67%.

21.4.5.1.2

**Method 2:
Base-Induced Isomerization of Acyclic Amides**

In early work the base-induced isomerization of *N*-propynylated phosphoramides was shown to give acyclic allenamides.^[183] This isomerization is now extended to the formation of the acyclic chiral allenamide **267** by treatment of the alkynic precursor with potassium *tert*-butoxide (Scheme 122).^[59] Similarly, the *N*-methylated allene **269** arises from the isomerization/alkylation of the alkyne **268** when it is treated with sodium hydride and iodomethane. Unfortunately, some of the isomer **270** contaminates the product, and here the alkyne/allene ratio observed may reflect the relative stability of the intermediate benzylic carbanion.^[186] The palladium-catalyzed dehydrogenation of the tertiary amine **271** fails to give any of the desired diene, instead base-isomerization with sodium hydroxide in dimethylformamide provides a 2.5:1 mixture of the allenamides **272A** and **272B** in good yield.^[191] Attempts to cyclize the acetal **273** by lithium-halogen exchange fail, leading only to a complex mixture of products; however, treatment with potassium *tert*-butoxide gives the isomer **274** (Scheme 122). This compound may then be ring closed.^[209]

Scheme 122 Synthesis of Allenamides by Base-Induced Isomerization of Acyclic Amides^[59,186,191,209]***N*-(*tert*-butoxycarbonyl)(4,4-diethoxybuta-1,2-dien-1-yl)-2-iodoaniline (274):**^[209]

t-BuOK (1.05 g, 9.0 mmol) was added to the acetal **273** (2.75 g, 6.0 mmol) in THF (30 mL) under N₂ at 0 °C. After 20 min of stirring, the mixture was treated with H₂O (30 mL), and the aqueous layer was separated, and extracted with Et₂O (2 × 30 mL). The organic layer and the extracts were combined, washed with brine (2 × 25 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure to give a yellow oil that slowly crystallized in the freezer; yield: 2.56 g (93%).

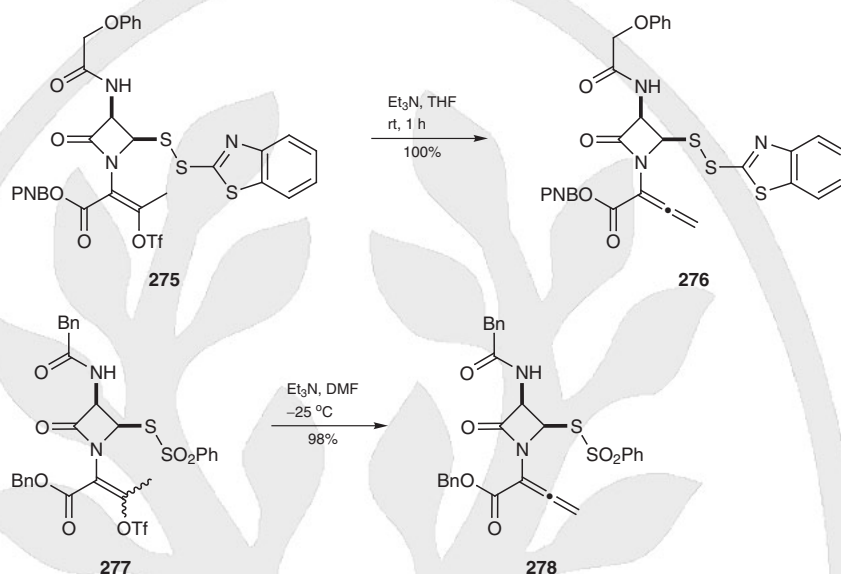
21.4.5.1.3

Method 3:**Elimination of Vinyl Trifluoromethanesulfonates**

In the case of more complex substrates elimination of trifluoromethanesulfonic acid can be used to generate allenes from the corresponding vinyl trifluoromethanesulfonates. Two examples are shown in Scheme 123, both contain an azetidinone unit. In the first the trifluoromethanesulfonate **275** is converted in a quantitative yield into the allenamide **276** by treatment with triethylamine in tetrahydrofuran at room temperature.^[189] This methodology has value in the synthesis of cefprozil.^[210] In the second example an

identical reaction converts the vinyl trifluoromethanesulfonate **277** into the allene **278**, which is also an important precursor for β -lactam antibiotics.^[188]

Scheme 123 Synthesis of Allenamides by Elimination of Vinyl Trifluoromethanesulfonates^[188,189]



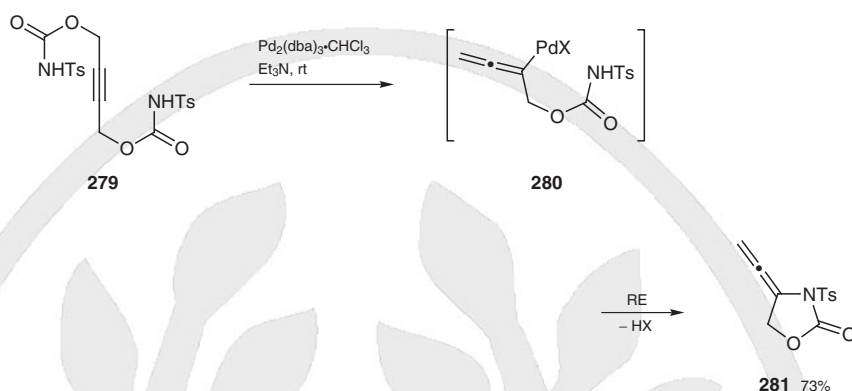
4-Nitrobenzyl 2-((2R,3R)-2-(1,3-Benzothiazol-2-ylthio)-4-oxo-3-((phenoxycarbonyl)amino)-azetidin-1-yl)buta-2,3-dienoate (276):^[189]

The trifluoromethanesulfonate **275** (143.5 mg, 0.186 mmol) was stirred in anhyd THF (3 mL) in the presence of Et₃N (0.026 mL, 1 equiv) at rt. The crude yield was found to be 100% and the product was used without further purification.

21.4.5.1.4

Method 4:
Palladium(0)-Catalyzed Cyclizations of Yne-Bis(carbonates)

The allenamide **281** can be synthesized by a palladium(0)-catalyzed cyclization of the bis(carbonate) **279**.^[197] The reaction proceeds in several steps, which include the elimination of carbon dioxide and 4-toluenesulfonamide, and the formation of an intermediate palladium complex **280**. This intermediate then undergoes intramolecular ring-closure (Scheme 124).

Scheme 124 Synthesis of an Allenamide by Palladium(0)-Catalyzed Cyclization of an Yne-Bis(carbonate)^[197]

In related chemistry the carbapenam skeleton has been constructed from a propynyl carbonate, via the formation of an N—Pd—C bonded species and then reductive elimination.^[211]

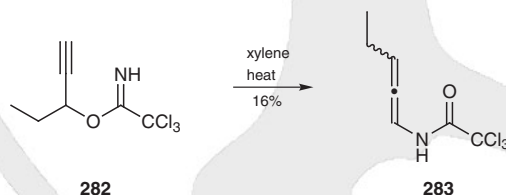
4-Ethenylidene-3-tosyl-1,3-oxazolidin-2-one (**281**):^[197]

THF (5 mL, dried over sodium benzophenone ketyl) and Et_3N (14 μL , 0.1 mmol) were individually introduced via syringes to a mixture of but-2-yne-1,4-diyl bis(tosylcarbamate) (**279**; 480 mg, 1 mmol) and $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (5.2 mg, 0.005 mmol). The soln was stirred under N_2 at rt for 7 h, and then it was concentrated under reduced pressure. The residue was purified by chromatography (silica gel, EtOAc/hexane) to afford a solid; yield: 193 mg (73%).

21.4.5.1.5

Method 5: By a [3,3]-Sigmatropic Rearrangement of a Propynyl Imidate

Thermolysis of the propynyl imidate **282** gives the allenamide **283** via a [3,3]-sigmatropic rearrangement but in very poor yield (Scheme 125); moreover, the allenamide undergoes tautomerization to the more stable dienamide if the reaction is prolonged.^[212]

Scheme 125 Synthesis of an Allenamide by [3,3]-Sigmatropic Rearrangement of a Propynyl Imidate^[212]

2,2,2-Trichloro-N-penta-1,2-dien-1-ylacetamide (**283**):^[212]

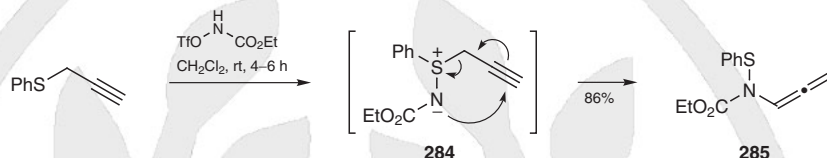
A soln of the imidate **282** (4.57 g, 20.0 mmol) and anhyd xylene (670 mL) was refluxed for 1.1 h. Concentration and purification of the residue by a combination of chromatography (silica gel, EtOAc/hexane 1:9), preparative TLC (EtOAc/hexane 1:19, four elutions), and sublimation (30 $^{\circ}\text{C}$, 0.005 Torr) gave the title compound; yield: 0.73 mg (16%).

21.4.5.1.5.1

**Variation 1:
[2,3]-Sigmatropic Rearrangement**

The S-amination of phenyl prop-2-yn-1-yl sulfide by ethyl N-[(trifluoromethanesulfonyl)oxy]carbamate occurs under acidic conditions. The intermediate sulfilimine **284** then undergoes a [2,3]-sigmatropic rearrangement to form the sulfenamide **285** (Scheme 126).^[213]

Scheme 126 Synthesis of an Allenamide by a [2,3]-Sigmatropic Rearrangement^[213]

**Ethyl (Phenylsulfanyl)propa-1,2-dien-1-ylcarbamate (285):**^[213]

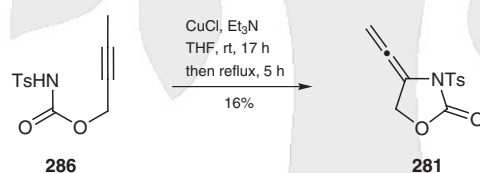
Ethyl N-[(trifluoromethanesulfonyl)oxy]carbamate (192 mg, 1.3 mmol) was added to phenyl prop-2-yn-1-yl sulfide (100 mg, 0.7 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at rt for 4–6 h, washed with sat. aq NaHCO_3 , dried (MgSO_4), and concentrated. The residue was purified either by crystallization ($i\text{Pr}_2\text{O}$) or by chromatography (silica gel, EtOAc) to give an oil; yield: 141 mg (86%).

21.4.5.1.6

**Method 6:
Copper(I)-Catalyzed Amide Additions to Alkynes**

In the presence of a copper(I) chloride, the sulfonamide **286** undergoes intramolecular cyclization to give the 4-methyleneoxazolidin-2-one **281**, however, this is another reaction plagued by a low product yield (Scheme 127).^[124]

Scheme 127 Synthesis of an Allenamide by Copper(I)-Catalyzed Amide Addition to an Alkyne^[124]

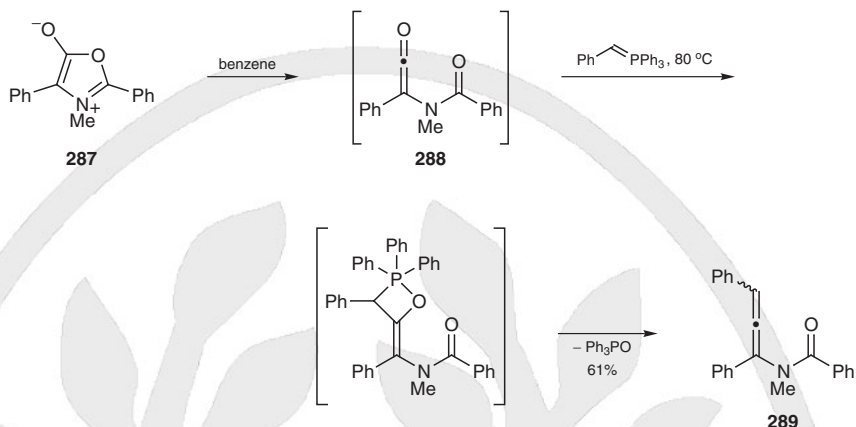
**4-Ethenylidene-3-tosyloxazolidin-2-one (281); Typical Procedure:**^[124]

Anhyd THF (5 mL) and Et_3N (14 μL , 0.1 mmol) were introduced via syringe into a flask purged with N_2 and containing but-2-yn-1-yl tosylcarbamate (**286**; 321 mg, 1.2 mmol) and CuCl (10 mg, 0.1 mmol). The mixture was stirred at rt for 17 h, and refluxed for 5 h. Progress was monitored by TLC [silica gel, EtOAc/benzene (**CAUTION: carcinogen**)]. The reaction was diluted with EtOAc (50 mL), and washed with aq NaHCO_3 . The organic phase was dried (MgSO_4) and condensed to give a waxy solid, which was purified by chromatography (silica gel, EtOAc/benzene 1:9) to give a colorless solid; yield: 51 mg (16%).

21.4.5.1.7

**Method 7:
Alkenation of Ketenes Using Wittig Conditions**

The mesomeric oxazole **287**, as its valence isomer **288**, reacts with benzyldiene(triphenyl)phosphorane to form the allenamide **289** (Scheme 128).^[214]

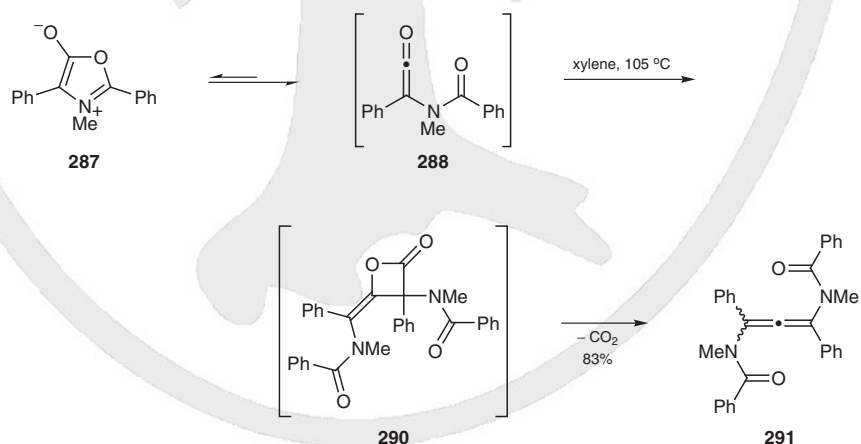
Scheme 128 Synthesis of an Allenamide by Wittig Alkenation of a Ketene^[214]**N-(1,3-Diphenylpropa-1,2-dien-1-yl)-N-methylbenzamide (289):**^[214]

Benzylidene(triphenyl)phosphorane (4.75 mmol) was added to a suspension of the mesoionic oxazole **287** (1.26 g, 5.0 mmol) in benzene (25 mL) (**CAUTION: carcinogen**), and the soln was stirred for 30 min at 80 °C under N₂. The yellow-brown solvent was removed to give a solid; yield: 1.0 g (61%). Crystallization (MeOH) gave colorless prisms.

21.4.5.1.8

Method 8:**By the [2 + 2] Dimerization of a Ketene and the Subsequent Elimination of Carbon Dioxide**

When the mesoionic oxazole **287** is thermolyzed in the absence of any other reagent it gives an intermediate oxetanone **290**. This intermediate may arise from the dimerization of the valence isomer of the starting material **288**; it eliminates carbon dioxide and gives the tetrasubstituted allene **291** (Scheme 129).^[215]

Scheme 129 Synthesis of an Allenamide by the [2 + 2] Dimerization of a Ketene and the Subsequent Elimination of Carbon Dioxide^[215]**N,N'-(1,3-Diphenylpropa-1,2-diene-1,3-diyl)bis(N-methylbenzamide) (291):**^[215]

The mesoionic oxazolone **287** in anhyd xylene (4 mL) was placed in an oven-dried flask and heated for 5 h at 105 °C while N₂ was passed through the vessel and allowed to exit

through a drying tube filled with calcium carbonate. A colorless crystalline solid began to separate from the soln, which was then cooled, and the solid was collected by filtration; yield: 1.26 g (83%). When the xylene mother liquor was reduced in volume more of the allenamide was isolated.



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Product Class 5: α -Heteroatom-Substituted Alkanamides

M. Pätzelt, S. Pritz, and J. Liebscher

General Introduction

Peptides are not considered in this article but in Product Class 21.11. Syntheses of alkanamides with α -heteroatom functionality by formation of the amide bond are also not included; they can be found in Product Class 21.1. Products in which the α -carbon atom and the α -heteroatom functionality belong to a heterocycle are also not considered, except for epoxides and aziridines.

21.5.1 Product Subclass 1: Alkanamides with One (or More) Group 17 Element in the α -Position

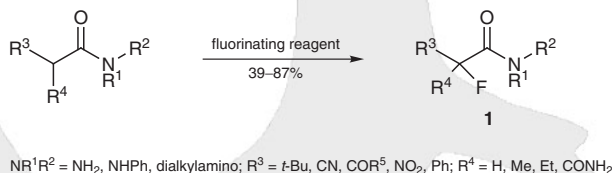
21.5.1.1 Synthesis of Product Subclass 1

21.5.1.1.1 Method 1: Substitution of One (or More) α -Hydrogen Atom

21.5.1.1.1.1 Variation 1: Substitution by Fluorine Atoms

The introduction of fluorine into the α -position of amides is possible using several fluorinating reagents such as Selectfluor {1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)},^[1] 2-fluoro-1,3,2-benzodithiazole 1,1,3,3-tetraoxide,^[2] *N*-fluorobis(trifluoromethylsulfonyl)amine,^[3] trifluoromethyl hypofluorite,^[4] fluorine,^[5] perfluoroalkyl hypofluorites,^[6] or perchloryl fluoride^[7] (Scheme 1). Sometimes, mixtures of mono- (e.g., **1**) and difluorination products are obtained.^[2] In some cases it is advantageous to generate the amide enolate or silyl enol ether first.^[3–7]

Scheme 1 α -Fluorination^[1–6]



In the case of α -(phenylsulfanyl)- or α -(phenylselanyl)acetamides, fluorination occurs as a type of Pummerer reaction, i.e. by primary attack at the sulfur or selenium atom, followed by rearrangement.^[8] 4-(Difluoroiodo)toluene,^[8] electrolysis in the presence of hydrogen fluoride–triethylamine,^[9–11] and iodine(V) fluoride^[12] are also useful fluorinating reagents; again, difluorination may occur in some cases.^[9]

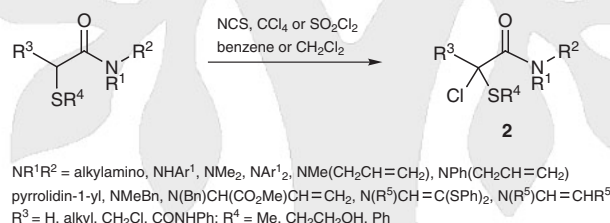
2-Benzoyl-2-fluoro-*N,N*-dimethylacetamide (1, $R^1 = R^2 = \text{Me}$; $R^3 = \text{Bz}$; $R^4 = \text{H}$); Typical Procedure:^[1]**CAUTION:** Fluorinating reagents are sometimes explosive and can cause toxicity hazards.**CAUTION:** α -Fluoro amides can be toxic.

The substrate (1 mmol) was stirred with Selectfluor (1 mmol) in MeCN (10 mL) at rt. When fluorination was complete (TLC, 3–67 h), the soln was concentrated under reduced pressure and the residue was partitioned between H₂O and CH₂Cl₂. The organic layer was washed with H₂O (2 \times), dried (MgSO₄), and concentrated under reduced pressure. The residue was further purified by recrystallization or chromatography; yield: 87%.

21.5.1.1.1.2

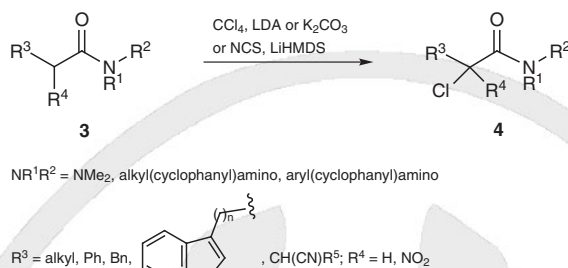
**Variation 2:
Substitution by Chlorine Atoms**

α -Chlorination of amides is easily possible, if an alkylsulfanyl or arylsulfanyl substituent is located in an α -position. In most cases, *N*-chlorosuccinimide^[13–23] is used, but sulfuryl chloride^[24,25] can also be applied (Scheme 2). The products are normally not isolated or purified. α -Chloro or α -sulfanyl amides are not very stable owing to easy formation of captodative-stabilized radicals by homolytic C—Cl bond cleavage. These radicals are versatile intermediates in intramolecular cyclization reactions to give nitrogen heterocycles if suitable substituents are attached to the amide nitrogen atom, such as allyl, benzyl, homoallyl, vinyl, or aryl. α -Chloro- α -(organosulfanyl) amides **2** can also be used in cationic intramolecular reactions.

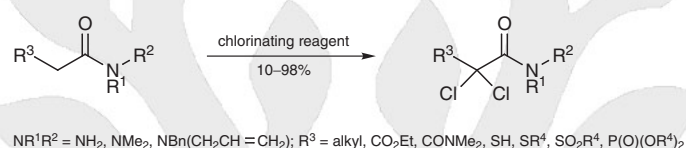
Scheme 2 α -Chlorination of α -(Alkylsulfanyl) or α -(Arylsulfanyl) Amides^[13–25]

More stable products are obtained if the thioether moiety of the α -(arylsulfanyl)- α -chloro amides is oxidized to the corresponding sulfur oxides with 3-chloroperoxybenzoic acid.^[26] If R^3 in the amide **2** is alkyl, the α -chlorination may be accompanied by elimination reactions.^[20]

Amides **3** lacking α -sulfur functionalities can be α -chlorinated, e.g. to give **4**, in the presence of a base such as lithium diisopropylamide,^[27] lithium hexamethyldisilazide,^[28] or potassium carbonate,^[29] via intermediate amide enolates (Scheme 3). Carbon tetrachloride,^[27,29] *N*-chlorosuccinimide,^[28] or potassium hypochlorite^[30] can be used as chlorinating reagents. Sometimes, double chlorination occurs.^[29]

Scheme 3 α -Chlorination via Amide Enolates^[27–30]

If electron-withdrawing groups or sulfanyl groups are found in the α -position of amides, α -chlorination is possible with elemental chlorine,^[31–33] sodium hypochlorite in the presence of sodium carbonate,^[34] or sulfonyl chloride^[33,35] and generally leads to disubstitution products if two hydrogen atoms are found in the α -position (Scheme 4).

Scheme 4 α,α -Dichlorination^[31–37]

Dichlorination of nonactivated amides is possible after prior transformation into chloriminium salts with phosgene, chlorination with chlorine, and hydrolytic workup.^[36,37] Base-catalyzed rearrangement of *N*-mesyloxy amides in the presence of triethylammonium chloride provides high yields of α -chloro amides under mild conditions.^[38]

***N*-Allyl-2-chloro-*N*-methyl-2-(methylsulfanyl)acetamide (2, $\text{R}^1 = \text{CH}_2\text{CH=CH}_2$; $\text{R}^2 = \text{R}^4 = \text{Me}$; $\text{R}^3 = \text{H}$); Typical Procedure:**^[14]

NCS (310 mg, 2.3 mmol) was added in portions to a soln of *N*-allyl-*N*-methyl-2-(methylsulfanyl)acetamide (360 mg, 2.23 mmol) in CCl_4 (10 mL) (**CAUTION: toxic**) at 0°C and the mixture was stirred at rt for 4 h. The precipitated succinimide was filtered off and the filtrate was concentrated under reduced pressure to give the product; yield: almost quant. The product was immediately dissolved in dry benzene (35 mL) (**CAUTION: carcinogen**) and submitted to radical cyclization in the presence of Bu_3SnH to afford 1,4-dimethyl-3-(methylsulfanyl)pyrrolidin-2-one.

2-Chloro-*N,N*-dimethyl-2-phenylacetamides 4 ($\text{R}^1 = \text{R}^2 = \text{Me}$; $\text{R}^3 = \text{Ph}$); General Procedure:^[29]

The appropriate *N,N*-dimethylacetamide (5 mmol) and *t*-BuOH (40 mmol) were dissolved in CCl_4 (18.8 mL) (**CAUTION: toxic**). After addition of powdered K_2CO_3 (3 g) the mixture was stirred at rt. It was then acidified with HCl. After addition of Et_2O , the organic layer was separated and washed with H_2O . The organic layer was concentrated under reduced pressure and the remaining product was recrystallized (cyclohexane); yield: 60–98%.

21.5.1.1.1.3

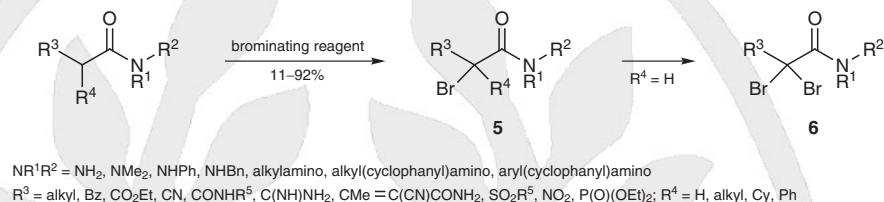
**Variation 3:
Substitution by Bromine Atoms**

α -Bromination of amides with elemental bromine in acetic acid or in chloromethanes ($\text{CH}_n\text{Cl}_{4-n}$, $n = 0, 1, 2$) in the presence of a base (sodium carbonate or triethylamine) is a useful method for the synthesis of α -bromo amides **5** with electron-withdrawing substituents R^3 (Scheme 5).^[39–46] Bromination of 2-oxocyclohexanecarboxamide can be directed either to position 3 or position 6, depending on whether or not sodium carbonate is used.^[43]

Sometimes, mixtures of mono- and dibromination products are obtained with elemental bromine even if the reactants are used in equimolar quantities. Bromination under irradiation can be applied to hexose-1-carboxamides when the α -position is not activated by an electron-withdrawing substituent.^[47]

α,α -Dibromo amides **6** with an additional electron-withdrawing substituent attached to the α -carbon atom are available by bromination of amides either in a stepwise manner or directly with excess bromine^[45,46,48,49] or sodium hypobromite^[50] (Scheme 5).

Scheme 5 α -Bromination^[39–46]



Amides lacking α -electron-withdrawing substituents can be doubly brominated with bromine via intermediate imidoyl chlorides.^[51] The application of α,α -dibromomalononic acid derivatives as brominating reagents for active methylene compounds prevents competing double bromination occurring with elemental bromine.^[52,53] *N*-Cyclohexyl-2-oxopropanamide can be brominated in 94% yield by 4-(dimethylamino)pyridinium bromide perbromide in acetic acid within 15 minutes.^[54]

N-Bromosuccinimide can be used in the bromination of activated and inactivated amides, including ribose-1-carboxamides and cyclophane amides.^[28,53,55,56] *N*-Unsubstituted amide enolate formation^[28] with lithium hexamethyldisilazane or addition of benzoyl peroxide is also useful.^[53]

Aqueous alkali hypobromites are useful for the monobromination of amides with a nitro group^[30] or phosphoester group in the α -position.^[50] Treatment of amide enolates obtained using lithium diisopropylamide with carbon tetrabromide can also afford α -bromoamides in high yields.^[57] The rearrangement of *N*-mesyloxy amides in the presence of lithium bromide and triethylamine is a high-yielding route to a wide variety of *N*-substituted α -bromoamides.^[38]

2-Bromo-2-cyanoacetamide (5, R¹ = R² = R⁴ = H; R³ = CN); Typical Procedure:^[41]

CAUTION: Bromine is a severe irritant of the eyes, mucous membranes, lungs, and skin. Liquid bromine causes severe and painful burns on contact with eyes and skin.

Into a vigorously stirred soln of cyanoacetamide (50.5 g, 0.6 mol) in AcOH/Ac₂O (7:1, 460 mL), Br₂ (95.5 g, 0.6 mol) in AcOH (190 mL) was added dropwise at 8–10 °C and the soln was stirred for an additional 2 h at the same temperature. The soln was concentrated under reduced pressure, whereupon the resulting residue solidified on cooling. Recrystallization (EtOH) gave needles; yield: 80.5 g (83%); mp 113–114 °C.

N-Allyl-2-bromoacetoacetamide (5, R¹ = CH₂CH=CH₂; R² = R⁴ = H; R³ = Ac); Typical Procedure:^[55]

NBS (5.34 g, 0.03 mol) was added to a soln of *N*-allylacetoacetamide (4.23 g, 9.93 mol) in dry acetone (20 mL) at rt over 3 h. The mixture was filtered to remove succinimide and the filtrate was concentrated to dryness. The residue was extracted (hexane) and the soln was washed with H₂O, dried, and the solvent removed under reduced pressure. The residue was distilled at 250 °C/1.0 Torr to give the product as an oil; yield: 6.06 g (92%).

C-(2,3,4,6-Tetra-O-benzoyl-1-bromo-1-deoxy- β -D-glucopyranosyl)formamide (5, $R^1 = R^2 = R^4 = H$; $R^3 = \text{Hexose}$); Typical Procedure:^[47]

CAUTION: Bromine is a severe irritant of the eyes, mucous membranes, lungs, and skin. Liquid bromine causes severe and painful burns on contact with eyes and skin.

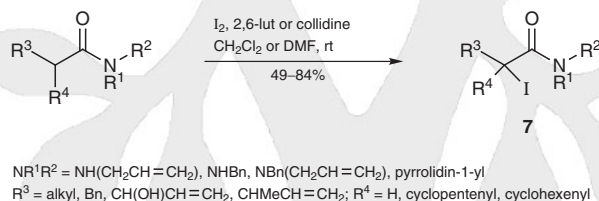
C-(2,3,4,6-Tetra-O-benzoyl- β -D-glucopyranosyl)formamide (200 mg, 0.32 mmol) was dissolved in CHCl_3 (6 mL). Br_2 (0.07 mL, 1.28 mmol) and some BaCO_3 were added, and the mixture was irradiated and refluxed by a heat lamp (375 W, white, distance from the lamp ca. 1–2 cm, height of the soln 1–1.5 cm). After 1 h the mixture decolorized and Br_2 (0.1 mL) was added again. This was repeated after another 0.5 h. After TLC had shown complete transformation (ca. 2 h from start) the mixture was filtered, washed with 5% aq NaHSO_3 and sat. aq NaHCO_3 , dried, and the solvent was removed. The residual syrup (264 mg) crystallized on addition of Et_2O to give the product; yield: 201 mg (89%); mp 170–173 °C.

21.5.1.1.1.4

Variation 4: Substitution by Iodine Atoms

Elemental iodine in the presence of *sym*-collidine (2,4,6-trimethylpyridine) or 2,6-lutidine (2,6-dimethylpyridine) represents a mild method for α -iodination of amides (e.g., to give **7**), where the C=C bond attached to the acyl group is maintained, thereby avoiding halocyclization (Scheme 6).^[58,59] Under proper conditions, high *syn/anti* selectivities can be achieved for the iodination of amides bearing a chiral center in the β -position.^[59]

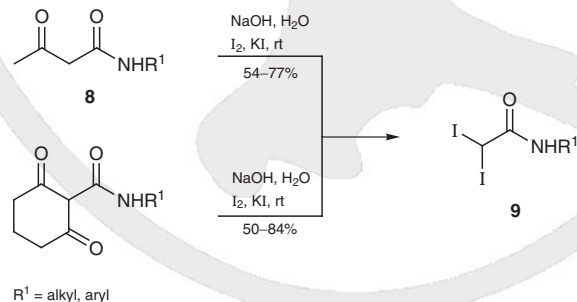
Scheme 6 α -Iodination^[58,59]



Diastereoselective α -iodination is achieved by treating the lithium enolate of chiral (2*S*,5*S*)-2,5-dimethyl-1-propanoylpyrrolidine with iodine.^[60]

Geminal α,α -diiodo amides **9** can be synthesized from β -oxo amides **8** by α -iodination with sodium hypoiodite, accompanied by acyl cleavage (Scheme 7).^[61]

Scheme 7 α,α -Diiodination with C–C Bond Cleavage^[61]



α -Iodo Amides **7**; General Procedure:

^[58]

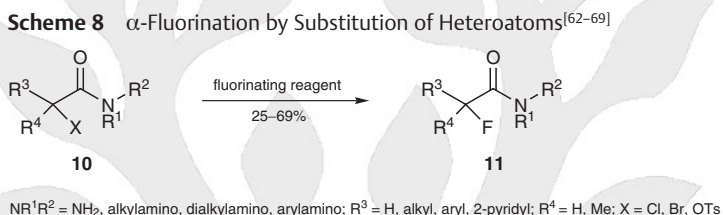
2,6-Lutidine (0.4 mL, 3 mmol) and I_2 (380 mg, 1.5 mmol) were added to a soln of the amide (1.0 mmol) in dry CH_2Cl_2 (8 mL) and the mixture was stirred at rt. The mixture was poured

into 2% HCl and extracted (CH_2Cl_2). The organic layer was washed with aq $\text{Na}_2\text{S}_2\text{O}_3$, dried (MgSO_4), and concentrated to dryness. The residue was purified by column chromatography to afford the product as a colorless oil; yield: 49–73%.

21.5.1.1.2 Method 2: Substitution of Heteroatoms

21.5.1.1.2.1 Variation 1: Substitution by Fluorine Atoms

Replacement of α -heteroatoms, e.g. in **10**, is a versatile route to α -fluoro amides **11**. Hydroxy, methanesulfonate, halide, 4-toluenesulfonate, or sulfate can be used as leaving groups, while potassium fluoride,^[62–65] tetrabutylammonium fluoride,^[66] and diethylamino-sulfur trifluoride^[67–69] are the most common fluoride sources (Scheme 8).



2-Fluoropropanamides **11** (R⁴ = Me); General Procedure:^[67]

At 0 °C a soln of DAST (10 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a soln of the α -hydroxypropanamide **10** (X = OH; 10 mmol) in CH_2Cl_2 (10 mL). After 2 h at 0 °C the mixture was washed with brine (2 × 10 mL) and concentrated. The residue was recrystallized (toluene); yield: 71–92%.

2-Fluoro-*N*-phenylacetamides **11** (R¹ = H; R² = Ph); General Procedure:^[64]

A stirred mixture of the α -halo amide or α -tosyloxy amide **10** (X = Cl, Br, OTs; 0.1 mol), dry KF (0.25 mol), and diethylene glycol (100 mL) was heated rapidly to 125–130 °C and kept at this temperature for 2 h. In the case of α -tosyloxy amides, the temperature was kept at 95–100 °C for 40 min. The product was cooled, diluted with H_2O (200 mL), and extracted with benzene (3 × 150 mL) (**CAUTION: carcinogen**). The benzene layer was washed with 5% NaHCO_3 , dried, and concentrated; yield: 25–69%.

21.5.1.1.2.2 Variation 2: Substitution by Chlorine Atoms

α -Chloro amides **12** can be synthesized by substitution of bromide or hydroxy groups using thionyl chloride,^[70–73] phosphoryl chloride,^[74] phosphorus pentachloride,^[75] methanesulfonyl chloride,^[76] antimony(V) chloride–tetrasulfur tetranitride,^[77] or chlorine^[78] as chlorinating reagents (Scheme 9). In the last case, additional substitution of α -hydrogen by chlorine can occur.^[78] α -Bromide, -methanesulfonate, or -toluenesulfonate can be substituted by nucleophilic chloride donors such as lithium chloride^[79,80] or tetrabutylammonium chloride.^[66] Inversion of configuration is found in substitution of toluenesulfonate.^[80]

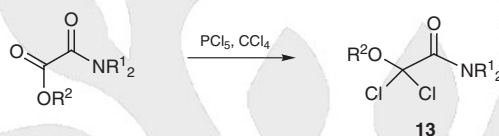
Scheme 9 α -Chlorination by Substitution of Heteroatoms^[66,70–80]

NR^1R^2 = alkylamino, dialkylamino, arylamino, diarylamino, $\text{NHCHR}^5\text{CONHR}^6$

$\text{R}^3 = \text{H}, \text{Ph}$; $\text{R}^4 = \text{H}, \text{aryl}, \text{azetidin-1-yl}, \text{Br}$; $\text{R}^5, \text{R}^6 = 9\text{-}H\text{-fluoren-9-yl}$; $\text{X} = \text{Br}, \text{OH}, \text{OMs}, \text{alkylsulfanyl}, \text{NH}_2$

Other leaving groups which can be used are sulfur moieties^[81,82] and amino groups^[83] in the presence of sulfonyl chloride or nitrosyl chloride, respectively. α -Diazo amides form α -chloro amides with hydrogen chloride^[84] in diethyl ether or (in a side reaction) with acyl chlorides.^[85]

Treatment of oxamide esters with phosphorus pentachloride results in the formation of α -alkoxy- α , α -dichloroacetamides **13** (Scheme 10).^[86]

Scheme 10 α , α -Dichlorination of Oxamide Esters^[86]

$\text{R}^1 = \text{H}, \text{Me}$; $\text{R}^2 = \text{alkyl}, \text{aryl}$

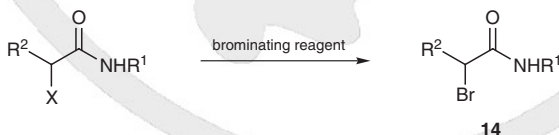
N-Benzyl-2-chloro-2-phenylacetamide (12, $\text{R}^1 = \text{Bn}$; $\text{R}^2 = \text{R}^4 = \text{H}$; $\text{R}^3 = \text{Ph}$):^[66]

To a benzene soln (100 mL) (**CAUTION: carcinogen**) containing *N*-benzyl-2-(mesyloxy)-2-phenylacetamide (1.92 g, 7 mmol) was added TBACl (4.85 g, 14 mmol), and the mixture was refluxed for 2 h. After concentrating under reduced pressure, H_2O (250 mL) and Et_2O (100 mL) were added to the residue. The organic layer was separated and washed with H_2O (100 mL). After drying (MgSO_4), the organic layer was concentrated under reduced pressure. The resulting white solid was triturated with hexanes (100 mL) to give the product; yield: 1.50 g (83%); mp 94–95 °C.

21.5.1.1.2.3

Variation 3: Substitution by Bromine Atoms

α -Ethoxy,^[87] α -halo,^[88] or α -mesyloxy amides^[66] can be transformed into α -bromo amides **14** with phosphorus tribromide, bromoethane–sodium bromide, or tetrabutylammonium bromide, respectively (Scheme 11). Formation of α -bromoacetamides is also possible from the corresponding α -diazo amide and acyl bromide.^[85]

Scheme 11 α -Bromination by Substitution of Heteroatoms^[66,87,88]

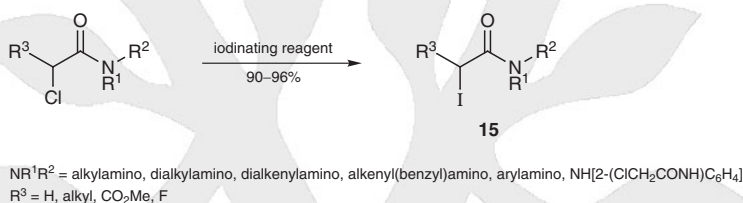
$\text{R}^1 = \text{Bn}, \text{CHMePh}$; $\text{R}^2 = \text{Ph}, \text{NHAc}, \text{F}$; $\text{X} = \text{Cl}, \text{I}, \text{OEt}, \text{OMs}$

21.5.1.1.2.4

Variation 4:
Substitution by Iodine Atoms

Substitution of α -heteroatoms by iodide is the most versatile method for the synthesis of α -iodo amides. Since further substitution of the iodide by nucleophiles is easily possible, such products are frequently used to link functions (fluorescent labels, cryptands, sensitizers) to substrates via an acetamide linker.^[89–93] On the other hand, α -iodo amides are important precursors for radical cyclizations, tandem reactions, and stereoselective reactions^[18,94–99] and can be used in metal-catalyzed coupling reactions.^[100,101]

α -Chloro atoms can be replaced by iodine atoms under mild Finkelstein conditions using sodium iodide in acetone, affording the corresponding α -iodo amides **15** in high yields (Scheme 12).^[18,89,90,94–97,100,102–104] The reagent can also be used to synthesize ^{131}I -labeled α -iodo amides^[102] and α -iodo amides derived from optically active amines.^[95,102] Less common is the application of potassium iodide in other solvents such as acetonitrile, methanol, butan-2-one, or tetrahydrofuran.^[91,92,98,110,105,106] Phase-transfer catalysis is suitable for replacement of α -halo groups by iodide.^[107] Finkelstein reactions can also be applied in the synthesis of natural products such as alkaloids, cephalosporins, and peptides.^[98,106] Bromide can also serve as the leaving group under similar conditions.^[99,107,108]

Scheme 12 α -Iodination by Substitution of Chlorine^[18,89,90,94–97,100,102–104]

Often, in situ substitution of α -chloro groups by iodide is used to enhance substitution by nucleophiles such as sulfur or nitrogen (see also Section 21.5.3.1.2.3).

If methanesulfonate is employed as the leaving group, tetrabutylammonium iodide can be used as an iodide donor.^[66] Treatment of ethyl *N*-(diazooacetyl)glycinate with iodine provides ethyl *N*-(diiodoacetyl)glycinate,^[84] while the interaction of *N*²-(diazooacetyl)glycinamides with hydroiodide results in *N*²-(iodoacetyl)glycinamides.^[109]

***N*-(Iodoacetyl)-D,L-phenylalanine (15, R¹ = R³ = H; R² = CHBnCO₂H); Typical Procedure:**^[104]

A mixture of (chloroacetyl)phenylalanine (5.7 g, 23.6 mmol), NaI (4.5 g, 30.0 mmol), and dry acetone (300 mL) was refluxed for 3 h in a 500-mL flask fitted with a stirrer, reflux condenser, and an inlet for N₂. The mixture was filtered, the residue was washed with dry acetone, and the combined filtrate and washings were concentrated under reduced pressure. The residual syrup was taken up in abs Et₂O, filtered, and concentrated under reduced pressure to give the crude product; yield: 7.5 g (96%); mp 120–124 °C. Recrystallization (toluene) afforded clusters of almost colorless needles; yield: 5.5 g; mp 140 °C.

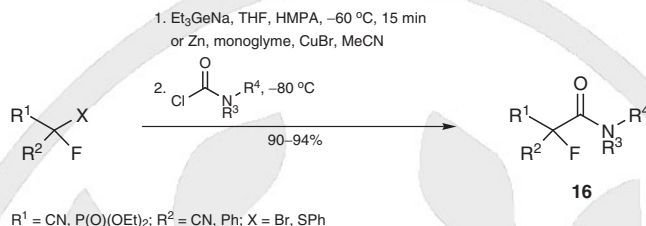
21.5.1.1.3

Method 3:
C—C Bond Formation between the Carbonyl Group and the α -Carbon Atom

Syntheses of α -haloalkanamides by C—C bond formation between the carbonyl group and the α -carbon atom are mainly applied to the synthesis of α -fluoro amides **16**. If chlorocarbamates are used as electrophiles, the nucleophilic α -fluoro species can be generated from the reaction partners in situ by replacement of phenylsulfanyl or bromo as leaving groups by germanes^[110] or zinc,^[111] respectively (Scheme 13). Isocyanates can al-

ternatively be applied as electrophiles. In these cases, organozinc^[112] or deprotonated species^[113,114] are used as nucleophiles.

Scheme 13 Formation of an α -C—C Bond^[110,111]



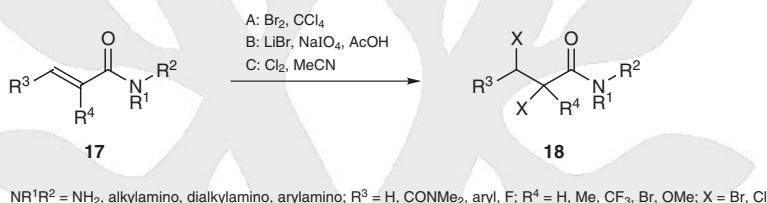
21.5.1.1.4

Method 4:

Addition of Halogen Atoms to α,β -Unsaturated Amides

α,β -Dibromo amides **18** can be prepared by reaction of α,β -unsaturated amides **17** with elemental bromine in haloalkane solvents^[115–118] or with an alkali metal halide–sodium periodate system (Scheme 14).^[119] Corresponding chlorinations are rare.^[120]

Scheme 14 Addition of Dihalogen to α,β -Unsaturated Amides^[115–120]



Addition of selenenyl or sulfenyl halides to α,β -unsaturated amides affords mixtures of regioisomers, where α -halo amides are the major products in some cases under suitable conditions^[121] (see also Section 21.5.2.1.4). Iodotosylation of acrylamides to give α -iodo- β -tosyloxy amides is possible with 4-toluenesulfonyl iodide or toluenesulfenate–iodine.^[122] Fluorinated α -iodo amides can be synthesized in high yields by radical addition of fluoroiodoalkanes or ketones to acrylamides under UV irradiation.^[123] The synthesis of 2-chloro-3-(*N*-chloro-*N*-ethoxycarbonylamino)propanamide is reported by chloroamination of acrylamide in the presence of copper(I) chloride.^[124]

2,3-Dibromopropanamide (**18**, $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$; $\text{X} = \text{Br}$); Typical Procedure:^[118]

CAUTION: Bromine is a severe irritant of the eyes, mucous membranes, lungs, and skin. Liquid bromine causes severe and painful burns on contact with eyes and skin.

A slurry of acrylamide (35 g, 0.57 mol) in CCl_4 (100 mL) (**CAUTION:** toxic) was treated with Br_2 (80 g, 0.5 mol). The precipitate was collected by filtration, washed (CCl_4), and recrystallized (abs EtOH); yield: 70 g (63%); mp 132 – 133°C .

21.5.1.1.5

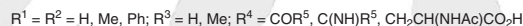
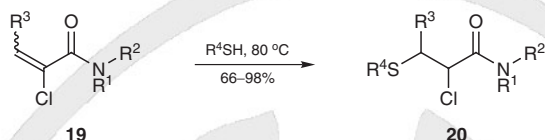
Method 5:

Addition to α,β -Unsaturated α -Halo Amides

Thiocarboxylic acids,^[125,126] imidothioic acids,^[127] or *N*-acetylcysteine^[128] can be added to the C=C bond of α -chloroacrylamides **19** in a Michael-like addition to afford high yields of α -chloro amides **20** with the corresponding sulfur function in the β -position (Scheme

15). The β -imidoylsulfanyl products are isolated as hydrochlorides and can serve as precursors for cysteinamides or cysteine.^[127]

Scheme 15 Addition of Thiol Derivatives to α,β -Unsaturated α -Halo Amides^[125–128]



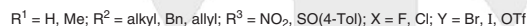
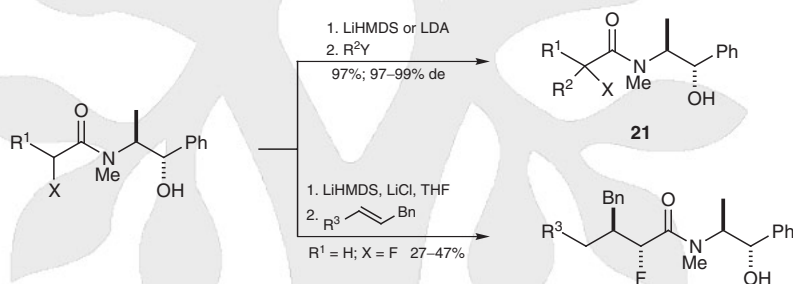
21.5.1.1.6

Method 6:

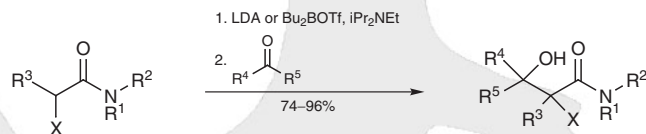
C—C Chain Elongation at the α -Carbon Atom

Lithium,^[129–133] sodium,^[134] or boron enolates^[135] of α -halo amides or α,α -difluoroacetamides^[133] can be used for C—C chain elongation with electrophiles, such as alkylating reagents (e.g., the formation of **21**),^[129,130,134] aldehydes or ketones,^[131,132,135] esters,^[133] or nitroalkenes^[136] (Schemes 16 and 17). High stereoselectivities can be achieved with α -halo amides derived from pseudoephedrine.^[129,130]

Scheme 16 C—C Chain Elongation by Alkylation with Alkyl Halides or Addition of Electron-Poor Alkenes^[129,130,134]



Scheme 17 C—C Chain Elongation by Addition of Carbonyl Compounds^[131–133,135]



On the other hand, dihaloenolates can be obtained from α,α,α -trihaloacetamides via replacement of α -chloro by metals such as zinc (Reformatsky type)^[137–139] or lead–aluminum^[140] and can react with alkylating reagents or aldehydes, respectively, providing chain-elongated α,α -difluoroacetamides.

The synthesis of α -halo amides by C—C bond formation can also be achieved by addition reactions to C=C bonds. Thus 2,2,3,3-tetrafluoro-3-methoxy-*N,N*-dimethylpropanamide can be obtained from trifluoro-*N,N*-dimethylacetamide and tetrafluoroethene in the presence of sodium methoxide. In this case, trifluoromethyl acts as a leaving group.^[141] Trichloroacetamides can add to octene in the presence of iron in a radical fashion^[142] or to 1,3-dienes.^[143]

2-Fluoro-N-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-N-methylpropanamide (21, $R^1 = H$; $R^2 = Me$; $X = F$); **Typical Procedure:**^[129]

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

Anhyd LiCl (1.27 g, 30.0 mmol) was flame dried under reduced pressure to ensure dryness and then allowed to cool under dry argon. $(TMS)_2NH$ (2.32 mL, 11.0 mmol) and THF (5.00 mL) were added to the solid LiCl after it had cooled and the resulting suspension was cooled to $-78^\circ C$, whereupon 2.56 M BuLi in hexanes (4.20 mL, 10.8 mmol) was added. The reaction vessel was briefly transferred to an ice bath (15 min) and was then cooled to $-78^\circ C$. A soln of pseudoephedrine α -fluoroacetamide (1.13 g, 5.00 mmol) in THF (15 mL) was added via cannula, and the addition was quantitated with THF (5 mL). After stirring at $-78^\circ C$ for 1.3 h, the soln was treated with MeI (0.934 mL, 15.0 mmol). The mixture was warmed to $-50^\circ C$ and stirred at this temperature for 30 min. Following aqueous workup, the product was purified by flash chromatography (EtOAc/hexanes 1:1) to provide the product as a viscous oil which solidified on standing; yield: 1.16 g (97%); 99% de; mp $76-79^\circ C$ (EtOAc/hexanes).

21.5.2 Product Subclass 2:
Alkanamides with One (or More) Group 16 Element in the α -Position

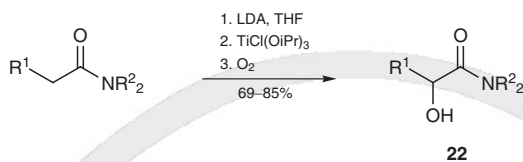
21.5.2.1 Synthesis of Product Subclass 2

21.5.2.1.1 Method 1:
Substitution of One (or More) α -Hydrogen Atom

Most methods to introduce group 16 elements into the α -position of alkanamides exploit CH acidity and often enolates are produced in a prior step. It is possible to substitute more than one α -hydrogen atom, introducing two or three heteroatoms or one heteroatom connected by a double bond.

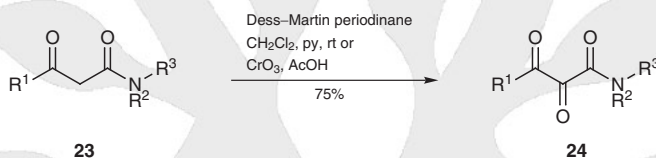
21.5.2.1.1.1 Variation 1:
Substitution by Oxygen Atoms

Amides can directly be oxidized in the α -position, affording corresponding α -hydroxy amides **22** or O-functionalized derivatives such as α -acyloxy, α -sulfonyloxy, or *N,N*-bis(trifluoromethyl)aminoxy amides. 2,3-Dichloro-5,6-dicyanobenzo-1,4-quinone,^[144] (diacetoxyiodo)benzene,^[145] bis(4-nitrobenzoylsulfonyl) peroxide,^[146] bis(*N,N*-trifluoromethyl)nitroxyl,^[147] sodium hypochlorite,^[43] or anodic oxidation^[148] can be used in these processes. More often, amide enolates, obtained from amides and, most conveniently, lithium diisopropylamide, have been used. Lithium *tert*-butylperoxide,^[149] dioxygen (in the case of titanium enolates)^[150] (Scheme 18) and *N*-sulfonyloxaziridines^[151-154] are useful oxidizing reagents in such cases. Chiral *N*-sulfonyloxaziridines derived from camphor allow asymmetric introduction of α -hydroxy groups into amide enolates.^[152,154] Usually, the enantio- or diastereoselectivities are modest. High yields of α -hydroxy amides can be achieved by rearrangement of *N*-mesyloxy amides under hydrolytic conditions.^[38]

Scheme 18 α -Hydroxylation via Titanium Enolates^[145,150]

$R^1 = \text{Bu, Ph, Bn}$; $\text{NR}^2_2 = \text{N-}i\text{Pr}_2, (\text{S})\text{-2-(hydroxymethyl)pyrrolidin-1-yl}$

Introduction of an oxygen function into the α -position of amides can also lead to α -oxo amides or their derivatives. Thus amides of α -amino acids can be electrochemically oxidized in the presence of chloride and methanol to the corresponding α -amino- α -methoxy amides via intermediate α -imino amides.^[155] Pummerer reaction of a chiral *S*-oxide of *N,N*-dimethyl-2-(4-tolylsulfanyl)acetamide gives rise to the formation of 2-acetoxy-*N,N*-dimethyl-2-(4-tolylsulfanyl)acetamide as a derivative of a glyoxylamide.^[156] β -Oxo amides **23** can be transformed into the corresponding acylglyoxylamides **24** by oxidation with chromium(VI) oxide^[39] or with Dess–Martin periodinane [1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one]^[157] (Scheme 19). The same products are obtained when β -hydroxy amides are treated with the Dess–Martin reagent.^[157]

Scheme 19 Acylglyoxylamides from β -Oxo Amides^[39,157]

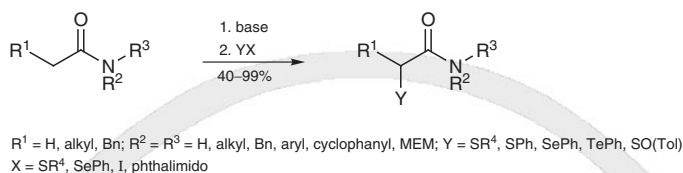
$R^1 = \text{Me, (CH}_2)_5\text{Me, } t\text{-Bu, Ph}$; $\text{NR}^2_2, \text{NR}^2\text{R}^3 = \text{piperidino, dialkylamino, NMePh}$

 α -Hydroxy Amides **22; General Procedure:**^[150]

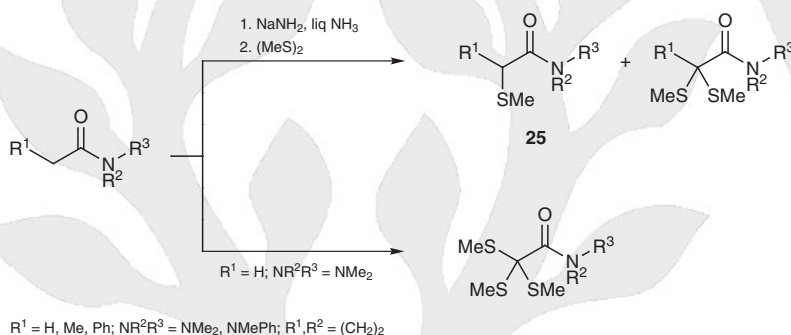
To a 0.50–0.75 M soln of LDA in THF (1.50 equiv), cooled to 0 °C, a soln of the amide (1 equiv) in THF (2 mL·mmol^{−1}) was added dropwise under an argon gas atmosphere. After stirring at 0 °C for 1 h, the mixture was treated with a 1.05 M soln of TiCl(OiPr)₃ (1.1 equiv) in pentane at −78 °C. Stirring was continued for 3 h while the temperature was allowed to reach −30 °C. The soln was cooled to the required oxidation temperature (−30 °C to −50 °C) and diluted with CH₂Cl₂ (20 mL·mmol^{−1}). A gentle stream of O₂ was bubbled through the mixture. After 30 min, the cold mixture was poured into sat. aq. NH₄F soln (50 mL·mmol^{−1}) and stirred at rt for 1 h. The organic layer was separated and the aqueous phase was extracted with *t*-BuOMe (2 × 20 mL·mmol^{−1}). The combined organic layers were washed with brine and dried (MgSO₄). After removal of the drying agent, the solvent was removed (40 °C/400 Torr) and the residue was purified by column chromatography; yield: 69–85%.

21.5.2.1.1.2**Variation 2:****Substitution by Sulfur, Selenium, or Tellurium Atoms**

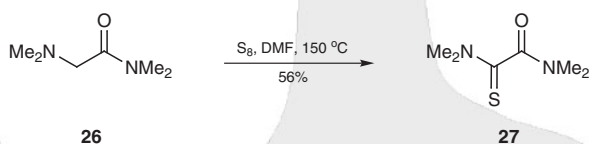
In order to replace hydrogen by sulfur, selenium, or tellurium, corresponding amide enolates are generated and reacted with electrophilic reagents such as disulfides,^[158] *S*-phenyl benzenethiosulfonate,^[28,159] *N*-(phenylselenanyl)phthalimide, diphenyl diselenide,^[158] or benzenetellurenyl iodide^[160] (Scheme 20). Besides monofunctional amides, succinamides^[158] and β -oxo amides^[161] can also be α -functionalized in this manner. Reaction of lithium enolates of acetamides with (*S*)-menthyl 4-toluenesulfinate provides optically active α -sulfinylacetamides, which are suitable for asymmetric aldol reactions.^[162]

Scheme 20 α -Sulfanyl, α -Selanyl, and α -Tellanyl Amides^[28,158–160]

If the amide enolates are generated with sodium amide in liquid ammonia, reaction with dimethyl disulfide can give di- and trisulfanylation, in addition to monosulfanylation to give **25** (Scheme 21).^[163] If lithium diisopropylamide is used, selective monosulfenylation can be achieved with *N*-methyl-*N*-phenylalkanamides.^[163]

Scheme 21 α -Sulfenylation of Amides^[163]

The introduction of two chlorosulfanyl groups in the α -position of malonamides and malonester amides can be achieved with sulfur dichloride without the application of a base.^[164] α, α -Diphenylthioacetamides, useful for the synthesis of *Strichnos* indole alkaloids, are accessible by Pummerer rearrangement of α -(phenylsulfinyl)acetamides in the presence of trifluoroacetic anhydride.^[165] Monothiooxalamides **27** can be synthesized by thionation of α -nitro- or α -aminoacetamides **26** with sulfur in dimethylformamide^[166] (Scheme 22) or with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide] or phosphorus pentasulfide.^[167]

Scheme 22 Thionation of *N,N*-Dimethyl- α -(dimethylamino)acetamide^[166]

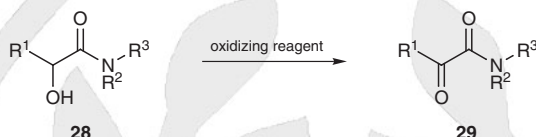
***N*-Methyl-2-(methylsulfanyl)-*N*-phenylpropanamide (25, $R^1 = R^2 = Me; R^3 = Ph$); Typical Procedure:**^[163]

A THF soln of LDA was prepared by the slow addition of 2.2 M MeLi (9 mL) to dry iPr_2NH (2.0 g, 0.02 mol) in THF (50 mL) at $-78^\circ C$. To this soln was added dropwise *N*-methyl-*N*-phenylpropanamide (1.63 g, 0.01 mol) in THF (10 mL) at $-78^\circ C$. The soln was stirred at $-78^\circ C$ for 30 min, after which $(MeS)_2$ (2.0 g, 0.02 mol) was added. After stirring for 2 h at $-78^\circ C$, the soln was allowed to warm to rt and quenched by the addition of H_2O (50 mL). The mixture was extracted with $CHCl_3$ (4 \times 50 mL), the organic extracts were combined, washed with dil HCl and sat. NaCl soln, and dried ($CaSO_4$). After filtration, the solvent was removed and the crystalline residue was recrystallized (hexane); yield: 1.83 g (87%); mp $71.5\text{--}73.0^\circ C$.

21.5.2.1.1.3

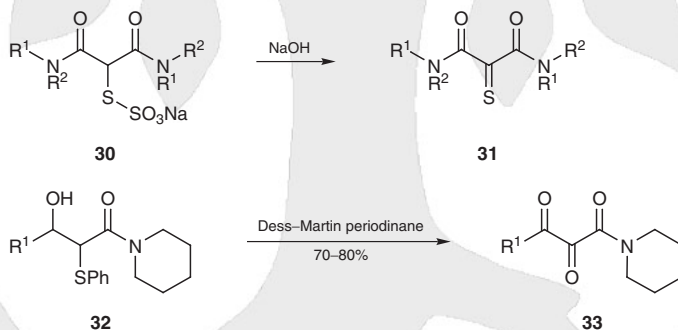
Variation 3:**Oxidation of α -Hydroxy and α -Sulfanyl Amides to α -Oxo and α -Thioxo Amides**

Several oxidizing reagents can be used for transforming α -hydroxy amides **28** into α -oxo amides **29** (Scheme 23).^[168–177]

Scheme 23 Oxidation of α -Hydroxy Amides to α -Oxo Amides^[168–177]

In the chromium series, pyridinium dichromate,^[168,170,174,177] pyridinium chlorochromate,^[176] and the Jones reagent (chromic acid)^[169] are successfully applied to simple amides such as lactamides as well as to chiral β -amino- α -hydroxy amides^[176] and α -hydroxy fatty acid amides.^[170,174,177] In the case of long-chain fatty acid amides, sodium hypochlorite-4-(acetylamino)-2,2,6,6-tetramethyl-1-piperidin-1-yloxy radical provides higher yields.^[170,174] Dess–Martin periodinane is also useful for the synthesis of natural-product related α -oxo amides in the fatty acid amide^[177] or peptide series.^[175] Swern oxidation is used to synthesize an *N*-alkylglyoxylamide.^[172,173] Arylglyoxylanilides are obtained by oxidation with barium manganate(VI), achieving 47–82% yields.^[171]

Amides bearing sulfur substituents in the α -position can also be used to synthesize amides of the 1,2,3-tricarbonyl series. Thus, Bunte salts **30**, obtained from corresponding α -bromo amides, afford 2-thioxomalonamides **31**.^[39] On the other hand, the sulfur moiety is lost and additional oxidation of the β -hydroxy function occurs on treatment of β -hydroxy- α -(phenylsulfanyl) amides **32** with Dess–Martin periodinane, providing 2,3-dioxo amides **33** (Scheme 24).^[178]

Scheme 24 Tricarbonyl Compounds from α -Sulfur-Substituted Derivatives^[39,178] **α -Oxo Amides **29**; General Procedure:**^[169]

The lactamide (80 mmol) was dissolved in acetone (50 mL) and cooled to 0°C. A soln containing $\text{Na}_2\text{Cr}_2\text{O}_7 \cdot \text{H}_2\text{O}$ (26 g, 87 mmol) in H_2O (50 mL) and H_2SO_4 (15 mL) was added via a dropping funnel. The mixture was warmed to rt and stirred for 30 min. TLC indicated complete conversion. The mixture was then diluted with Et_2O and the two phases were separated. The aqueous phase was extracted with Et_2O (5 \times 30 mL) and the combined organic phases were stirred with solid Na_2SO_3 for 1 h to reduce unreacted dichromate. After filtration, the solvent was removed under reduced pressure and the product was further purified by column chromatography; yield: 51–96%.

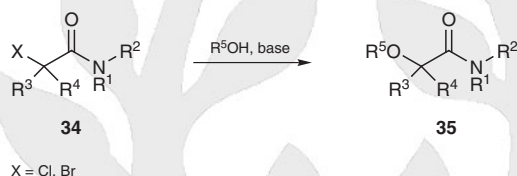
21.5.2.1.2

Method 2:
Substitution of Heteroatoms

21.5.2.1.2.1

Variation 1:
Substitution by Oxygen Atoms

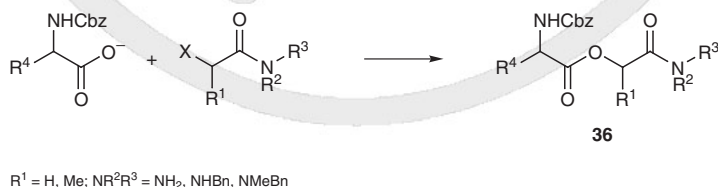
α -Bromo and α -chloro amides **34** are frequently applied in S_N reactions with oxygen nucleophiles. Except for phenols, examples with alcohols are rare. Sodium hydride,^[179] potassium hexamethyldisilazide,^[180] or sodium^[181] are used to generate the corresponding alkoxides **35** (Scheme 25). In the last case, diols, triols, and tetrols are alkylated with α -chloroacetamides at all hydroxy groups.^[181]

Scheme 25 α -Alkoxy and α -Aryloxy Amides from α -Halo Amides^[179–194]

In the case of α -halo- β -hydroxy amides, intramolecular nucleophilic substitution can be used to synthesize oxiranecarboxamides.^[26,195] In a similar manner, six-membered ring heterocycles can be obtained by intramolecular substitution of an α -acetoxy group.^[196]

Many α -aryloxy amides^[183–186,190,193,194] and some α -pyridyloxy amides^[187,192,197] are synthesized from corresponding α -chloro and α -bromo amides and hydroxyarenes. Most often, alkali metal carbonates are used as bases and the substitution can be further supported by applying Finkelstein conditions, i.e. the addition of alkali metal iodides or bromides. The alkylation of phenols or pyridinols with *N*-unsubstituted or *N*-monosubstituted α -halo amides is important in the overall transformation of these aromatic systems into the corresponding amines via Smiles rearrangement.^[186,187,197] α -Amino- α -halo amides can be transformed into *N,O*-acetals by reaction with alkoxides or phenoxides. Alkylation with α -halo amides is also successfully applied in the synthesis of glycodendrimers^[194] and in the calixarene series to modify all or some of the phenolic hydroxy groups.^[188,189,191] Bis(α -haloacyl)amines, derived from aliphatic diamines, can be used to link phenolic or calixarene moieties together.^[189,190] On the other hand, two or three chloroacetamides can be linked by corresponding di- or trihydroxyarenes or (hydroxy-alkyl)phenols.^[184,185,193]

The application of carboxylates as nucleophiles in reactions with α -chloro or α -bromo amides results in the formation of α -acyloxy amides.^[198–202] If the attacking carboxylate derives from an α -amino acid, depsipeptides such as **36** can be synthesized in this way and the reaction can be implemented without racemization (Scheme 26).^[198–200] In the latter case, silver(I) oxide is used to support the transformation. The reaction is also applied in an intramolecular fashion by macrolactonization, leading to antibiotics.^[201]

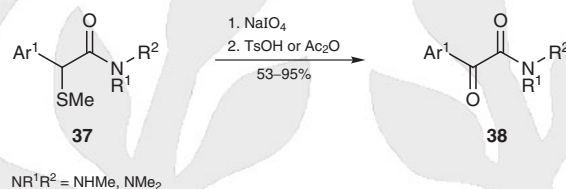
Scheme 26 Depsipeptides from α -Halo Amides^[198–202]

α -Diazo amides can be converted into α -hydroxy or α -alkoxy amides under various conditions. However, yields are usually modest.^[203–205]

Nucleophilic substitution of an α -trimethylammonio group in α -(acylamino) amides by a hydroxy group leads to *N,O*-acetals of glyoxylamides.^[87] Ring opening of *N*-trityl- or *N*-*tert*-butyl- α -lactams with alcohols or water affords 2-alkoxy or 2-hydroxy amides, respectively.^[206,207]

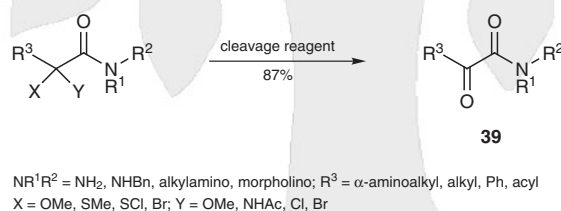
α -Oxo amides can be obtained from phosphorus ylide amides by ozonolysis or by reaction with singlet oxygen. The reaction can be applied to cyclopeptides.^[208,209] Pummerer reaction of 2-aryl-2-(methylsulfanyl)acetamides **37** gives access to arylglyoxylamides **38** (Scheme 27).^[210]

Scheme 27 Arylgyoxylamides by Pummerer Reaction^[210]



Cleavage of α -acetals^[211] or α -thioacetal derivatives^[212,213] of amides provides α -oxo amides **39** (Scheme 28). The former synthesis is applied in amino acid and peptide chemistry. Another route to α -oxo amides is based on the hydrolytic cleavage of amides bearing benzotriazole and a second leaving group in the α -position (see Scheme 39, Section 21.5.2.1.3).^[214,215] The precursors can be obtained from isocyanates and the corresponding benzotriazolylmethyl carbanions as acyl anion equivalents. Cyanohydrins, obtained by ring opening of 1-cyanooxirane-1-carboxamides with hydrochloric or hydrobromic acid, can be converted into β -halo- α -oxo amides in the presence of nickel(II) acetate.^[216] Treatment of α,α -dibromobenzoylacetamides with silver(I) or sodium acetate provides 1,2,3-tricarbonyl products.^[39] Hydrogenation of 2-(benzyloxy)acrylamides removes the benzyloxy group by formation of α -oxo amides.^[217] Oxalamides are formed by irradiation of oxadiazolecarboxamides in the presence of water, but not in a preparatively useful manner.^[218]

Scheme 28 α -Oxo Amides from α,α -Disubstituted Amides^[39,211–215,217]



Ring opening of aminocarbonyl-substituted heterocycles or pyrazin-2-ones can also lead to α -oxo or α -hydroxy amides, but this method does not have much synthetic importance.^[219,220] α -Oxo amides can be transformed into the corresponding dimethyl acetals, as shown in the saframycin series.^[221] Amino acetals of mesoxal diamides can be obtained from 2,4-dinitrobenzylidenemalonamides by rearrangement reactions.^[222] It is also possible to use oxalimide derivatives as starting materials for the introduction of oxygen functionality. Thus, reaction of oxalyl chloridamide with tocopherol is used to synthesize the corresponding oxalester amides,^[223] and *N,N'*-dibenzylmonothiooxalimide is desulfurized to the corresponding oxalimide in 92% yield under oxidative conditions.^[224]

2-(Aryloxy)- and 2-(Hetaryloxy)-2-methylpropanamides **35** (R¹ = R² = H; R³ = R⁴ = Me; R⁵ = Aryl, Hetaryl); General Procedure:^[186]

The appropriate phenol (2 g) was stirred in dry dioxane (20 mL) with NaH (1.1 equiv) for 1 h. 2-Bromo-2-methylpropanamide (1.0 equiv) was added and the mixture was heated at

100 °C for 4 h. After cooling, the precipitated NaBr was filtered off, the filtrate was concentrated under reduced pressure, and the residual solid was triturated with dilute base and recrystallized (toluene) to give the product; yield: 48–98%.

Depsipeptides 36 ($R^2 = H$; $R^3 = Bn$; $X = Br$); General Procedure:^[200]

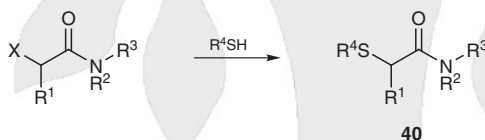
Ag₂O (348 mg, 1.5 mmol) was added to a soln of the *N*-Cbz-amino acid (1.5 mmol) and the *N*-benzyl-2-bromoalkanamide (1.5 mmol) in MeCN (5 mL). The mixture was stirred at rt or refluxed until complete. The progress of the reaction was monitored by TLC (silica gel, EtOAc/toluene 1:4). Ag salts were removed by passing the soln through a short column of alumina covered with Celite (1 g), using a little MeCN as eluent; the filtrate was concentrated and the residue was dried (P₄O₁₀) under reduced pressure until constant weight. Crystallization of the crude oil was effected with Et₂O/petroleum ether (bp 40–70 °C); yield: 85–93%.

21.5.2.1.2.2

**Variation 2:
Substitution by Sulfur Atoms**

Substitution of α -halo atoms in carboxamides by sulfur moieties is easily possible (e.g., to give **40**, Scheme 29). Thus aliphatic thiols,^[88,182,225–227] aromatic thiols,^[228–230] and sulfanyl heteroaromatic compounds^[231–234] can all be used. By this strategy, cyclic products, e.g. cyclopeptide-related thioethers, are also synthesized.^[235,236] Dithiols can be alkylated at both sulfur atoms, a methodology which can also be applied to the synthesis of thia-crown ethers with acetamide substituents.^[235] Double alkylation of geminal dithiols can be achieved by α -bromoacetamides.^[237] If two chloro atoms are found in the α -position of amides, both of them are replaced by phenylsulfanyl groups.^[228] An α -phenylsulfanyl group in carboxamides can serve as a radical precursor.^[228,229] α -Fluoro can be replaced by alkanethiolate if a cyclic imido group is attached to the α -position of the amide.^[88]

Scheme 29 Substitution of α -Halo Atoms by Sulfur Moieties^[88,182,225–234]



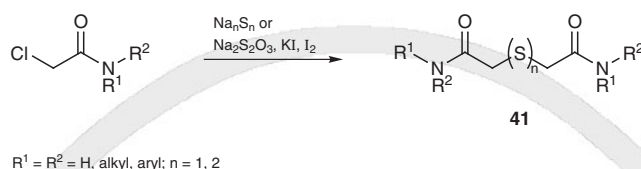
$R^1 = H$, alkyl, aryl, CN, F, Cl, SPh, NHAc; $R^4 =$ alkyl, aryl, hetaryl; $X = F$, Cl, Br, I

Diastereoselective introduction of alkylsulfanyl and arylsulfanyl groups is demonstrated with chiral *N*-(bromoacyl)oxazolidinones. The products serve as precursors for optically active 2-sulfanyl alcohols.^[238] Isothioureas can be obtained by reaction of α -halo amides with thiourea, but sometimes can easily cyclize to 2-amino-4-hydroxy-1,3-thiazoles.^[182,239]

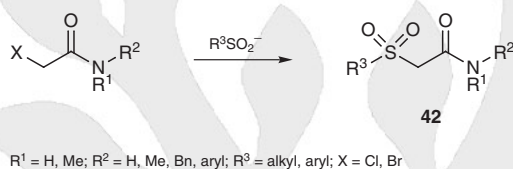
The reaction with heterocyclic thiols or thiones is also used for ring annulation to the starting heterocyclic system^[234] and for linking spin labels [2,2,6,6-tetramethylpiperidin-1-oxyl, (TEMPO)] to nonnatural nucleobases of nucleotides.^[233] Similarly, the haloacetamide moiety is used to link fluorescein labels to cysteine or cysteine-containing peptides,^[226] saccharides to proteins,^[240] or benzene rings to each other in thiacyclopentane assemblies.^[241] In all cases the function to be linked is attached to the amide nitrogen atom.

The reaction of dialkyl sulfides^[105,242,243] with *N,N*-dialkyl- α -bromoacetamides provides sulfonium salts as precursors for sulfur ylides.

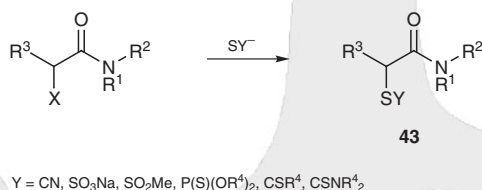
Sodium sulfide or disulfide can react with 2 equivalents of α -halo amides, affording the corresponding sulfides **41** ($n = 1$)^[244] or disulfides **41** ($n = 2$)^[245] (Scheme 30). The latter can also be obtained with sodium thiosulfate and potassium iodide–iodine,^[246] while normal Bunte salts are formed in the absence of potassium iodide–iodine.^[88]

Scheme 30 Reaction of Two Equivalents of α -Halo Amides with Sodium Sulfide, Disulfide, or Thiosulfate^[244,245]

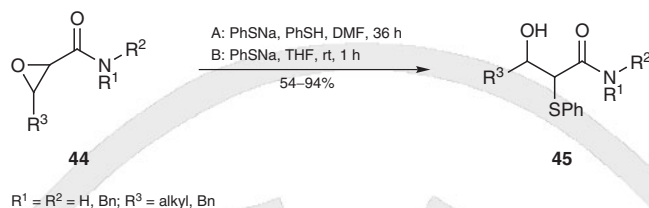
Thioacetate and thiobenzoate are used as masked hydrosulfides.^[241,247–249] The resulting acylsulfanyl amides can be transformed into α -sulfanyl amides.^[241,247,248] This method is also applied to the methanesulfonate of (*R*)-*N,N*-dimethylmandelamide, where methanesulfonate acts as a leaving group and complete inversion of configuration can be achieved.^[250] For introduction of the α -sulfanyl group into α -halo amides, hydrosulfide-exchange resin is applied.^[251] α -Sulfonyl amides **42** can be synthesized by reactions of α -halo amides with arene- or alkanesulfonates (Scheme 31).^[182,252–254]

Scheme 31 Substitution of α -Halo Atoms by Sulfonates^[182,252–254]

Potassium isothiocyanate affords α -thiocyanato amides **43** ($\text{Y} = \text{CN}$) in reactions with α -halo amides (Scheme 32),^[182,255] but can sometimes lose the cyano group by cyclization to afford cyclic thioethers.^[256] Dithiophosphoric acid diesters can react with α -halo amides to form the corresponding dithiophosphoric acid triesters **43** [$\text{Y} = \text{P}(\text{S})(\text{OR}^4)_2$] (Scheme 32), which are interesting as herbicides and insecticides.^[250] The reaction of sodium methanethiosulfonate with α -halo amides gives access to α -(mesylsulfanyl) amides **43** ($\text{Y} = \text{SO}_2\text{Me}$), which are used as linkers for saccharides to proteins.^[248] Nucleophilic substitution of α -halides by dithiocarboxylates,^[257] dithiocarbamates,^[258,259] and diethyl tetra-thiomalonate^[260] affords the corresponding S-alkylation products **43** ($\text{Y} = \text{CSR}^4$, CSNR^4_2).

Scheme 32 Substitution of α -Halo Atoms by Other Sulfur Nucleophiles^[182,248,250,255,257–260]

An α -ethoxy substituent can be replaced by alkanethiolates or benzenethiolate via intermediate *N*-acyliminium ions if an additional acetyl amino function is found at the α -position of the amides.^[88] Optically active β -hydroxy- α -(phenylsulfanyl) amides **45** can be obtained by reaction of oxirane-2-carboxamides **44** with benzenethiolate (Scheme 33).^[261,262] In some cases, regioisomeric α -hydroxy- β -(phenylsulfanyl) amides are formed as byproducts and can become major products by changing the reaction conditions. Thioacetals of α -oxo amides can be obtained with methyl trimethylsilyl sulfide.^[263]

Scheme 33 Ring Opening of Oxiranes with Benzenethiolate^[261,262]

4-[(*tert*-Butoxycarbonyl)(methyl)amino]-2-[(4-methoxybenzyl)sulfanyl]butanamide [40, $\text{R}^1 = \text{CH}_2\text{CH}_2\text{N}(\text{Me})\text{Boc}$; $\text{R}^2 = \text{R}^3 = \text{H}$; $\text{R}^4 = 4\text{-MeOC}_6\text{H}_4\text{CH}_2\text{S}$]:^[225]

DBU (2.64 g, 17.3 mmol) was added to a stirred soln of 4-[(*tert*-butoxycarbonyl)(methyl)amino]-2-chloro/iodobutanamide (1:1 mixture) (4.20 g, 15.8 mmol) and (4-methoxyphenyl)methanethiol (2.67 g, 17.3 mmol) in benzene (100 mL) (**CAUTION: carcinogen**) under reflux and stirring was continued for 16 h. The mixture was cooled and the solvent was removed under reduced pressure. The residue was partitioned between CHCl_3 and H_2O and the separated organic layer was washed with 10% citric acid, H_2O , 5% NaHCO_3 , and H_2O again, then dried (MgSO_4) and concentrated. The residue was chromatographed (silica gel, benzene/EtOAc 1:1) to give the product as a colorless oil; yield: 4.26 g (82%).

***N,N*-Diethyl-2-(phenylsulfonyl)acetamide (42, $\text{R}^1 = \text{R}^2 = \text{Et}$; $\text{R}^3 = \text{Ph}$):^[254]**

Bu_4NOH (40% in H_2O) (237 mg, 0.913 mmol) and NaSO_2Ph (150 mg, 0.913 mmol) were dissolved in H_2O (7 mL), and the mixture was stirred for 5 min, extracted with CH_2Cl_2 , and dried (Na_2SO_4). Removal of the solvent under reduced pressure furnished $\text{Bu}_4\text{NSO}_2\text{Ph}$ as a colorless oil; yield: 320 mg (91%). This compound (527 mg, 1.37 mmol), dissolved in THF (5 mL), was added to a soln of 2-bromo-*N,N*-diethylacetamide (267 mg, 1.37 mmol) in THF (5 mL). The mixture was refluxed for 19 h. H_2O (10 mL) was added and the product was extracted (CHCl_3). Flash chromatography (silica gel, EtOAc/hexane 1:1) furnished the crystalline product; yield: 280 mg (70%); mp 78–80 °C.

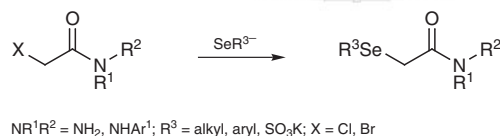
2-Cyano-*N,N*-dimethyl-2-(thiocyanato)acetamide (43, $\text{R}^1 = \text{R}^2 = \text{Me}$; $\text{R}^3 = \text{Y} = \text{CN}$):^[255]

To a suspension of powdered KSCN (2.04 g, 21 mmol) in MeCN (30 mL) was added 2-bromo-2-cyano-*N,N*-dimethylacetamide (4.0 g, 21 mmol) and stirring was continued at rt for 20 min. Inorganic salts began to form immediately. The salts were filtered off and the solvent was removed under reduced pressure using a rotary evaporator. The residue was cooled and triturated with benzene (20 mL) (**CAUTION: carcinogen**). The yellow solid thus formed was collected, washed with cold Et_2O (2 mL), and recrystallized (EtOH); yield: 2.71 g (77%); mp 96.5–97.5 °C.

21.5.2.1.2.3

Variation 3:**Substitution by Selenium or Tellurium Atoms**

Several selenium nucleophiles such as alkyl^[264] or aryl selenides^[265] or selenosulfate^[266] can substitute α -halogen atoms in amides (Scheme 34). The latter reaction is used in the synthesis of the corresponding selenoaldehyde of glyoxylamide by subsequent elimination of sulfate.^[266]

Scheme 34 Substitution of α -Halo Atoms by Selenium Nucleophiles^[264–266]

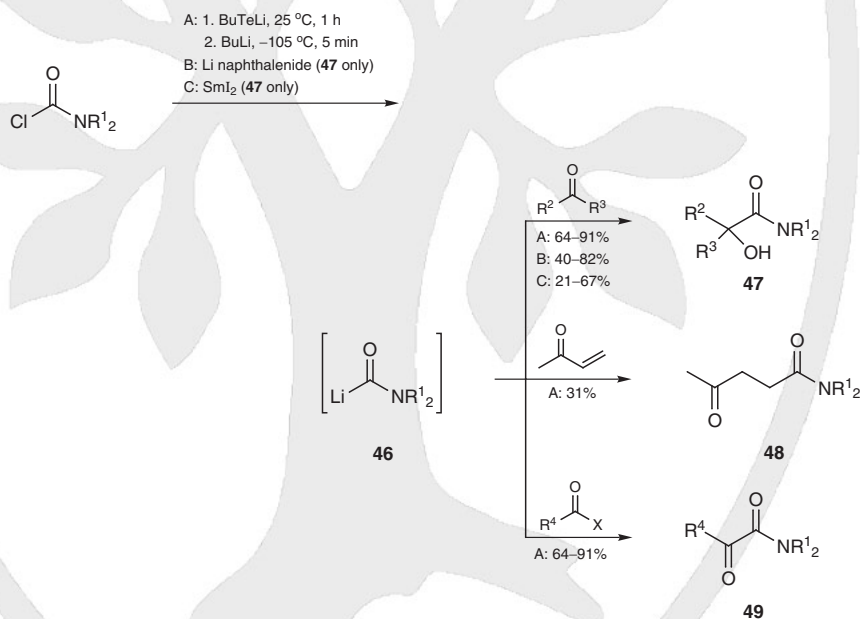
Alkylation of 2-selenopyridones with α -halo amides occurs at the selenium atom and can be used to annulate selenophenes to the starting pyridine ring.^[267,268] A hydrazinoyl chloride of oxalanilide reacts with potassium selenocyanate by substitution of chloride followed by cyclization to 1,3,4-selenodiazolimines.^[269]

α -Tellanyl amides can be prepared by reaction of α -haloacetamides with benzenetellurolate^[270] or dibutyl telluride.^[271]

21.5.2.1.3

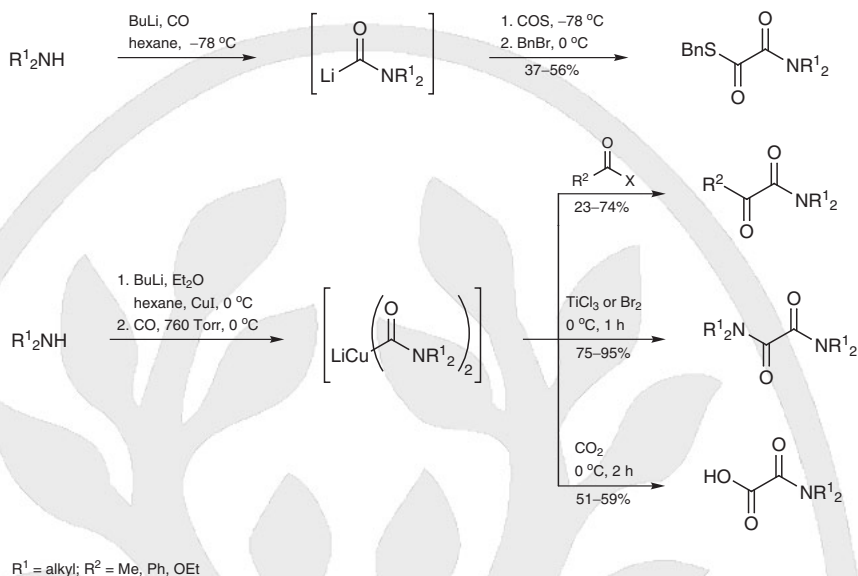
Method 3:**C—C Bond Formation between the Carbonyl Group and the α -Carbon Atom**

C—C bond connection between a CONR^1_2 moiety and an α -heteroatom-substituted organic unit to amides which are substituted by a group 16 element in an α -position can be achieved in three principal ways, namely by reaction of CONR^1_2 anion equivalents with electrophiles, by reaction of isocyanates or carbamic acid derivatives with carbanions, and by radical combination. Carbamoyllithium reagents **46**, prepared from carbamoyl chlorides via carbamoyltellurates and transmetalation with butyllithium, are versatile precursors for α -hydroxy amides **47**, α -oxo amides **49**, oxalamides, and 4-oxo amides **48** (Scheme 35),^[272] but few experimental details are provided. In a similar manner, α -hydroxy amides **47** can be obtained from carbamoyl chloride and lithium naphthalenide^[273] or samarium(II) iodide^[274] under Barbier conditions.

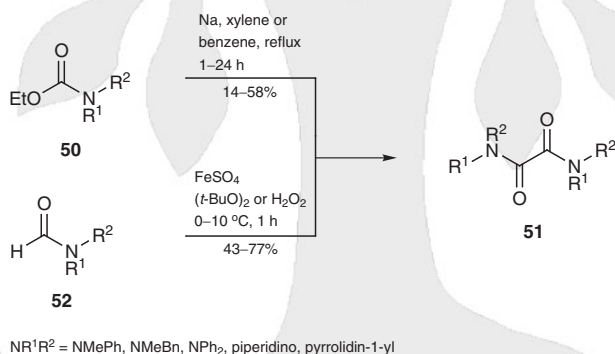
Scheme 35 C—C Bond Formation via Carbamoyllithium Reagents^[272–274]

NR^1_2 = dialkylamino, piperidino; R^2 = H, Me, Ph; R^3 = Me, Ph; R^4 = Me, Ph, NEt_2 ; X = Cl, alkoxy

Carbamoylmatal reagents, such as carbamoyllithium,^[275] carbamoylcopper,^[276,277] or carbamoylnickel compounds,^[278] are alternatively accessible by carbonylation (Scheme 36). This versatile chemistry can be applied to a wide range of oxalamides and α -oxo amides.

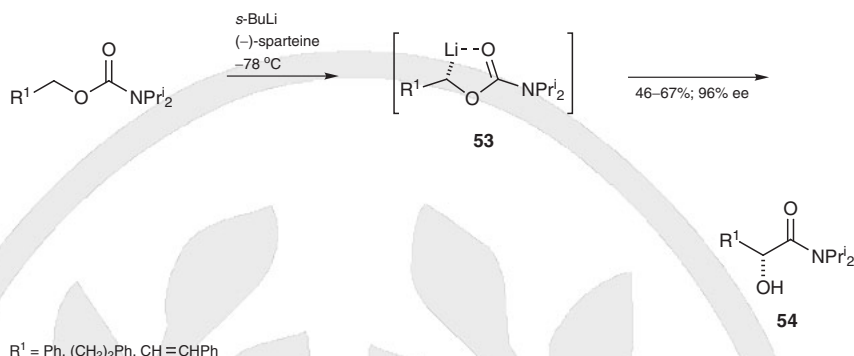
Scheme 36 Oxalamides and α -Oxo Amides by Reactions of Carbamoylmetal Reagents Obtained by Carbonylation^[275]

Symmetric oxalamides **51** can also be obtained starting from carbamates **50**^[279] by reduction or from formamides **52**^[280,281] under oxidative radical conditions (Scheme 37). In general, oxalamides are more straightforwardly accessible starting from oxalic acid derivatives rather than by C—C bond formation. For details of the formation of amides from carboxylic acid derivatives see Section 21.1.2.

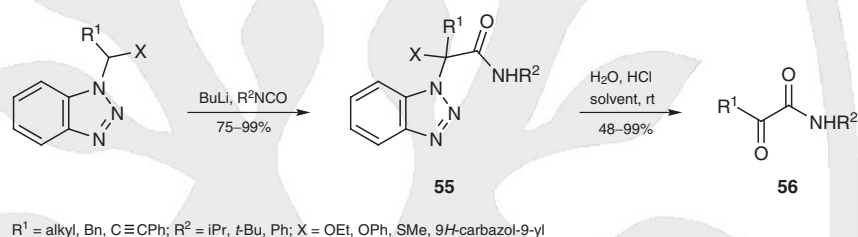
Scheme 37 Symmetric Oxalamides by C—C Bond Formation^[279–281]

High yields of 4,4-diaryl- α -hydroxy-*N,N*-dimethylamides are achieved in the reaction of 1,1-diarylethenes with dimethylformamide and sodium.^[282] However, the reaction is limited to this special type of alkene.

Examples of electrophilic introduction of the aminocarbonyl moiety by means of carbamic acid derivatives via C—C bond connection are rare.^[283,284] Lithiated oxiranes or diazomethane can be used as partners. As an intramolecular version, α -lithiated carbamates, e.g. **53**, obtained either by carbolithiation^[285] or hydrogen–lithium exchange,^[286] can undergo a 1,2-carbamoyl shift to provide α -hydroxy amides **54** (Scheme 38). An asymmetric version of this reaction is reported where corresponding stannanes can also be used.^[286]

Scheme 38 1,2-Carbamoyl Shift of α -Lithiated Carbamates to α -Hydroxy Amides^[286]

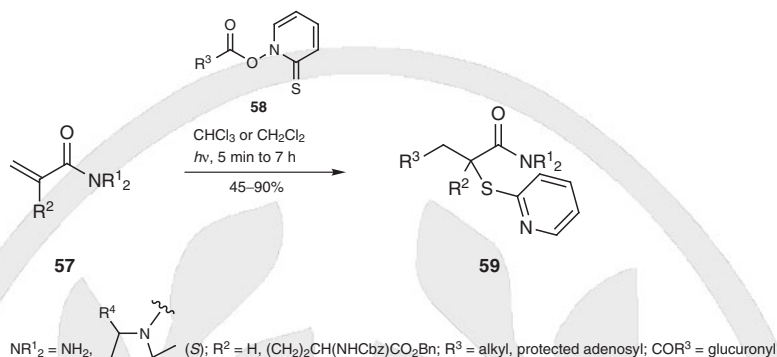
On the other hand, reaction of lithiated 1-alkylbenzotriazoles with isocyanates is a powerful method to synthesize α -(benzotriazolyl) amides **55**, which can be transformed into α -oxo amides **56** (Scheme 39).^[214,215,287]

Scheme 39 α -(Benzotriazolyl) Amides from Isocyanates^[214,215,287]**2-Hydroxy-*N,N*-diisopropylalkanamides 47 ($R^1 = \text{iPr}$); General Procedure:**^[273]

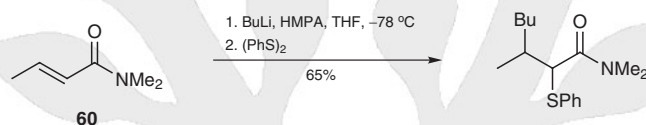
Method B: To a suspension of Li (100 mg, 14 mmol) the corresponding carbonyl compound (3.0 mmol), and naphthalene (20 mg, 0.16 mmol) in THF (5 mL) was added a mixture of the carbamoyl chloride (2.5 mmol) in THF (10 mL) at -78°C under an argon atmosphere. The mixture was stirred for about 45 min at the same temperature until the typical green color of lithium naphthalenide appeared. Then the temperature was allowed to rise to 0°C (ca. 1 h) and the resulting mixture was hydrolyzed with H_2O (20 mL), neutralized with 2 M HCl, and extracted with EtOAc ($3 \times 20 \text{ mL}$). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure (15 Torr). The resulting residue was then purified by flash chromatography (silica gel, hexane/EtOAc) to afford the product; yield: 40–82%.

21.5.2.1.4**Method 4:****Addition of a Heteroatom Functionality to α,β -Unsaturated Amides**

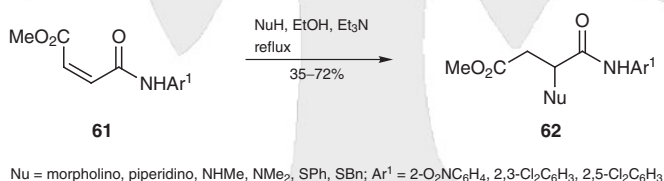
Heteroatom functionalities can be introduced to α,β -unsaturated amides **57** by addition to the $\text{C}=\text{C}$ or $\text{C}\equiv\text{C}$ bond in different ways. Thus radical addition of Barton esters **58** provides α -(2-pyridylsulfanyl) amides **59** in moderate to good yields (Scheme 40).^[99,288,289] This methodology can also be applied in natural-product-related chemistry.^[288,289] When the starting amides are derived from chiral oxazolidines or thiazolidines, stereoselective addition of up to 73:1 dr can be achieved.^[99]

Scheme 40 Radical Addition of Barton Esters to α,β -Unsaturated Amides^[99,288,289]

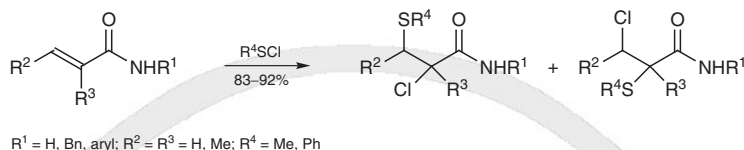
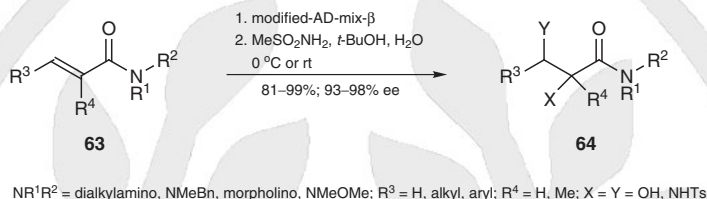
Nucleophilic introduction of an α -heteroatom moiety can be achieved by conjugate addition of butyllithium to *N,N*-dimethylcrotonamide (*N,N*-dimethylbut-2-enamide) (**60**) and quenching with diphenyl disulfide (Scheme 41).^[290]

Scheme 41 α -(Phenylsulfanyl) Amides from α,β -Unsaturated Amides^[290]

Maleanilide methyl esters **61** add amines to give α -aminoanilides, or benzenethiol or phenylmethanethiol regioselectively to provide α -(phenylsulfanyl)- or α -(benzylsulfanyl)anilides **62**, respectively (Scheme 42).^[291] In an analogous manner, *N*-phenyl- or *N*-benzyl- α -(arylsulfanyl)succinamides can be obtained from *N*-arylfumaramide and benzenethiol in the presence of triethylamine,^[291] while 2-(ethylsulfanyl)maleamide is obtained from acetylenedicarboxamide and ethanethiol.^[292]

Scheme 42 Addition to Maleanilide Methyl Esters^[291]

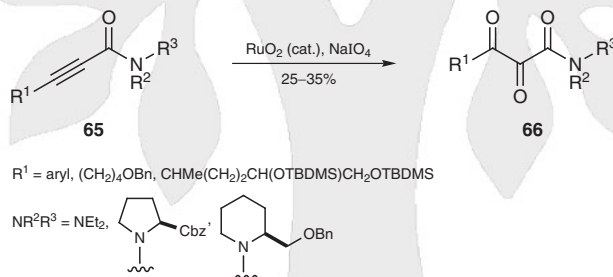
The addition of benzeneselenenyl chloride to acrylamides in the presence of zinc(II) chloride provides high yields of 3-chloro-2-(phenylselenanyl)propanamides,^[293] while in the absence of zinc(II) chloride, additional 2-chloro-3-(phenylselenanyl)amides are formed as minor products.^[294] Sulfenyl chlorides react similarly with α,β -unsaturated amides (Scheme 43).^[22,295,296] Most electrophilic introductions of heteroatom functionality into the α -position of α,β -unsaturated amides concern oxygen functionalities. Thus asymmetric dihydroxylation of acrylamides **63** with modified-AD-mix- β gives 2,3-dihydroxypropanamides **64** (X = Y = OH) in excellent yields,^[297] while α -hydroxy- β -(tosylamino) amides **64** (X = OH; Y = NHTs) can be obtained by diastereoselective aminohydroxylation together with the corresponding β -hydroxy- α -(tosylamino) amides **64** (X = NHTs; Y = OH) (Scheme 44).^[298] The former are the major products in most cases.

Scheme 43 Addition of Sulfenyl Chlorides to α,β -Unsaturated Amides^[22,295,296]**Scheme 44** Asymmetric Dihydroxylation of α,β -Unsaturated Amides^[297,298]

Oxiranecarboxamides can be synthesized from α,β -unsaturated amides in several ways. Thus, *tert*-butyl hydroperoxide can be applied in the presence of butyllithium via conjugate addition.^[173,299–301] This method has wide scope and allows diastereoselective epoxidation in up to 99:1 dr, if the amides used are derived from chiral amines.^[299]

Cinnamoylproline-derived peptides and esters can be epoxidized diastereoselectively by dioxygen catalyzed by polyaniline-supported cobalt(II)–salen.^[302]

Peroxytrifluoroacetic acid is used for epoxidation of the cyclohexadiene-1-carboxamide series.^[303] 2,3-Dioxo amides **66** can be prepared by oxidation of propynamides **65** with sodium periodate in the presence of ruthenium(IV) oxide (Scheme 45).^[304] This methodology is applied in the rapamycin series, but provides only modest yields.

Scheme 45 2,3-Dioxo Amides by Oxidation of Propynamides^[304]

Air oxidation can be used for the synthesis of special derivatives of 2,3-dioxo amides from α,β -unsaturated amides.^[305] [2 + 2] Cycloaddition of 3-aminopropynamides and *N*-sulfinylarenesulfonamides followed by ring opening affords hetero analogues of 2-oxomalonamides.^[306]

2-Hydroxy-*N,N*-dimethyl-3-(tosylamino)propanamide (64, $R^1 = R^2 = \text{Me}; R^3 = R^4 = \text{H}; \text{X} = \text{OH}; \text{Y} = \text{NHTs}$):^[298]

$\text{K}_2\text{OsO}_2(\text{OH})_4$ (89.3 mg, 0.24 mmol) was added to a soln of *N,N*-dimethylacrylamide (4.81 g, 58.5 mmol) and chloramine-T trihydrate (14.0 g, 49.7 mmol) in a mixture of MeCN (50 mL) and H_2O (50 mL) under stirring. The color of the mixture changed from orange to deep orange-red. After stirring at rt for 14 h, Na_2SO_3 (10 g) and EtOAc (50 mL) were added. The three-phase mixture was vigorously stirred for 1 h while the solids dissolved. The organic phase was removed and the aqueous layer was extracted with EtOAc (2 \times 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The remaining oil was mixed with Et_2O (30 mL) to obtain the

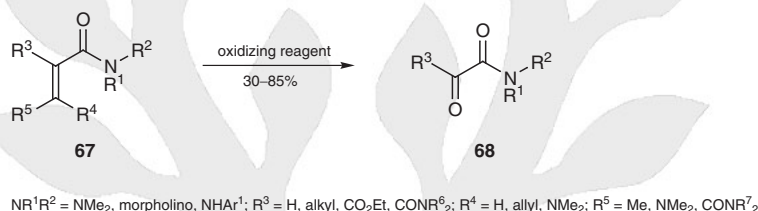
crystalline product as a 10:1 mixture of regioisomers, which were collected by filtration; yield: 13.8 g (99%). The pure product could be obtained by recrystallization (MeOH); mp 123–124 °C.

21.5.2.1.5

Method 5: Oxidation with C—C Bond Cleavage

Most examples of the synthesis of α -heteroatom-substituted amides by oxidative C—C bond cleavage concern enamino amides **67** (R^4 or $R^5 = \text{NMe}_2$), which are converted into α -oxo amides or 2-oxomalonamide derivatives **68** by ozonolysis,^[307–309] singlet oxygen,^[307,310] or sodium periodate^[311] (Scheme 46). The starting enamino amides can be obtained by reaction of the corresponding amides with dimethylformamide derivatives. Thus the overall reaction represents the transformation of $\alpha\text{-CH}_2$ into $\alpha\text{-C=O}$. Ozonolysis can also be applied to α,β -unsaturated amides lacking the β -dimethylamino group.^[172,312,313]

Scheme 46 α -Oxo Amides by Oxidation with C—C Bond Cleavage^[172,307–313]



The strategy of introducing α -oxo functions by oxidative C—C bond cleavage is also applicable to the chemistry of the immunosuppressant FK 506.^[308,309,314] Glycol cleavage of N,N' -di-*tert*-butyltartaramide with sodium periodate leads to N -(*tert*-butyl)glyoxylamide.^[172]

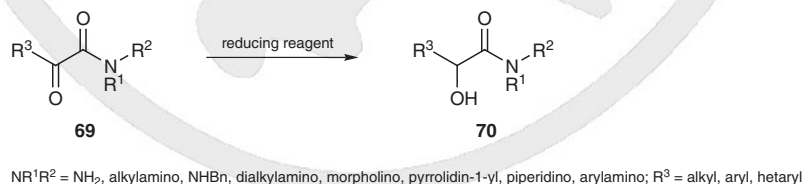
Oxidation of β -oxo amides with excess ammonium cerium(IV) nitrate in the presence of methanol and dioxygen results in the formation of oxamates by C—C bond cleavage.^[315]

21.5.2.1.6

Method 6: By Reduction of α -Oxo Amides

A variety of reducing reagents such as alkali metal or ammonium borohydrides,^[316–323] Selectrids (e.g., potassium tri-*sec*-butylborohydride),^[321] lithium aluminate at low temperature,^[324] zinc in the presence of alcohols and salts,^[325] sodium dithionite,^[326] or dimethyl(phenyl)silane^[322] can be used to synthesize α -hydroxy amides **70** from α -oxo amides **69** (Scheme 47).

Scheme 47 Reduction of α -Oxo Amides to α -Hydroxy Amides^[316–326]



Stereoselective formation of α -hydroxy amides can be achieved with α -oxo amides derived from chiral amines, such as chiral amino alcohols,^[319,321,324,326] α -amino esters,^[320] or imidazolidinones^[322,323] based on natural amino acids. Ultrasonication can be useful for achieving stereoselectivity.^[326]

Catalytic hydrogenation is also a powerful tool for transforming α -oxo amides into α -hydroxy amides. Ruthenium clay,^[327] chiral rhodium complexes^[328–330] which can be fixed on silica supports,^[331] palladium/charcoal,^[323] Raney nickel,^[323] or platinum/alumina in the presence of cinchonidine^[169] can be used as catalysts and up to 97% ee can be achieved with chiral ligands.

2-[3-(4-Chlorophenyl)-4,6-dimethoxyindol-2-yl]-2-hydroxy-*N*-methylacetamide [70, $R^1 = H$; $R^2 = Me$; $R^3 = 3-(4\text{-Chlorophenyl})-4,6\text{-dimethoxyindol-2-yl}$]:^[317]

3-[(4-Chlorophenyl)-4,6-dimethoxyindol-2-yl]glyoxylamide (1.66 g, 4.45 mmol) was partially dissolved in MeOH (40 mL) and excess NaBH_4 was added. The soln was stirred under N_2 for 20 min. H_2O was added dropwise until the soln just began to turn cloudy. The volume was immediately reduced to approximately one third under reduced pressure until a white precipitate formed. The precipitate was collected by filtration, washed with H_2O , dried, and column chromatographed (MeOH/ CHCl_3 1:19) to yield the product as a white solid; yield: 1.44 g (86%); mp 112 °C.

(2*S*)-2-Hydroxy-1-[(2*S*)-2-(methoxymethyl)-2,3-dihydro-1*H*-indol-1-yl]-2-phenylethan-1-one [70, $\text{NR}^1\text{R}^2 = (2\text{S})\text{-2-(Methoxymethyl)-2,3-dihydro-1H-indol-1-yl}$; $\text{R}^3 = \text{Ph}$]:^[321]

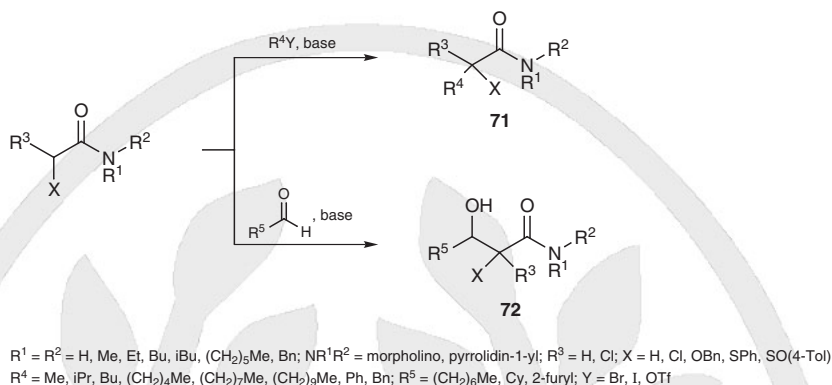
A 1.0 M soln of K-Selectride in THF (1.27 mL) was added dropwise to a soln of 1-[(2*S*)-2-(methoxymethyl)-2,3-dihydro-1*H*-indol-1-yl]-2-phenylethane-1,2-dione (339 mg, 1.15 mmol) in THF (15 mL) at -78°C . After stirring at -78°C for 1 h, the mixture was quenched with 1 M HCl and extracted (CH_2Cl_2). The organic layer was dried (MgSO_4) and filtered. The filtrate was concentrated under reduced pressure. Purification by column chromatography (silica gel, EtOAc/hexane 1:3) afforded the product; yield: 311 mg (91%); $[\alpha]_{\text{D}}^{22} +76.3$ (c 0.534, CH_2Cl_2).

21.5.2.1.7

Method 7:

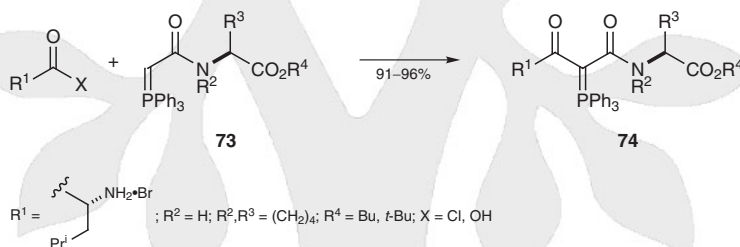
C—C Chain Elongation at the α -Carbon Atom

Chain elongation of amides by α -C—C bond formation is possible with electrophiles, nucleophiles, or in a radical fashion. Thus, amide enolates react with alkylating reagents^[26,332] or with aldehydes in aldol reactions^[26,175,178,333] (Scheme 48). The amino groups can bear hydrogen atoms. Often, additional heteroatoms are attached to the α -position. If an α -sulfoxide is found in the product **71**, this group can be removed by ethylmagnesium bromide and the enolate formed can be submitted to further aldol reaction.^[26] Asymmetric α -alkylation can be achieved with amides derived from chiral cyclic amines.^[332] Aldol products **72** with 2-(phenylsulfanyl) groups ($\text{X} = \text{SPh}$; $\text{R}^3 = \text{H}$) can be transformed oxidatively into 1,2,3-tricarbonyl compounds.^[178]

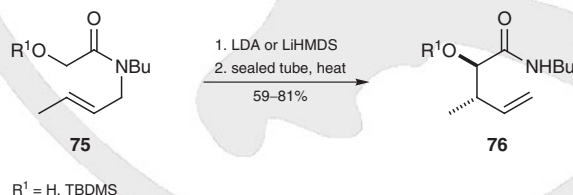
Scheme 48 α -Alkylation and Aldol Reaction of α -Heteroatom-Substituted Amides^[26,175,178,332,333]

If 2,2-dichloroacetamides are reacted with aldehydes, 3-chloro- α -oxo amides are obtained via intermediate chlorooxiranes.^[333] Chiral oxiranecarboxamides are accessible by reaction of sulfur ylides (substituted by dialkylaminocarbonyl) with sugar-derived aldehydes^[243,334,335] or by chiral sulfur ylides and achiral aldehydes.^[242]

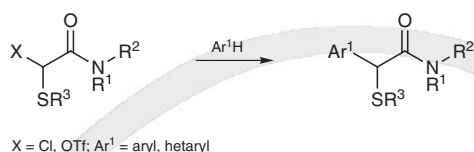
Phosphorus ylides **73** derived from *N*-(α -bromoacetyl)amino esters can be acylated by C—C bond formation to provide β -oxo amides **74**, which are useful precursors for 1,2,3-tricarbonyl compounds (Scheme 49).^[208,209]

Scheme 49 α -Acylation of Phosphorus Ylides^[208,209]

α -Allyloxy amides can afford α -hydroxy amides by asymmetric chain elongation if submitted to [2,3]-Wittig rearrangement via corresponding enolates.^[336] Aza-Claisen rearrangement of substituted *N*-allylamides **75** provides 2-hydroxypent-4-enamides **76** in a stereoselective manner (Scheme 50).^[337]

Scheme 50 Aza-Claisen Rearrangement to 2-Hydroxypent-4-enamides^[337]

α -C—C bond formation at amides is also possible by substitution of a nucleofugal leaving group (chloride, trifluoromethanesulfonate) by arenes or hetarenes (Scheme 51). Starting materials are obtained via Pummerer-type rearrangement.^[210,338,339] The thioether functionality of the product can be reductively removed by Raney nickel.

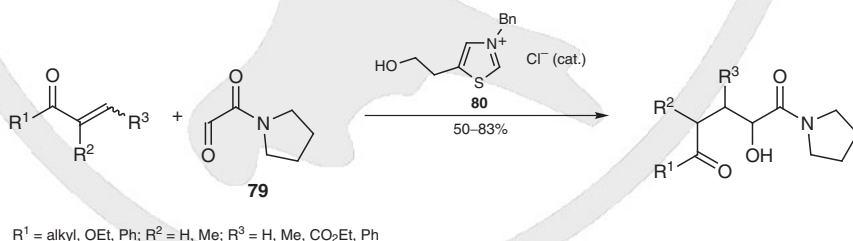
Scheme 51 α -C—C Bond Formation by Substitution of Chloride or Trifluoromethanesulfonate^[210,338,339]

Chain elongation by organometallic reagents starts with amides that possess a carbonyl or ester group in an α -position. 1,2-Addition of Grignard reagents,^[340–342] organolithium,^[341] organosamarium,^[343] or organozinc compounds under Barbier conditions,^[344] allylsilanes^[342] or allylstannane compounds^[342] to α -oxo amides **77**, sometimes assisted by Lewis acids, results in α -hydroxy amides **78** (Scheme 52). Asymmetric 1,2-addition of organometallic reagents is achieved with α -oxo amides derived from chiral amines.^[319,340–342,344] The amide can serve as a chiral auxiliary when the amino group is finally released by reaction of the amide moiety with methylolithium,^[342,344] by hydrolysis,^[319,340] or by reduction.^[341] Oxalamide esters can undergo single or double 1,2-addition, affording α -oxo amides^[341] or α -hydroxy amides,^[341] respectively.

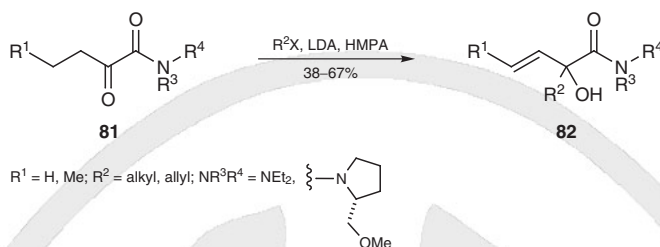
Scheme 52 Addition of Organometallic Reagents to α -Oxo Amides^[319,340–342,344]

α -(Benzoylamino) amides of dipeptide series with α -sulfur functionalities can be homologized in a radical fashion by aldehydes or ketones in the presence of samarium(II) iodide^[345,346] or with homoallyl sulfoxides.^[347] Friedel–Crafts-type reaction of trifluoropyruvamide with aromatic compounds gives diastereoselective access to Mosher-related amides.^[348]

Straightforward α -trifluoromethylation of α -oxo amides is achieved with trimethyl(trifluoromethyl)silane in the presence of tetrabutylammonium fluoride.^[349] Umpolung reactions making use of the catalytic thiazolium salt **80**^[350] or dithianes^[351] allow addition of Michael systems to the α -position of α -oxo amides **79** or oxalic ester amides (Scheme 53).

Scheme 53 Addition of Michael Systems to the α -Position of α -Oxo Amides^[350]

Umpolung synthesis is also achieved when α -oxo amides **81** are deprotonated twice and subsequently reacted with alkylating reagents, affording α -hydroxy amides **82** (Scheme 54).^[352] Aldol reaction of 2-methyl-4,5-dihydroimidazoles with α -oxo amides affords α -hydroxy amides, which easily cyclize to pyrrolodihydroimidazoles.^[353]

Scheme 54 α -Hydroxy Amides by Umpolung Reaction of α -Oxo Amides^[352]

Phosphonopyruvates can be synthesized by reaction of phosphonates with oxalic ester amides.^[354] A similar reaction of oxalamide chloride with (cyanomethylidene)triphenylphosphorane provides a phosphorus ylide, which is a useful precursor for tricarbonyl compounds.

In situ generated trifluoropyruvamides form oxiranecarboxamides with ethyl diazoacetate.^[355] Pinacol reaction of α -oxo amides with samarium(II) iodide affords optically active 2,3-dihydroxysuccinamides in diastereoselective fashion.^[356]

1-[2-Chloro-2-(4-tolylsulfinyl)pentanoyl]piperidine [71, $\text{NR}^1\text{R}^2 = 1\text{-Piperidyl}$; $\text{R}^3 = \text{Cl}$; $\text{R}^4 = \text{Pr}$; $\text{X} = \text{SO}(4\text{-Tol})$]:^[26]

CAUTION: Hexamethylphosphoric triamide is a possible human carcinogen and an eye and skin irritant.

A soln of 1-[2-chloro-2-(4-tolylsulfinyl)ethanoyl]piperidine (600 mg, 2 mmol) in THF (5 mL) was added dropwise with stirring to a soln of LDA (2.4 mmol) at -60°C . After 10 min, PrI (390 μL , 4 mmol) and HMPA (700 μL , 4 mmol) were added. The temperature of the mixture was allowed to warm to 0°C for 3 h. The reaction was quenched with sat. aq NH_4Cl and was extracted with EtOAc. The product was purified by column chromatography (silica gel) to give the product as a colorless oil; yield: 660 mg (99%).

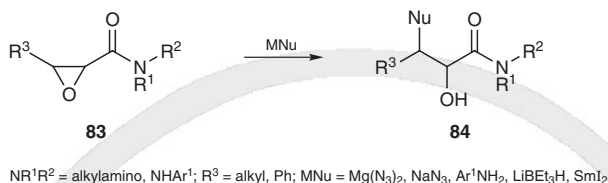
3-Cyclohexyl-3-hydroxy-2-(phenylsulfonyl)-1-piperidylpropan-1-one (72, $\text{NR}^1\text{R}^2 = 1\text{-Piperidyl}$; $\text{R}^3 = \text{H}$; $\text{R}^5 = \text{Cy}$; $\text{X} = \text{SPH}$):^[178]

A 1 M soln of LDA in THF (1.43 mL, 1.43 mmol) was added to a soln of [1-(2-phenylsulfonyl)acetyl]piperidine (327 mg, 1.38 mmol) and cyclohexanecarbaldehyde (170 μL , 1.4 mmol) in THF (6.9 mL) at 0°C . Sat. aq NH_4Cl was added after 1 h and the mixture was allowed to warm to rt. Then the aqueous and organic layers were partitioned and the aqueous layer was extracted (EtOAc). The combined organics were dried (MgSO_4), concentrated, and chromatographed (silica gel, hexane/EtOAc 4:1 to 3:1) to give a pale yellow oil which consisted of a separable mixture of diastereomers (3.5:1); yield: 437 mg (88%).

21.5.2.1.8

Methods 8: Miscellaneous Procedures

A useful route to α -hydroxy amides **84** is based on ring opening of oxiranecarboxamides **83** by nucleophiles such as azide,^[173,301,357] arylamines in the presence of polyaniline-supported cobalt(II) salen,^[358] hydride,^[359] or halide^[360] (Scheme 55). The regioselectivity depends on the type of nucleophile and in part on the reaction conditions. Reductive cleavage with samarium(II) iodide can afford α -hydroxy amides without a heteroatom substituent in the β -position.^[361]

Scheme 55 Ring Opening of Oxiranecarboxamides^[173,301,357–360]

21.5.3

Product Subclass 3:**Alkanamides with One (or More) Group 15 Element in the α -Position**

21.5.3.1

Synthesis of Product Subclass 3

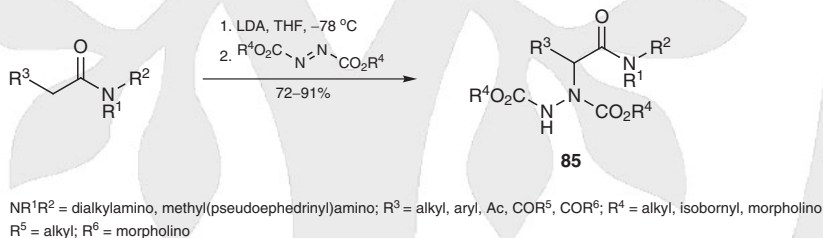
21.5.3.1.1

Method 1:**Substitution of One (or More) α -Hydrogen Atom**

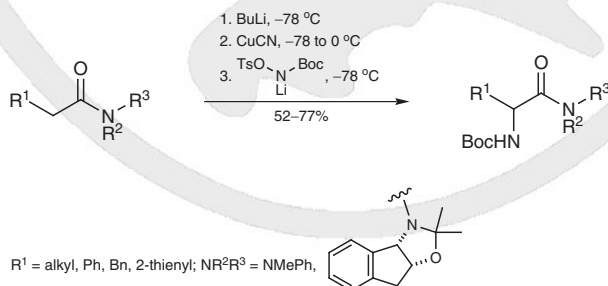
21.5.3.1.1.1

Variation 1:**Substitution by Nitrogen Atoms**

In amides, one or two α -hydrogen atoms can be replaced by nitrogen functionalities. For example, addition of amide enolates, usually generated with lithium diisopropylamide, to azodicarboxylates is a high-yielding route to α -hydrazino amides **85** (Scheme 56).^[362–364] Alternatively, the addition of the amide can be carried out in the presence of nickel(II) acetylacetonate.^[365] High stereoselectivity can be achieved with chiral amides.^[362]

Scheme 56 Synthesis of α -Hydrazino Amides^[362–365]

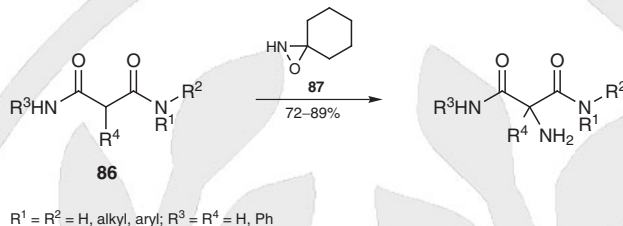
After generation of the enolate, *tert*-butoxycarbonylamino groups can be introduced into the α -position of amides by *N-tert*-butoxycarbonyl-*O*-tosylhydroxylamine (Scheme 57)^[366] or diphenylphosphoryl azide–di-*tert*-butyl dicarbonate.^[367] High diastereoselectivities are achieved with amides derived from chiral oxazolidines.^[366]

Scheme 57 Electrophilic α -Amination of Amides via Amide Enolates^[366,367]

Oxaziridine **87**, easily available by reaction of cyclohexanone with chloramine, can aminate malonamides **86** in the presence of bases such as 1,4-diazabicyclo[2.2.2]octane

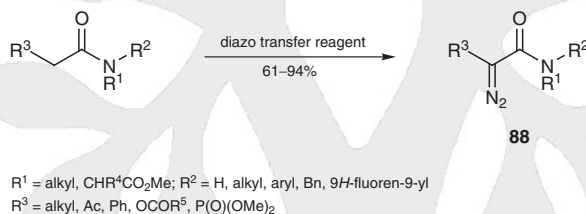
(Scheme 58).^[368] If the starting malonamides lack a substituent in the α -position, double amination occurs, resulting in α,α -diaminomalonamides or the corresponding imines. Similar compounds can also be obtained starting from cyanoacetamides in the presence of sodium hydroxide via intermediate imidazolidinones.^[368]

Scheme 58 α -Amination of Malonamides by an Oxaziridine^[368]



Diphenylphosphoryl azide,^[369] methanesulfonyl azide,^[370–372] arylsulfonyl azides,^[373–375] and 2-azido-*N*-methylpyridinium tetrafluoroborate^[376] can be used for diazo transfer to a variety of amides (Scheme 59). In the case of acetacetamides the acyl group can either be split off during the diazo transfer under basic conditions, thus giving rise to α -diazoacetamides,^[370,372] or can be maintained,^[11,15] depending on the reaction conditions. Alternatively, α -diazo amides **88** can be synthesized by diazotization of α -aminoacetamides with sodium nitrite or dinitrogen tetroxide.^[204,377]

Scheme 59 α -Diazo Amides via Diazo Transfer^[369–376]

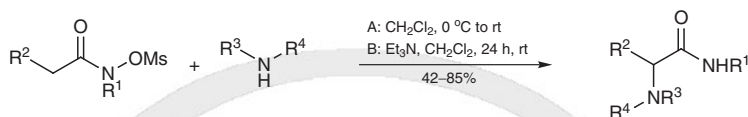


Reaction of CH-acidic amides with arenediazonium salts is a general method for the synthesis of α -hydrazono amides **89** (Scheme 60).^[378–380] Corresponding α -oximes can be obtained by reaction of amides with alkali metal nitrites under acidic conditions or with alkyl nitrites.^[381–384]

Scheme 60 α -Hydrazono Amides from Arenediazonium Salts^[378–380]



Amines,^[385] sodium azide,^[385] or hydrazines^[386] can be used for the introduction of amino, azido, or hydrazino groups, respectively, into the α -position, if the starting amides bear mesyloxy groups at the amide nitrogen atom (Scheme 61).

Scheme 61 α -Amino and α -Hydrazino Amides from *N*-(Mesyloxy) Amides^[385,386]

R^1 = alkyl; R^2 = Ph, 3-F₃CC₆H₄; R^3 = R^4 = alkyl, cycloalkyl, NHR^5 , NR^6_2

N-(1-Cyano-2-naphthyl)oxalamides are formed in an unusual manner from the reaction of 2-nitronaphthalene with cyanoacetamides.^[387]

Di-*tert*-butyl (2*S*)-1-[(1-(3,4-Dimethoxyphenyl)-2-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl](methyl)amino]-2-oxoethyl]hydrazine-1,2-dicarboxylate [85, R^1 = Me; R^2 = CH(Me)CH(OH)Ph; R^3 = 3,4-(MeO)₂C₆H₃; R^4 = *t*-Bu]; **Typical Procedure:**^[362]

A 1.5 M soln of BuLi in hexane (3.87 mL, 5.8 mmol) was added to a cooled (−78 °C) soln of *i*Pr₂NH (0.81 mL, 5.8 mmol) in dry THF (2 mL). The mixture was stirred for 20 min at this temperature, then allowed to come to rt, and stirred for an additional 10 min. The mixture was cooled again to −78 °C and a soln of 2-(3,4-dimethoxyphenyl)-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylacetamide (1.00 g, 2.9 mmol) in THF (15 mL) was added dropwise over 5 min. The resulting soln was stirred for 1 h at −105 °C, at which temperature a soln of di-*tert*-butyl azodicarboxylate (0.67 g, 2.9 mmol) in dry THF (10 mL) was added dropwise over 10 min. The resulting soln was stirred for 1 h at −105 °C, allowed to come to rt, and quenched with sat. NH₄Cl (30 mL). The mixture was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic fractions were collected, dried (Na₂SO₄), and filtered. The solvent was removed under reduced pressure to afford a yellowish oil, which was purified by flash chromatography (silica gel, hexanes/EtOAc 1:4); yield: 1.48 g (89%); mp 89–92 °C (Et₂O); $[\alpha]_D^{20}$ +110.7 (*c* 0.9, CH₂Cl₂); dr > 95:5.

α -Diazo Amides 88 (R^1 = Me; R^2 = Ph); General Procedure:^[369]

To a soln of the carboxamide (3 mmol) in dry THF (9 mL) a 1.5 M soln of LDA in cyclohexane (2.2 mL, 3.3 mmol) was added at 0 °C under argon. After stirring the mixture for 1 h, diphenylphosphoryl azide (0.907 g, 3.3 mmol) was added slowly. The mixture was stirred for 65 h, the temperature increased from 0 °C to rt, then Et₂O/hexane (1:1) was added and the suspension filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography (silica gel, deactivated with NH₃, hexane/EtOAc or hexane/Et₂O); yield: 61–76%.

Methyl 3-[(1-Alkyl-2-methoxy-2-oxoethyl)amino]-2-diazo-3-oxopropanoates 88 [R^1 = H; R^2 = CH(R^4)CO₂Me; R^3 = CO₂Me]; General Procedure:^[374]

A soln of 4-(acetylamino)benzenesulfonyl azide (12.4 mmol), Et₃N (12.9 mmol), and methyl 3-amino-3-oxopropanoate (12.9 mmol) in dry benzene (20 mL) (**CAUTION: carcinogen**) was allowed to stand at rt for 2 h, after which time a solid precipitated. After standing for 48 h at rt the solvent was removed under reduced pressure and the residue was separated from the byproducts by flash chromatography (silica gel, EtOAc/petroleum ether 3:7 or 2:3) to afford the pure product; yield: 70–94%.

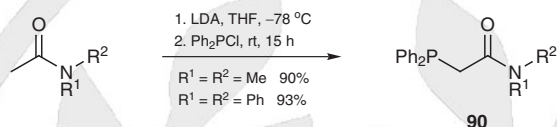
3-Amino-2-(arylhydrazono)-3-thioxopropanamides 89 (R^1 = R^2 = H; R^3 = CSNH₂); General Procedure:^[379]

3-Amino-3-thioxopropanamide (8.5 mmol) was dissolved in EtOH (30 mL) and NaOAc (18.3 mmol) was added. The cold soln was treated dropwise with a cold soln of the aryldiazonium salt and left for some time in the ice bath. The precipitate that formed was collected, washed with H₂O, and recrystallized; yield: 80–85%.

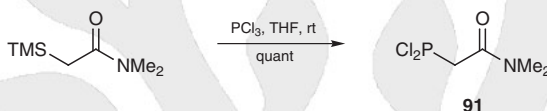
21.5.3.1.1.2

Variation 2:
Substitution by Phosphorus Atoms

Substitution of hydrogen atoms of *N,N*-disubstituted acetamides with a diphenylphosphino group can be achieved in high yields by treating the lithium enolate with chlorodiphenylphosphine, e.g. to give **90** (Scheme 62).^[388]

Scheme 62 α -Phosphorylation of Amide Enolates^[388]

Treatment of the lithium enolate of dimethylacetamide with chlorotrimethylsilane gives the C-silylation product, which reacts with phosphorus trichloride to form 2-(dichlorophosphino)-*N,N*-dimethylacetamide (**91**) (Scheme 63).^[389]

Scheme 63 Synthesis of 2-(Dichlorophosphino)-*N,N*-dimethylacetamide^[389]

Ylidenephosphoranes can be synthesized by electrochemical oxidation of triphenylphosphine in the presence of β -oxo amides.^[390] A more common approach to such products is based on nucleophilic substitution of α -halo amides (Section 21.5.3.1.2.4).

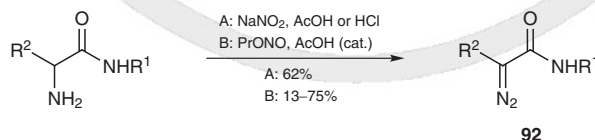
***N,N*-Diphenyl-2-(diphenylphosphino)acetamide (90, $R^1 = R^2 = \text{Ph}$); Typical Procedure:**^[388]

A 1.6 M soln of BuLi in hexane (17.8 mL, 28.4 mmol) was added dropwise to a soln of $i\text{Pr}_2\text{NH}$ (2.874 g, 28.4 mmol) in THF (100 mL) at -78°C . After the mixture had been stirred for 2 h, a soln of *N,N*-diphenylacetamide (6.023 g, 28.4 mmol) in THF (50 mL) was added slowly within 5 min. The mixture was stirred for 2 h at -78°C and then transferred into a Schlenk flask containing $\text{Ph}_2\text{P-Cl}$ (6.266 g, 28.4 mmol) in THF (50 mL). After stirring for 15 h at rt, the solvent was removed under reduced pressure. The residue was treated with hot toluene (100 mL) and the resulting suspension was filtered through a glass frit. The pale yellow filtrate was then concentrated and precipitated with pentane. The white precipitate thus obtained was recrystallized (degassed EtOH) to give colorless crystals; yield: 10.440 g (93%); mp $132\text{--}133^\circ\text{C}$.

21.5.3.1.1.3

Variation 3:
Transformation of α -Amino Amides into α -Imino Amides and α -Diazo Amides

α -Amino amides can be transformed into α -diazo amides **92** by diazotization with sodium nitrite under acidic conditions (Scheme 64).^[204,378,391]

Scheme 64 Diazotization of α -Amino Amides^[204,378,391]

$R^1 = \text{H, aryl, Bn}$; $R^2 = \text{H, P(O)(OEt)}_2$

In the total synthesis of nocardicins, treatment of the corresponding α -amino amides with hydrogen peroxide in the presence of sodium tungstate or with 3,5-di-*tert*-butylbenzo-1,2-quinone and hydroxylamine is used to introduce the α -oxime moiety.^[392] Synthesis of 2-iminomalonamide is possible by heating 2,2-diaminomalonamide in refluxing benzene.^[393]

21.5.3.1.2 Method 2: Substitution of Heteroatoms

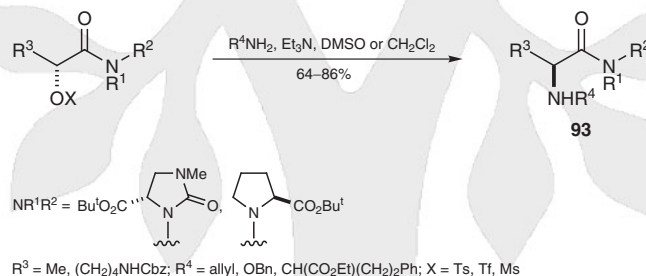
21.5.3.1.2.1 Variation 1: Substitution of Sulfur Atoms by Nitrogen Atoms

Compared with substitutions of other heteroatoms, replacements of sulfur atoms by nitrogen moieties are rare and involve *S,N*-acetals (substitution of isopropylsulfanyl by ammonia)^[394,395] of oxalamide derivatives. Dithiooxalic esters can be transformed into the corresponding thiooxalamides and hydrazides by reaction with amines or hydrazines, respectively.^[396–398] The products are useful precursors for heterocycles.

21.5.3.1.2.2 Variation 2: Substitution of Oxygen or Nitrogen Atoms by Nitrogen Atoms

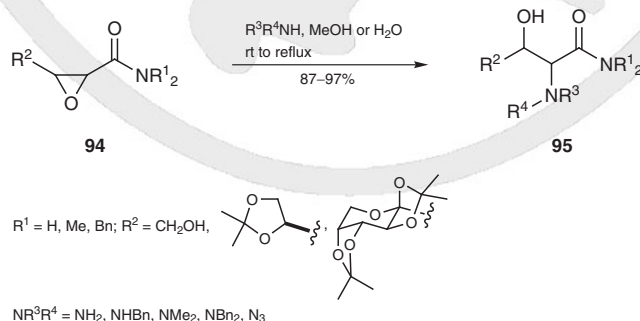
α -Tosyloxy, α -trifluoromethylsulfonyloxy, and α -mesyloxy groups can be replaced by amines^[399–401] or azide^[402,403] in the presence of triethylamine with inversion of configuration, providing optically active α -amino **93** or α -azido amides, respectively (Scheme 65).

Scheme 65 α -Amino Amides from Substituted α -Sulfonyloxy Amides^[399–401]



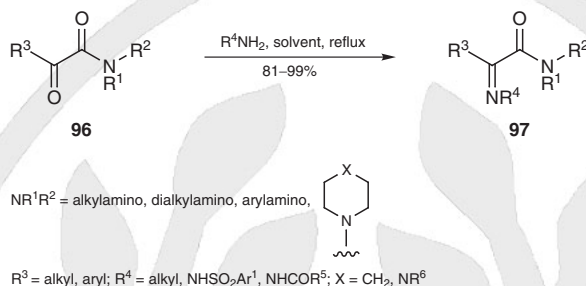
Ring opening of enantiopure *trans*-oxiranecarboxamides **94** with amines provides chiral α -amino- β -hydroxy amides **95**.^[243,404] However, alternative attack of amines at the β -position of oxiranecarboxamides to give regioisomeric β -amino- α -hydroxy amides is also possible, depending on the nature of substituents (Scheme 66). In an analogous manner, α -azido- β -hydroxy amides **95** ($NR^3R^4 = N_3$) can be obtained.

Scheme 66 Ring Opening of Oxiranecarboxamides^[243,404]



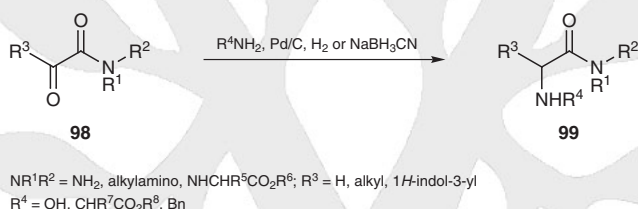
Imines and hydrazones of α -oxo amides can be synthesized in high yields from corresponding α -oxo amides **96** and amines, silylated amines, or hydrazines (Scheme 67).^[318,405–407]

Scheme 67 Condensation of Primary Amines and Hydrazines with α -Oxo Amides^[318,405–407]



Reductive amination of α -oxo amides or glyoxylamides **98** with α -amino acid derivatives,^[176,408] hydroxylamine,^[409,410] or substituted benzylamines^[411] as the amine component and palladium/charcoal–hydrogen or sodium cyanoborohydride as the reducing reagent provides α -amino amides **99**, usually in high yields (Scheme 68).

Scheme 68 Reductive Amination of α -Oxo Amides^[176,408–411]



Oxalamides can easily be obtained by reaction of oxalamide esters or oxalic acid monoamides following the usual methods of amide formation (for further details, see Section 21.1). Substitution of α -nitrogen moieties by nitrogen nucleophiles is rare. In the glyoxylamide series the α -trimethylammonio group can be replaced using substituted hydroxylamines (Scheme 69).^[87]

Scheme 69 Substitution of an α -Ammonio Group^[87]



***N,N*-Dibenzyl-2-(dibenzylamino)-2-deoxy-4,5,6,7-di-*O*-isopropylidene- β -D-glycero-D-talo-oct-4-ulo-4,8-pyranosonamide (**95**, $\text{R}^1 = \text{R}^3 = \text{R}^4 = \text{Bn}$; $\text{R}^2 = \text{Protected Pyranoside}$); Typical Procedure:**^[243]

A stirred soln of *N,N*-dibenzyl-2,3-anhydro-4,5:6,7-di-*O*-isopropylidene- β -D-glycero-D-galactooct-4-ulo-4,8-pyranosonamide (70 mg, 0.14 mmol) and Bn_2NH (60 μL , 0.31 mmol) in dry MeOH (2 mL) was heated in a sealed tube at 80 °C for 48 h. The mixture was concentrated and the residue was chromatographed (silica gel, Et_2O /hexane 1:4) to afford the product as a colorless syrup; yield: 85 mg (87%); $[\alpha]_{\text{D}}^{22} +3$ (*c* 1.2).

N-[2-Oxo-1-phenyl-2-piperidin-1-ylethylidene](trimethylsilyl)methylamine [97,
 $R^1, R^2 = (CH_2)_5$; $R^3 = Ph$; $R^4 = CH_2TMS$]; **Typical Procedure**:^[407]

CAUTION: Aluminum trichloride dust is a severe irritant to all tissues and reacts violently with water.

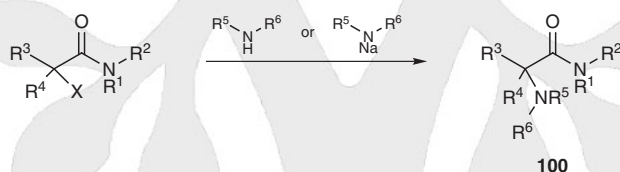
In a 100-mL round-bottomed flask, fitted with a Clarke–Rahrs column with a H₂O separator and a reflux condenser, were placed 1-(phenylglyoxyloyl)piperidine (3.2 g, 14.7 mmol), TMSCH₂NH₂ (2.1 g, 20.0 mmol), and a catalytic amount of AlCl₃ in benzene (50 mL) (**CAUTION: carcinogen**). The whole mixture was vigorously refluxed in an oil bath at 110 °C. After being stirred for 48 h, the mixture was concentrated under reduced pressure and the residual oil was subjected to column chromatography (silica gel, iPr₂O/benzene 1:1) to give the pure oily product; yield: 4.4 g (99%); bp 240–250 °C/0.2 Torr.

21.5.3.1.2.3

Variation 3: Substitution of Halogen Atoms by Nitrogen Atoms

Substitution of α -halogen atoms by nitrogen nucleophiles is an important method to synthesize α -amino amides **100**, and numerous examples are found in the literature using a variety of amines, amides, or nitrogen heterocycles. Chloro, bromo, and iodo amides are commonly used (Scheme 70).^[68,412–416] Reports of α -fluoro substitution by amines are rare.^[68] The methodology is often applied in the synthesis of pharmacologically active compounds. The method is also used in the synthesis of diamines by subsequent reduction of the amide group.

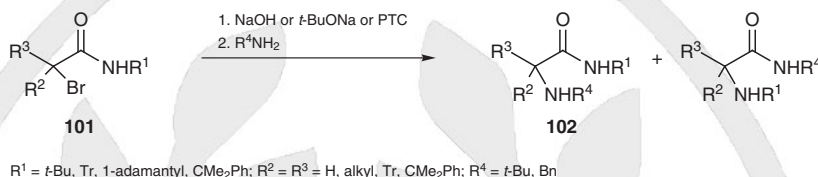
Scheme 70 Synthesis of α -Amino Amides from α -Halo Amides^[68,412–416]



α -Chloro amides can be transformed in situ into the more reactive α -iodo amides under Finkelstein conditions, e.g. with potassium iodide.^[412,413] If amines are used as nucleophiles in substitution reactions at α -halo amides, the evolving hydrogen halides are trapped either by excess amine^[414] or by additional bases such as alkali metal carbonates^[415] or alkali metal hydroxides.^[416] These syntheses have wide scope. Although the majority of examples concern α -haloacetamides, higher amides and even sterically congested products can also be obtained.^[416] Ammonia can be alkylated once,^[417] twice,^[418–420] or three times^[421,422] by α -halo amides. Double alkylation of secondary amines with α -halo amides results in quaternary ammonium salts,^[182] as does monoalkylation of tertiary amines.^[182] Linear or cyclic diamines,^[415,423] triamines,^[424] or tetraamines^[413,425] can be alkylated at all nucleophilic amino functions by α -halo amides. The methodology is also applied to synthesize chelating ligands for metals with aza-crown ether moieties.^[413,423–425] It is further possible to introduce natural products and their analogues into the α -position of amides by substitution of halide.^[426,427] Nitrogen heterocycles of amide or imide structures, e.g. phthalimide,^[182,428] nucleobases,^[429] or others,^[430,431] are applied as corresponding alkali metal salts^[182] or in the presence of a base (potassium carbonate, potassium hydroxide, *N,N*-diisopropylethylamine).^[429–431] Phase-transfer catalysis^[432] or solid-phase synthesis^[433] can also be used. Basic conditions are unnecessary if the heterocycle is acidic^[434] or if the products are to be isolated as salts.^[435] The stereoselectivity of the substitution of α -halo in α -chiral α -halo amides by amines can be governed by silver compounds, i.e. soluble silver salts cause inversion, but with solid silver(I) oxide there is retention of con-

figuration.^[436,437] Nucleophilic substitution of the N-monosubstituted α -bromo amide **101** with primary amines in the presence of base or under phase-transfer catalysis proceeds via α -lactams and allows the synthesis of extremely sterically hindered products (Scheme 71).^[438,439] Regioselectivity of the ring opening depends on the substituents at both nitrogen atoms.^[439] With secondary amines, only one isomer (corresponding to **102**) is formed.

Scheme 71 Reaction of α -Bromo Amides with Amines^[438,439]

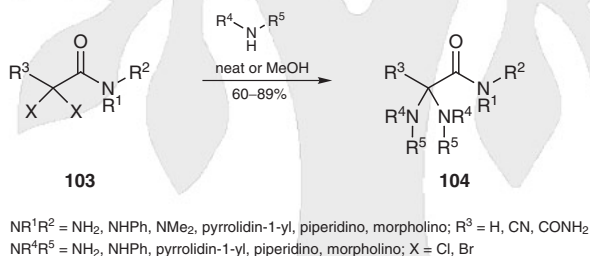


Quaternary ammonium salts can be obtained by reaction of tertiary amines with α -halo amides.^[436,440,441] The quaternization of pyridines can also be achieved at a solid support (Rink amide resin)^[442] or in vesicular or micellar phases.^[443]

Hydrazines or N-amino heterocycles can be alkylated by α -halo amides. The regioselectivity depends on the type of substituents attached to the hydrazine moiety.^[444–447] Sometimes, hydrazones are obtained with phenylhydrazine, owing to easy oxidation of the resulting (phenylhydrazino) amides.^[446] Reaction of hydrazines with (haloacyl)hydrazines can be used for the synthesis of (hydrazino)azapeptides and for (cyclohydrazino)-peptides.^[444,446] The reaction can also be applied to α -(acylamino)- α -bromo amides^[87] and to N,N-disubstituted and N,N'-disubstituted hydrazines.

If α,α -dichloro or α,α -dibromo amides **103** react with amines, usually both halogen atoms are substituted, thus forming α,α -diamino amides **104** (Scheme 72).^[394,448,449]

Scheme 72 Reaction of α,α -Dihalo Amides with Amines^[394,448,449]



α -Benzotriazolyl- α -morpholino amides can be obtained as glyoxylamide equivalents by reaction of α,α -dichloroacetamides with benzotriazole and morpholine in the presence of triethylamine.^[450]

In α -fluoro- α -iodoacetamides **105** (X=F) the halides can be exchanged stepwise by amino nucleophiles, including cyclic imides and amines,^[88] i.e. α -amino- α -halo amides **106** and α,α -diamino amides **107** are formed, respectively (Scheme 73). It is worth mentioning that even fluoride can be substituted in these cases.^[88] α -(Acylamino)- α -bromo amides **105** (X=Br) analogously afford amins on reaction with amines.^[87]

α -Azido amides **109**,^[451–456] including amides derived from chiral amines,^[451,453] can be obtained in high yields from α -chloro amides **108** and sodium azide in polar solvents or under phase-transfer catalysis (Scheme 74).^[453] The methodology can be applied to natural products such as aminosugars or steroids^[454] and in peptide synthesis.^[455,456] Subsequently, azido amides can be reduced to α -amino amides.^[451]

$$\begin{array}{ccc}
 \text{R}^3\text{-CH(Cl)-C(=O)-N(R}^1\text{)R}^2 & \xrightarrow[\text{62-99\%}]{\text{NaN}_3, \text{DMSO or acetone or PTC}} & \text{R}^3\text{-CH(N}_3\text{)-C(=O)-N(R}^1\text{)R}^2 \\
 \text{108} & & \text{109}
 \end{array}$$

$$\begin{array}{ccc}
 \text{Cl-CH}_2\text{-C(=O)-N(R}^1\text{)(R}^2\text{)} & \xrightarrow[\text{R}^1 = \text{R}^2 = \text{H; R}^3 = \text{2-furyl } 82\%]{\text{R}^3\text{-CH=N-OH (114), EtOH, 50 }^\circ\text{C, 2 h}} & \text{R}^3\text{-CH=N}^+\text{O}^-\text{-CH}_2\text{-C(=O)-N(R}^1\text{)(R}^2\text{)} \text{ (115)} \\
 \text{113} & &
 \end{array}$$

N,N-Diallyl-2-chloroacetamide (34.7 g, 0.20 mol) was added to a soln of potassium phthalimide (37.0 g, 0.2 mol) in DMF (250 mL) at 52–60 °C over 0.5 h. The soln was held at 65–70 °C for 2 h, cooled to rt, and poured into H₂O (500 mL). The product was collected by filtration and washed with H₂O; yield: 52.3 g (92%); mp 102–103 °C (EtOH/H₂O).

(2S)-2-(*tert*-Butylamino)-N-[(1R)-phenylethyl]propanamide [N^2 -*tert*-Butyl-N-[(1R)-1-phenylethyl]-L-alaninamide] [100, $R^1 = R^4 = R^6 = H$; $R^2 = (1R)\text{-CHPhMe}$; $R^3 = \text{Me}$; $R^5 = t\text{-Bu}$]; **Typical Procedure:**^[436]

To a soln of (2S)-2-bromo-N-[(1R)-1-phenylethyl]propanamide (256 mg, 1 mmol) in toluene (5 mL) were added *t*-BuNH₂ (114 mg, 2 mmol) and Ag₂O (232 mg, 1 mmol). The suspension was sonicated (1 h) and then centrifuged. The supernatant was concentrated and the crude mixture was separated by HPLC (silica gel, MeCN/H₂O 1:9 to 3:2) to give the product as an oil; yield: 236 mg (95%); 99.5% de.

α,α -Diaminoacetamides 104 ($R^1 = R^2 = R^3 = H$); General Procedure:^[448]

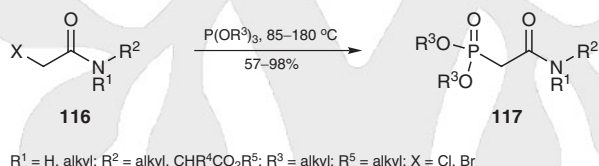
The appropriate amine (0.5 mol) was added slowly to dichloroacetamide (0.1 mol) under stirring and the mixture was refluxed for 2–6 h. The cold mixture was extracted (anhyd Et₂O or CH₂Cl₂), leaving the amine hydrochloride. The solvent was removed and the remaining product was recrystallized (Et₂O or CH₂Cl₂) to afford the colorless product; yield: 60–89%.

21.5.3.1.2.4

Variation 4: Substitution by Phosphorus Atoms

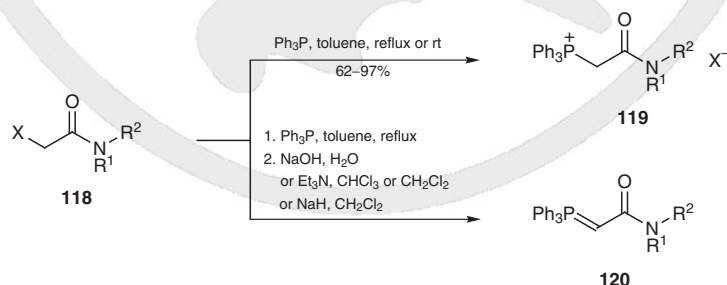
Amides substituted by phosphorus groups in the α -position, such as [(aminocarbonyl)methyl]phosphonates and α -(triphenylphosphonium) amides, or corresponding [(aminocarbonyl)methylene]phosphoranes, are important precursors for α,β -unsaturated amides. α -(Aminocarbonyl)phosphonates **117** are conveniently obtained by Arbuzov reaction of α -halo amides **116** with trialkyl phosphites (Scheme 77).^[459–462]

Scheme 77 Arbuzov Reaction of α -Halo Amides^[459–462]



α -(Triphenylphosphonium) carboxamides **119** with a wide variety of substituents can be synthesized by reaction of the corresponding α -chloro or α -bromo amide **118** with triphenylphosphine in inert solvents. The resulting phosphonium salts are generally isolated and can be transformed into the corresponding triphenylphosphoranylidene amide **120** by treatment with bases such as sodium hydroxide, triethylamine, or sodium hydride (Scheme 78).^[208,463–466] In this way, triphenylphosphoranylidene dipeptides can also be synthesized in excellent yields.^[464]

Scheme 78 Formation of Phosphoranylidene Amides^[208,463–466]



$R^1 = H, \text{ alkyl, aryl}; R^2 = \text{alkyl, Bn, aryl}, \text{CH}(\text{iBu})\text{CO}_2R^4; R^4 = \text{alkyl}; X = \text{Cl, Br}$

Alkyl 2-[[Dialkoxyphosphoryl]acetyl]amino]alkanoates 117 [$R^1 = H$; $R^2 = CHR^4CO_2R^5$; $R^3 = Alkyl$]; **General Procedure:**^[459]

CAUTION: Trimethyl phosphite is flammable and has a powerful, obnoxious odor. Induces headache. Severe skin and eye irritant. Corrosive and irritating to the respiratory tract.

The *N*-(haloacetyl)amino acid (0.05 mol) was suspended in the trialkyl phosphite (0.2 mol). The suspension was vigorously stirred, and gradually heated to 100 °C for chloroacetyl derivatives or to 85 °C for bromoacetyl derivatives. The exothermic reaction began at this point and the temperature of the mixture rose to 120–130 °C. The resultant soln was refluxed for 1–3 h and the volatile components were removed under reduced pressure. The residual pale yellow oil was extracted with hexane (2 × 60 mL) and the hexane extract was concentrated to give the product of satisfactory purity; yield: 84–98%. Further purification was achieved by distillation.

[(*N*-Methyl-*N*-phenylcarbamoyl)methyl]triphenylphosphonium Salt 119 ($R^1 = Me$; $R^2 = Ph$); **Typical Procedure:**

A soln of the α -halo amide (0.10 mol) and Ph_3P (0.10 mol) in toluene (100 mL) was refluxed under vigorous stirring for 24 h ($X = Cl$) or was stirred for 12 h at rt ($X = Br$). The product precipitated, was collected by filtration at rt, washed with toluene, and dried; yield: 82%; mp 200–202 °C.

***N*-Methyl-*N*-phenyl-2-(triphenylphosphoranylidene)acetamide (120, $R^1 = Me$; $R^2 = Ph$); Typical Procedure:**

Et_3N (150 mmol) was added to a soln of the phosphonium halide (100 mmol) in $CHCl_3$ or CH_2Cl_2 (500 mL). After stirring at rt for 3 h the solvent was removed under reduced pressure and the material was treated with benzene (**CAUTION: carcinogen**). The triethylammonium halide remained undissolved. It was removed by filtration and washed with some benzene. The combined benzene layers were concentrated under reduced pressure and the oily remainder was treated with Et_2O for crystallization; yield: 80%; mp 150–151 °C.

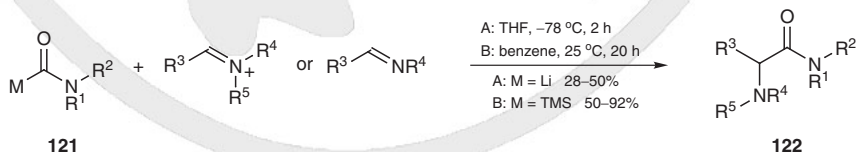
21.5.3.1.3

Method 3:

C—C Bond Formation between the Carbonyl Group and the α -Carbon Atom

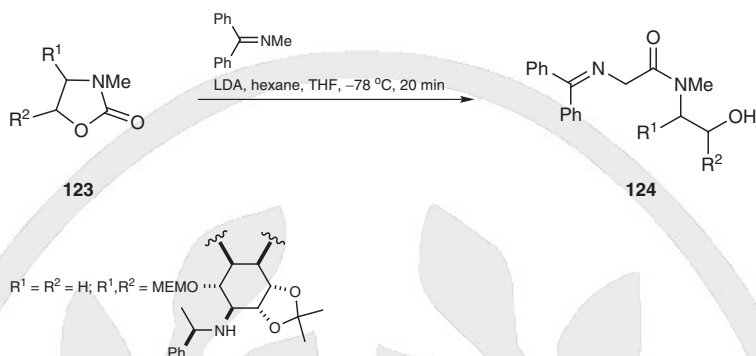
α -Amino amides **122** can be synthesized by formation of a C—C bond between the amide functionality and the α -position using nucleophiles such as carbamoyllithiums^[273] or carbamoylsilanes **121**^[467] and nonacidic imines or iminium salts as electrophilic reagents (Scheme 79). If chloro-*N,N*-dimethylmethyleimine chloride is used as the electrophile, 2 equivalents of carbamoylsilane can react to afford 2-(dimethylamino)malonamide.^[467] In equimolar quantities, dimethylformamide,^[273] isocyanates,^[273] or chlorocarbamates^[272] form oxalamides with carbamoyllithium reagents.^[273]

Scheme 79 α -Amino Amides from Carbamoyl Anions^[273,467]

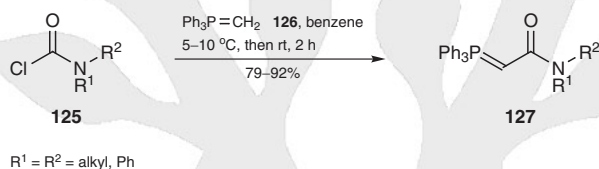


$NR^1R^2 = NMe_2$, $N(CH_2CH=CH_2)_2$, $NHCHMePh$; $R^3 = H$, alkyl, Ph, 2-furyl, $CH=CHPh$; $R^4 = Me$, Ph; $R^5 = Me$

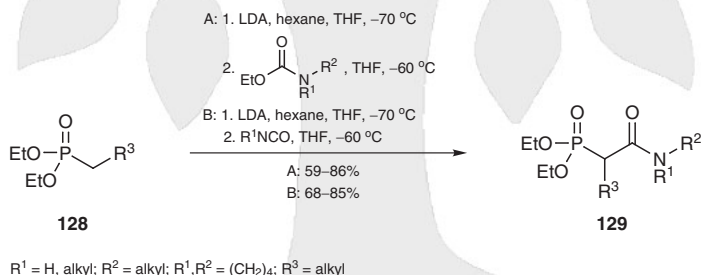
Nucleophilic ring opening of oxazolidin-2-ones **123** by lithiated *N*-methylbenzophenone imine, giving access to α -(diphenylmethylidene)amino amides **124** in modest yields, is applied in the synthesis of the aminoglycoside antibiotic fortamine (Scheme 80).^[468]

Scheme 80 Ring Opening of Oxazolidinones^[468]

(Carbamoylalkylidene)triphenylphosphoranes **127**, representing Wittig reagents with α -amide moieties, can be synthesized by reaction of methylenetriphenylphosphoranes **126** with carbamoyl chlorides **125** (Scheme 81).^[469] Sometimes the products are isolated as phosphonium salts.

Scheme 81 Synthesis of Phosphoranes via C—C Bond Formation^[469]

Similarly, α -carbamoylphosphonates **129** can be obtained from phosphonates **128**, lithium diisopropylamide, and urethanes^[470] or isocyanates^[471] (Scheme 82).

Scheme 82 Synthesis of α -Carbamoylphosphonates^[470,471]

Diethyl α -(diethylcarbamoyl)difluoromethylphosphonate can be synthesized in modest yield by copper(I) bromide catalyzed reaction of diethylcarbamoyl chloride with bromo[(diethoxyphosphoryl)(difluoro)methyl]zinc(II).^[111]

α -Amino Amides 122; General Procedure:^[467]

Method B: A Schlenk tube fitted with a Teflon vacuum stopcock and a micro stirbar was flame heated under reduced pressure and refilled with argon. An iminium salt (0.5–1.5 mmol) was introduced in a dry box and the tube was then attached to an argon line. An equivalent amount of (*N,N*-dimethylcarbamoyl)trimethylsilane was then added, together with anhyd benzene (2 mL) (**CAUTION: carcinogen**). In most cases the reaction was complete within 20 h at 25 °C. The volatiles were removed under reduced pressure and the residue was evaporatively distilled or the mixture was quenched with aq NaHCO_3 , dried, and distilled or directly recrystallized; yield: 55–89%.

2-(Triphenylphosphoranylidene)acetamides 127; General Procedure:^[469]

A soln of the carbamoyl chloride (50 mmol) in benzene (100 mL) (**CAUTION: carcinogen**) was added at 5–10 °C under stirring to a soln of methylenetriphenylphosphorane in benzene (250–300 mL), obtained from methyltriphenylphosphonium bromide (105.5 mmol). Stirring was continued at rt for 2 h. The precipitated methyltriphenylphosphonium chloride was filtered off by suction and thoroughly washed with benzene (250 mL). The combined organic layers were concentrated under reduced pressure and the residue was recrystallized (benzene/EtOAc 3:7); yield: 79–92%.

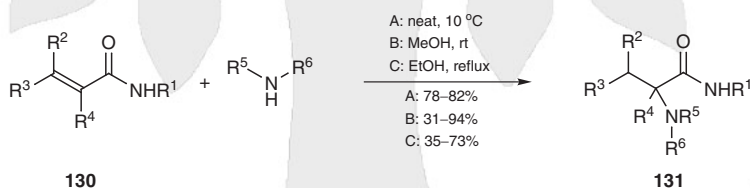
2-(Diethoxyphosphoryl)acetamides 129; General Procedure:^[470]

An LDA soln was prepared by the addition of THF (20 mL) and $i\text{Pr}_2\text{NH}$ (44 mmol) dissolved in THF (20 mL) to a 1.6 M soln of BuLi in hexane (27.5 mL, 44 mmol) under N_2 at –30 °C. The soln was allowed to warm to 0 °C for 10 min and was then cooled to –70 °C. At this temperature a soln of the dialkyl phosphonate (20 mmol) in THF (20 mL) was gradually added and the mixture was stirred for an additional 15 min. After the addition of a soln of an isocyanate or carbamate (21 mmol) in THF (15 mL), the mixture was stirred at –60 °C for 30 min. The temperature of the mixture was allowed to reach 0 °C within 15 min and was hydrolyzed with 2 M HCl (30 mL). The mixture was then decanted and the aqueous phase was extracted with CH_2Cl_2 (3 \times 30 mL). The combined organic layers were dried (MgSO_4) and concentrated. The remaining crude product was purified by distillation or recrystallization; yield: 62–85%.

21.5.3.1.4

Method 4:**Addition of a Nitrogen Functionality to α,β -Unsaturated Amides**

The addition of amines to α,β -unsaturated amides **130** is normally directed to the β -position. If, however, electron-withdrawing substituents, such as ester, aroyl, or two chlorine atoms, are attached to the β -position, the regioselectivity is reversed and α -amino amides **131** are obtained (Scheme 83).^[291,472–474]

Scheme 83 Addition of Amines to α,β -Unsaturated Amides^[291,472–474]

$\text{R}^1 = \text{Ac}$, alkyl, aryl; $\text{R}^2 = \text{H}$, CO_2H , CO_2R^7 , Cl; $\text{R}^3 = \text{H}$, COAr^1 , Cl; $\text{R}^4 = \text{H}$, NHAc
 $\text{NR}^5\text{R}^6 =$ alkylamino, dialkylamino, pyrrolidin-1-yl, piperidino, morpholino, arylamino

Dipotassium osmate catalyzed aminohydroxylation of α,β -unsaturated amides with chloramine-T leads to mixtures of regioisomeric amino alcohols, where, however, the α -amino- β -hydroxy amide is often the minor isomer (see Section 21.5.2.1.4).^[298]

α -Nitroso amides can be synthesized in 67–96% yield by treatment of α,β -unsaturated amides with nitrogen monoxide in the presence of triethylsilane and catalytic amounts of a cobalt(II) complex.^[475]

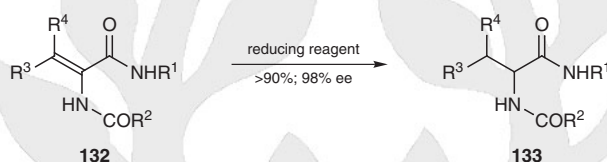
Methyl 4-[(2-Methyl-5-nitrophenyl)amino]-4-oxo-3-piperidin-1-ylbutanoate [131, $\text{R}^1 = 2\text{-Me-5-O}_2\text{NC}_6\text{H}_3$; $\text{R}^2 = \text{CO}_2\text{Me}$; $\text{R}^3 = \text{R}^4 = \text{H}$; $\text{R}^5, \text{R}^6 = (\text{CH}_2)_5$]; Typical Procedure:^[472]

Methyl 4-[(2-methyl-5-nitrophenyl)amino]-4-oxobut-2-enoate (0.26 g, 1 mmol), piperidine (0.26 g, 3 mmol), and MeOH were mixed and then left overnight. In the morning the pure product was collected by filtration and washed with $i\text{Pr}_2\text{O}$; yield: 0.26 g (74%); mp 127–128 °C.

21.5.3.1.5

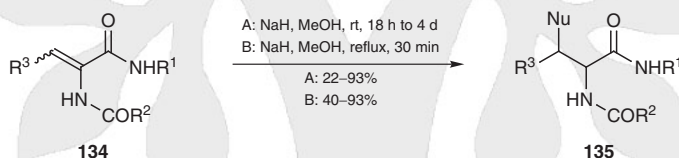
Method 5:**Addition to α,β -Unsaturated α -Amino Amides**

α,β -Unsaturated α -amino amides **132**, commonly named as dehydroamino amides, can be hydrogenated in the presence of various metal catalysts, such as palladium/char-coal,^[476–479] Raney nickel,^[480] platinum(IV) oxide,^[477] rhodium complexes,^[477,479] iridium complexes,^[481] or with zinc^[480] in the presence of hydrochloric acid/acetic acid, to afford the corresponding saturated α -amino amides **133** (Scheme 84). Rhodium and iridium complexes with chiral ligands allow highly enantioselective or diastereoselective hydrogenation,^[477,479] while auxiliary techniques with chiral amino groups in the amide moiety give only modest stereoselectivities.^[478]

Scheme 84 Reduction of α,β -Unsaturated α -Amino Amides^[476–481]

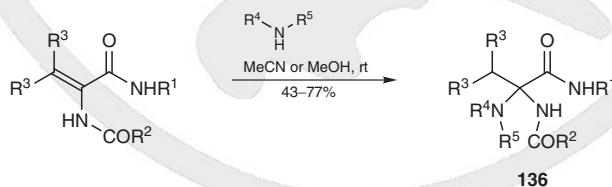
$R^1 = H, \text{ alkyl, Bn}; R^2 = \text{Me, Et}; R^3 = H, \text{ Me, aryl}; R^4 = H, \text{ Me}$

Dehydroamino amides **134** with acyl groups attached to the α -amino function can add nitrogen nucleophiles, such as amines^[482] or hydroxylamine,^[483] or thiolates^[482] to the β -position with formation of α -(acylamino)- β -amino or α -(acylamino)- β -(alkylsulfanyl) amides **135**, respectively (Scheme 85).

Scheme 85 Addition of Nucleophiles to α -Amino Amides^[482,483]

$R^1 = H, \text{ Bn}; R^2 = \text{Me, Ph}; R^3 = H, \text{ Cy, aryl, CH=CHMe, CH=CHPh}; \text{Nu} = \text{NH}_2, \text{ alkylamino, dialkylamino, NHOH, SMe}$

However, addition of amines to dehydroamino amides can alternatively occur at the α -position, affording amins **136**, probably via intermediate iminium salts or imine tautomers (Scheme 86). This alternative outcome of the addition depends on the substituents in the substrate.^[474,484]

Scheme 86 Formation of α,α -Diamino Amides from α,β -Unsaturated α -(Acylamino) Amides^[474,484]

$R^1 = \text{Et, Ac}; R^2 = \text{Me, O}t\text{-Bu}; R^3 = H, \text{ Cl}; NR^4R^5 = \text{NH}_2, \text{ NHPr, alkylamino, NH(CH}_2\text{CH=CH}_2\text{), NHBn, piperidino}$

***N*²-Acetyl-*N*-benzylleucinamide (133, R¹ = Bn; R² = Me; R³ = *i*Pr; R⁴ = H); Typical Procedure:**^[477]

2-(Acetylamino)-*N*-benzyl-4-methylpent-2-enamide (13.7 mg, 0.053 mmol) and degassed MeOH (3 mL) were placed under H₂ at 760 Torr. A soln of Rh(nbd)Cl dimer (ca. 1 mg) and (*R,R*)-DIPAMP 1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane (ca. 0.5 mg) in degassed MeOH (2 mL) was prehydrogenated (760 Torr) for 10 min. The resulting soln was then syringed into the dehydrodiamide in MeOH and monitored by TLC over time. Upon completion, the mixture was concentrated under reduced pressure, diluted with dry THF (3 mL), and filtered through a short plug of silica gel to afford the product; yield: 13.6 mg (98%); 95% ee.

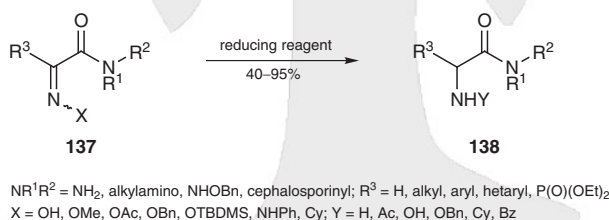
 α -(Acetylamino)- β -aminopropanamides 135 (R² = Me; R³ = H; Nu = NH₂, Alkylamino, Dialkylamino, NHOH); General Procedure:^[482]

A soln of the dehydroamino amide (7 mmol) in the amine (140 mmol) was stirred at rt for 18 h to 4 d. The amine was removed under reduced pressure and the resulting residue was triturated with Et₂O (50 mL) to give the crystalline product; yield: 22–93%.

21.5.3.1.6

**Method 6:
Addition to α -Imino Amides**

Oximes of α -oxo amides **137** (X = OH) can be reduced to the corresponding α -(hydroxyamino) amides **138** (Y = OH) by borane.^[485,486] Other reducing reagents, such as aluminum amalgam,^[392] zinc in acetic acid,^[487] hydrogen with palladium/charcoal^[411] or platinum(IV) oxide,^[318] lithium aluminum hydride,^[488] or sodium bis(2-methoxyethoxy)aluminum hydride,^[488] cleave the N—O bond of oximes **137** (X = OH, OR¹), thus leading to α -amino amides **138** (Y = H), which can be acylated before isolation. The methodology can also be applied to the synthesis of dipeptides related to β -lactam antibiotics^[487] and other natural products.^[489] Stereoselective reduction can occur at oximes derived from chiral α -oxo amides.^[488] Hydrazones of α -oxo amides **137** (X = NHPh) are transformed into α -(acetylamino) amides **138** (Y = Ac) with zinc in acetic acid and acetic anhydride by N—N bond cleavage (Scheme 87).^[490]

Scheme 87 Reduction of α -Oxo Amide Oximes and Hydrazones^[318,392,411,486–488] **α -(Hydroxyamino)- and α -(Benzyloxyamino)-*N*-methylamides 138 (R¹ = H; R² = Me; Y = OH, OBn); General Procedure:**^[486]

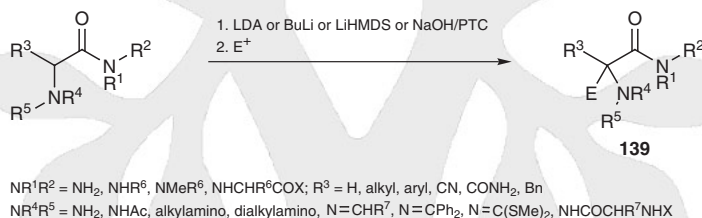
A stirred soln of the oxime (2 mmol) and pyridine•BH₃ complex (10 mmol) in dry EtOH (4 mL) was treated at rt with 7 M ethanolic HCl (3 mL) at such a rate that the temperature of the mixture remained below 40 °C. Stirring was continued at rt for 16 h, after which time the solvent was removed. CH₂Cl₂ (25 mL) was added together with solid Na₂CO₃ (1 g). After stirring for several hours, the suspension was filtered and the solvent was removed under reduced pressure. The residue was chromatographed by HPLC (silica gel, CH₂Cl₂/MeOH) to give the pure product; yield: 40–90%.

21.5.3.1.7 Method 7:
C—C Chain Elongation at the α -Carbon Atom

21.5.3.1.7.1 Variation 1:
Of α -Amino Amides

C—C chain elongation at the α -position of α -amino amides attracts much interest as stereogenic centers are established and a wide range of α -amino acid derivatives, including quaternary α -amino amides^[491,492] and peptides,^[493–495] become available. Many of these reactions go via intermediate amide enolates, which react with several electrophiles, e.g. alkylating reagents,^[491–494,496–499] aldehydes,^[493,500] or Michael acceptors to form chain elongated amides **139** (Scheme 88).^[495,501,502] The α -amino group can be free or protected, e.g. as an imine^[491,492,496] or a bis(methylsulfonyl)methylidene derivative.^[503] Enolate formation is possible using strong bases, such as lithium diisopropylamide,^[498] lithium hexamethyldisilazanide,^[499] butyllithium,^[498] *sec*-butyllithium,^[497] or potassium *tert*-butoxide,^[494] in liquid ammonia,^[501] or under phase-transfer catalysis.^[491,492,496,503] High *syn* selectivities can be achieved for the addition of α -aminoacetamides to Michael acceptors.^[502] Diastereoselective α -alkylation is possible if the amides used as the starting material are derived from chiral amines, such as chiral amino alcohols or phenylethylamine^[497–499,503] or in the peptide series.^[493,494] As an alternative pathway to enantiopure α -amino amides or corresponding α -amino acids, enzymatic kinetic resolution of the α -amino amides obtained by α -alkylation is useful.^[492]

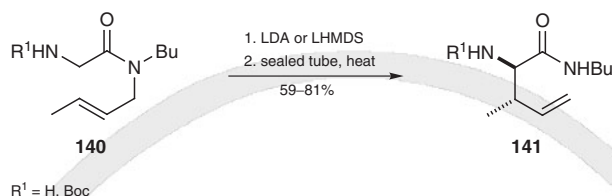
Scheme 88 C—C Bond Formation via Amide Enolates^[491,492,496,498,499,503]



Optically active β -alkyl- β -hydroxyaspartic acid *N,N*-dimethylamides can be obtained from α -isocyano-*N,N*-dimethylacetamide and α -oxo esters in the presence of chiral gold(I) complexes via dihydrooxazoles which are hydrolyzed.^[504] C—C chain elongation of α -amino amides is also possible by photochemical means, as shown by the incorporation of glycine in dipeptides or in substituted *N*-acylglycines. Alkenes, toluenes, acetic anhydride, or formate are used as reactants.^[505–508] However, only modest yields are achieved.

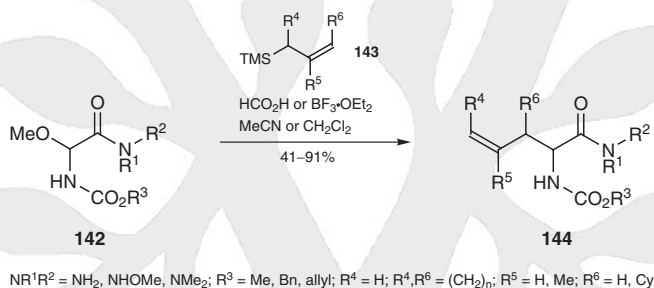
Nonphotochemical radical addition of peptides to alkenes can be achieved starting from xanthates, which themselves can be synthesized from the corresponding amide via α -bromination.^[348]

Stereoselective aza-[2,3]-Wittig sigmatropic rearrangement of substituted α -(allyl-amino)acetamides^[509] and aza-Claisen rearrangement of substituted *N*-allyl- α -aminoacetamides **140**^[339] provide 2-aminopent-4-enamides **141**, but with a narrow substitution pattern (Scheme 89).

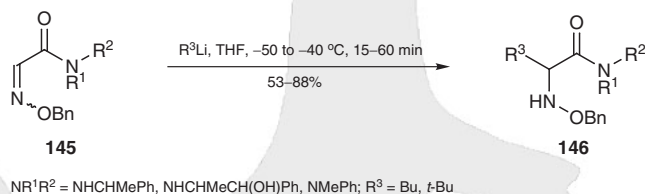
Scheme 89 C–C Chain Elongation via Aza-Claisen Rearrangement^[339]

Photochemical rearrangement of α -alkoxyacetamides, where a cyclic enone substituent migrates from the amide nitrogen atom to the α -carbon atom, provides α -branched α -alkoxyacetamides of a very limited substitution pattern.^[510]

Optically active α -amino amides derived from prolinol can be synthesized by ring opening of fused tetrahydro-1,4-oxazine-3-ones by stereoselective reaction with Grignard reagents or with allylsilanes in the presence of titanium(IV) chloride.^[511] The latter reactions proceed via intermediate *N*-acyliminium salts. Similar conditions are also used in the synthesis of a variety of racemic α -amino amides **144** starting from α -methoxyglycinamides **142** and allylsilanes **143** (Scheme 90).^[512]

Scheme 90 C–C Bond Formation at α -Methoxyglycinamides by Allylsilanes^[512]

O-Benzyloximes of glyoxylamides **145** can be transformed into α -(benzyloxyamino) amides **146** with alkylolithium reagents by introducing alkyl substituents (Scheme 91).^[513] Chiral amino groups exert modest chiral induction.

Scheme 91 Transformation of α -Oxo Amide Oximes^[513]

2-(*tert*-Butoxycarbonylamino)-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylbutanamide [139, $\text{R}^1 = (1*S*,2*S*)-\text{CHMeCH(OH)Ph}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{R}^5 = \text{H}$; $\text{R}^4 = \text{Boc}$; $\text{E} = \text{Et}$]; **Typical Procedure:**^[498]

A 2.71 M soln of BuLi in hexanes (791 μL , 2.14 mmol) was added slowly to a slurry of anhyd LiCl (176 mg, 4.15 mmol) and $i\text{Pr}_2\text{NH}$ (310 μL , 2.21 mmol) in THF (4 mL) at -78 °C. After stirring at -78 °C for 10 min, a soln of (*S,S*)-(+)-*N*-Boc-pseudoephedrine glycineamide (223 mg, 0.692 mmol) in THF (4 mL + 2 mL wash) was added via cannula to the LDA slurry. After stirring for 20 min at -78 °C, the suspension was warmed to 0 °C. After stirring for 20 min at 0 °C, EtI (66 μL , 0.830 mmol) was added to the pale yellow suspension. After stirring for 1 h at 0 °C, the reaction was terminated by the addition of 1 M HCl (30 mL). The biphasic mix-

ture was extracted with two portions of EtOAc (50 and 40 mL). The organic layers were combined and the resulting soln was washed with sat. aq NaHCO₃, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The product was purified by chromatography (silica gel, EtOAc/hexanes 2:3 to 1:1) to afford the product as an oil; yield: 169 mg (79%); 93% de.

α -Amino Amides 139 (NR⁴R⁵ = N=CHBn); General Procedure:^[491]

To a vigorously stirred soln of the *N*-benzylidene amino acid amide (50 mmol), Bu₄N⁺ HSO₄⁻ (30 mmol) in CH₂Cl₂ (1 L) and 10 M NaOH (600 mL) at rt, the corresponding alkyl halide (0.52 mol) was added in one portion. The mixture was stirred for 4–18 h. The aqueous layer was discarded and the organic layer was washed with H₂O (2 × 100 mL). To the organic layer, 2 M HCl (500 mL) was added and the mixture was vigorously stirred for 15 min. The aqueous layer was separated and the organic layer was extracted with 0.1 M HCl (100 mL). The combined aqueous layers were washed with CH₂Cl₂ (2 × 150 mL), neutralized with 10 M NaOH, and extracted with CH₂Cl₂ (3 × 200 mL). After washing with H₂O, the organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The solid residue was recrystallized (EtOAc or toluene); yield: 45–92%.

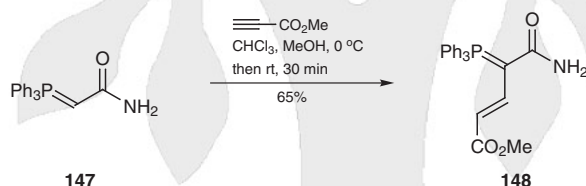
21.5.3.1.7.2

**Variation 2:
Of α -Phosphoryl Amides**

α -[(Aminocarbonyl)methyl]phosphonates and α -(triphenylphosphoranylidene) amides can undergo C—C bond formation at the α -position with electrophiles without loss of the phosphorus moiety. Thus, alkylation can be achieved in modest yields.^[514]

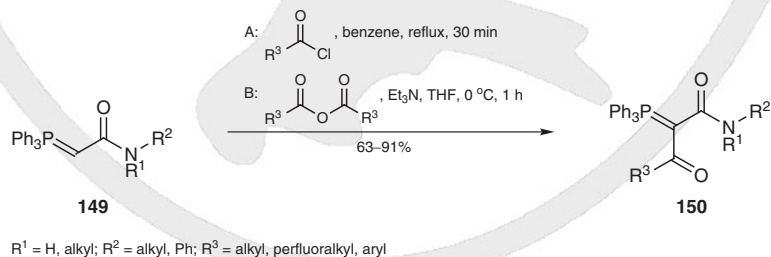
Michael-type addition of (triphenylphosphoranylidene)acetamide (**147**) to methyl propanoate leads to the β,γ -unsaturated amide **148** (Scheme 92).^[515]

Scheme 92 Addition of a Phosphoranylidene Amide to Methyl Propynoate^[515]



α -Phosphorylated β -oxo amides **150** can be synthesized by acylation of (triphenylphosphoranylidene)acetamides **149** with anhydrides^[516] or acyl chlorides^[517] (Scheme 93).

Scheme 93 Acylation of Phosphorus Ylides^[516,517]



The addition of isocyanates or isothiocyanates to methylenephosphoranes gives access to phosphorylated malonamide derivatives.^[517]

***N,N*-Diethyl-4,4,4-trifluoro-3-oxo-2-(triphenylphosphoranylidene)butanamide (150,**
 $R^1 = R^2 = \text{Et}$; $R^3 = \text{CF}_3$); Typical Procedure:^[516]

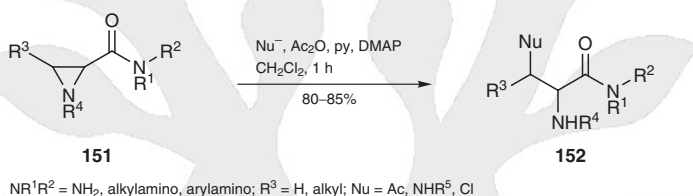
Method B: [2-(Diethylamino)-2-oxoethyl]triphenylphosphonium bromide (1.82 g, 4 mmol) in anhyd THF (20 mL) was cooled in an ice–water bath under N_2 and treated with Et_3N (0.81 g, 8 mmol), with stirring. After string for 15 min, the mixture was treated dropwise with TFAA (0.86 g, 4.1 mmol) and allowed to stir for 1 h. The mixture was poured into H_2O and filtered. The precipitate was purified by recrystallization (MeOH) to give the pure product; yield: 1.64 g (87%); mp 198–200 °C.

21.5.3.1.8

Methods 8: Miscellaneous Procedures

Ring opening of *cis*- and *trans*-aziridinecarboxamides **151** gives access to α -amino amides **152** while a nucleophile (acetoxy,^[518] alkyl,^[519] alkylamino,^[520] chloro^[521]) is introduced into the β -position. Since the aziridines are available in optically active form and the ring opening is regio- and stereoselective, optically active α -amino amides can be obtained in this way (Scheme 94).

Scheme 94 Ring Opening of Aziridinecarboxamides^[518–521]



Nucleophilic ring opening of 2-aminoazirine-3-carboxamides with acetic acid or acyl chlorides forms α -(acylamino)malonamide derivatives.^[522,523] 5-Oxo-1,2-oxazolidine-3-carboxamides, obtained via 1,3-dipolar cycloaddition of nitrones derived from glyoxylamides and 1-chloroacrylonitrile, can be ring opened by catalytic hydrogenation to give chiral aspartic amides.^[524]

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Product Class 6: α,β -Unsaturated Amides: Alk-2-ynamides, Arenecarboxamides, and Alk-2-enamides

M. F. Lipton and M. A. Mauragis

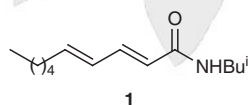
General Introduction

Previously published information regarding this product class can be found in *Houben-Weyl*, Vol. 5, pp 934–1113.

α,β -Unsaturated amides constitute an important structural element in many natural products and biologically important molecules, including the manumycin family of antibiotics,^[1] unsaturated fatty acid amides of the *Compositae*, *Piperaceae*, and *Rutceae* plant families, exemplified by pellitorine (**1**, Scheme 1), an attractive synthetic target^[2,3] with insecticidal activity.^[4] They are also important intermediates in the construction of complex alkaloids.^[5,6,7] Although less prevalent in nature, α -aryl, α -hetaryl, and acetylenic amides constitute important synthetic intermediates, the latter being precursors for the construction of *E,E*-dienamides in a highly stereoselective fashion. Except for the Ritter reaction of cyanoacetylene with alcohols in strong acid to generate ynamides,^[8] most unsaturated amides can be constructed via similar chemistry.

Typically, unsaturated amides have fairly low intrinsic toxicity. They can be handled safely on a laboratory scale with standard good laboratory practice. They are frequently solids and exhibit very high stability and low volatility. In most cases they may be purified without incident by chromatography on silica gel, and may be stored indefinitely. Although they are susceptible to hydrolysis by both acid and base, forcing conditions are generally required.

Scheme 1 Pellitorine

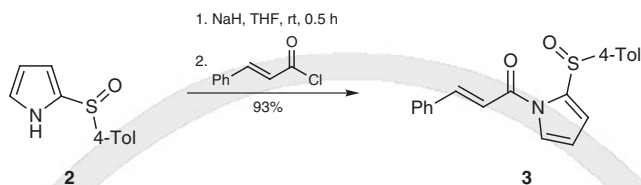
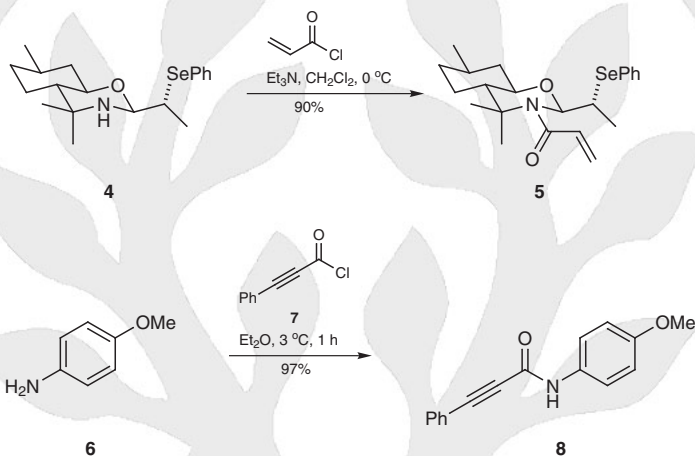


Synthesis of Product Class 6

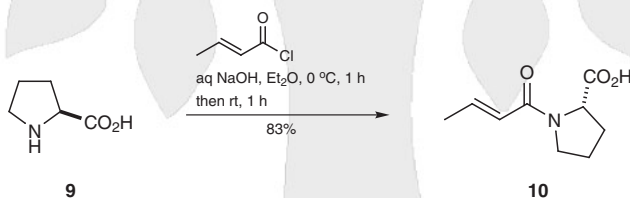
Method 1:

Coupling of Activated Acyl Units and Amines

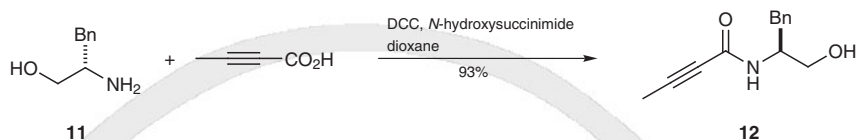
Methods for the generation of α,β -unsaturated amides are abundant in the literature. The simplest of these involves the coupling of activated α,β -unsaturated carboxylic acids with amines catalyzed by base. Sodium hydride, as well as lithium bases, can be used to activate amines as demonstrated by the synthesis of amide **3** from 2-(4-tolylsulfinyl)-1H-pyrrole (**2**) as shown in Scheme 2.^[9] However, the more sensitive chiral Evans oxazolidinones have a tendency to polymerize under such conditions and procedures employing milder Grignard bases are recommended for use with these substrates.^[10] Coupling of amines with acid chlorides in the presence of acid scavengers under anhydrous conditions can also be used (e.g., in the synthesis of amide **5** from amine **4** as shown in Scheme 3).^[11] The reaction of acid chloride **7** with an excess of amine **6** is also possible for the synthesis of amide **8**.^[12]

Scheme 2 Reaction of an Acid Chloride with an Amide Base^[9]**Scheme 3** Reaction of Acid Chlorides with Amines^[11,12]

Alternatively amines, such as **9**, can be coupled with acid chlorides to give amides, such as **10**, using Schotten–Baumann conditions (Scheme 4).^[13,6,14]

Scheme 4 Reaction of an Acid Chloride with an Amine Using Schotten–Baumann Conditions^[6]

Other syntheses of amides that have seen wide usage involve the use of chloroformates to generate mixed anhydrides,^[15] 4-nitrobenzenesulfonylation (nosylation),^[16] *N*-acylbenzotriazole formation,^[17] carbodiimide-mediated activations,^[18,19] and the use of phosphites.^[20] These methods are not specific to the formation of unsaturated amides, but their enormous popularity warrants their mention here. The intermediate unsaturated acyl species, which in some cases may be isolated, are straightforwardly coupled with primary and secondary amines. This yields unsaturated amides with the double bond configuration defined by that of the starting carboxylic acid. These methods are mild and specific, and are generally compatible with a variety of functionalities, as demonstrated by the synthesis of amide **12** by the carbodiimide-mediated coupling of but-2-ynoic acid with amine **11** (Scheme 5).^[19]

Scheme 5 Synthesis of an Alk-2-ynamide via a Mixed Anhydride Promoted by a Carbodiimide Reagent^[19]**2-(4-Tolylsulfinyl)-1-[(2E)-3-phenylprop-2-enoyl]-1H-pyrrole (3):**^[9]

A soln of 2-(4-tolylsulfinyl)-1H-pyrrole (**2**; 1.00 g, 4.9 mmol) in dry THF (10 mL) was added dropwise to an ice-cooled 60% dispersion of NaH in mineral oil (200 mg, 5.0 mmol) in dry THF (30 mL). The mixture was stirred at rt for 0.5 h and (*E*)-cinnamoyl chloride (833 mg, 5.0 mmol) in dry THF (10 mL) was added to the mixture. After being stirred for 1.5 h, the mixture was quenched with H₂O (15 mL) and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine (30 mL), dried, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc 3:2 to 1:1); yield: 1.52 g (93%).

3-Acryloyl-4,4,7-trimethyl-2-[(1R)-(phenylselanyl)ethyl]octahydro-2H-1,3-benzoxazine (5):^[11]

To a soln of amine **4** (1.0 g, 2.8 mmol) and Et₃N (0.260 mL, 3.2 mmol) in dry CH₂Cl₂ (20 mL) was slowly added neat acryloyl chloride (0.435 mL, 3.1 mmol) under argon at 0 °C. The mixture was stirred for an additional 30 min at rt and then diluted with hexane (50 mL). The solid was removed by filtration and the solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, CH₂Cl₂); yield: 1.1 g (90%).

N-(4-Methoxyphenyl)-3-phenylprop-2-ynamide (8):^[12]

A soln of 4-methoxyaniline (**6**; 73.9 g, 0.6 mol) in Et₂O (600 mL) was added slowly to a soln of acid chloride **7** (49.4 g, 0.3 mol) in Et₂O (250 mL) cooled at 3 °C. The mixture was stirred for 1 h at 3 °C, quenched with ice, and the product was extracted with Et₂O (3 × 500 mL). Removal of the solvent under reduced pressure provided the product, which was recrystallized (EtOH); yield: 71.0 g (97%); mp 131 °C.

1-[(2E)-But-2-enoyl]-L-proline (10):^[6]

A mixture containing L-proline (**9**; 7.68 g, 66.7 mmol) in 1 M aq NaOH (130 mL) and (*2E*)-but-2-enoyl chloride (6.1 g, 60 mmol) in Et₂O was vigorously stirred for 1 h at 0 °C and for a further 1 h at rt. After separation of the organic layer, the aqueous layer was washed with CHCl₃ (20 mL), acidified to pH 1 with 6 M HCl, and extracted with CHCl₃ and EtOAc. The extracts were dried (Na₂SO₄), concentrated under reduced pressure, and the residue was reprecipitated (2 ×) from a mixture of CHCl₃ and hexane; yield: 8.96 g (83%).

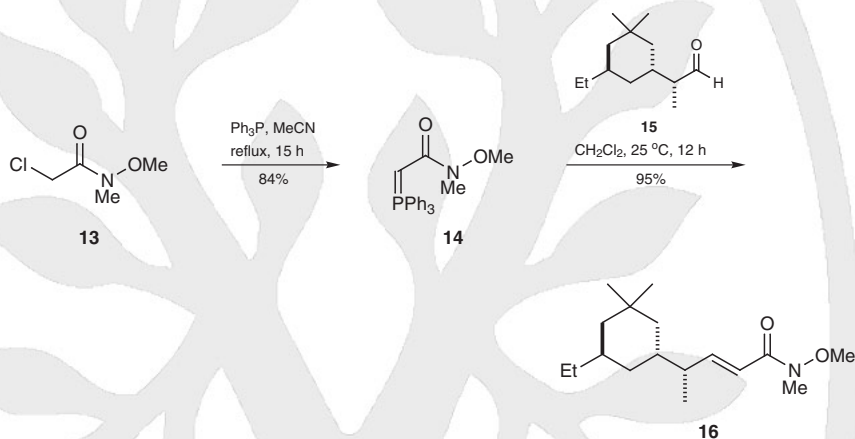
N-[(1S)-Benzyl-2-hydroxyethyl]but-2-ynamide (12):^[19]

To a stirred soln of but-2-ynoic acid (0.128 g, 1.52 mmol) in anhyd dioxane (30 mL), *N*-hydroxysuccinimide (0.361 g, 1.75 mmol), and DCC (0.285 g, 1.88 mmol) were sequentially added. After stirring for 2.5 h at rt, (*2S*)-2-amino-3-phenylpropan-1-ol (**11**; 0.285 g, 1.88 mmol) was added. The mixture was stirred overnight, the precipitated *N,N'*-dicyclohexylurea was removed by filtration, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with sat. NaCl (2 ×). The aqueous layers were extracted with EtOAc (20 mL) and the combined organic extracts were dried (Na₂SO₄). The solvent was removed under reduced pressure and the product was purified by chromatography (silica gel, hexane/EtOAc 2:3); yield: 0.307 g (93%).

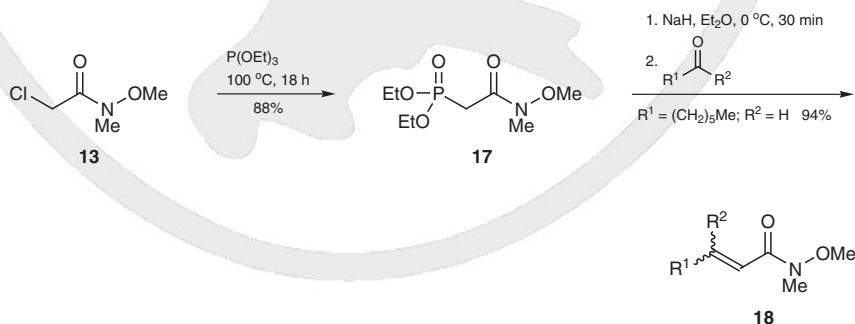
21.6.1.2

Method 2:
Connective Alkene Formation by Wittig Reaction

Phosphoranes and phosphonates, both prepared efficiently from the parent α -chloroacetamide (see Section 21.5.3.1.2.4), have been employed in the synthesis of α,β -unsaturated Weinreb amides via Horner–Emmons or Wittig couplings. Use of ketones in these couplings often provides mixtures of *E*- and *Z*-isomers, but aldehydes are highly stereoselective, producing the *E*-isomer. For example, refluxing the α -chloroacetamide **13** with triphenylphosphine gives the crystalline ylide **14** in 84% yield. Mixing of the ylide **14** and the aldehyde **15** provides the α,β -unsaturated amide **16** in 95% yield after chromatography (Scheme 6).^[21] The α,β -unsaturated Weinreb amide **16** has been used in the preparation of the C25 to C34 subunit of cytovaricin.

Scheme 6 Synthesis of an Amide via a Phosphoranylidene Amide^[21]


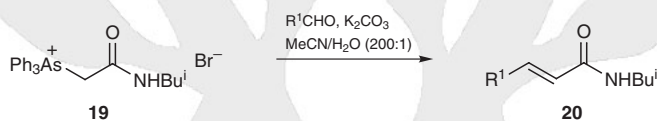
Alternatively, Horner–Emmons variants have been described.^[22,23] α -Phosphorylacetamide **17**, easily prepared by the reaction of α -chloroacetamide **13** with triethyl phosphite at elevated temperatures, can be used in a general method to generate α,β -unsaturated Weinreb amides of predominately *E* geometry in high yield.^[22,23] Thus, treatment of the amide **17** with base followed by ketones or aldehydes, either under standard conditions or Masamune–Rousch conditions, affords the α,β -unsaturated Weinreb amides **18** with *E/Z* selectivities of 81:19 or better (Scheme 7). Interestingly, standard coupling conditions provided uniformly higher yields in the 74–96% range.

Scheme 7 Synthesis of Amides via an α -Phosphorylacetamide^[23]


R ¹	R ²	Reaction Time (h)	Ratio (<i>E/Z</i>)	Yield (%) of 18	Ref
(CH ₂) ₅ Me	H	1	95:5 ^a	94	[23]
(<i>E</i>)-CH=CHMe(CH ₂) ₂ CH=CHMe ₂	H	1	100:0 ^a	89	[23]
CH ₂ CHMe(CH ₂) ₂ CH=CHMe ₂	H	1	100:0 ^a	94	[23]
Ph	H	1	100:0 ^a	91	[23]
Me	Ph	24	81:19 ^b	76	[23]
(CH ₂) ₅		1	–	91	[23]

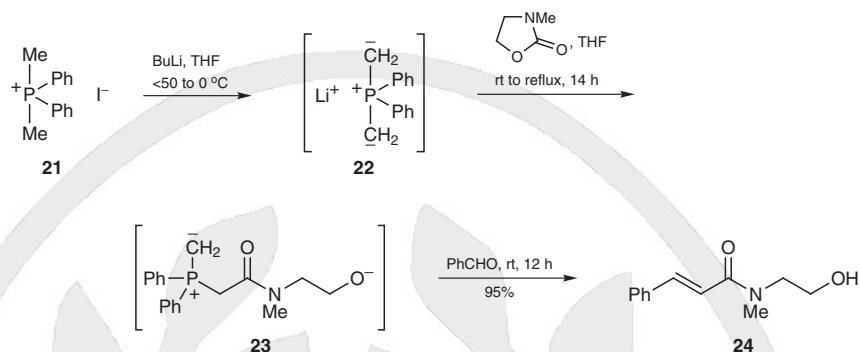
^a Determined by GC analysis.^b Determined by ¹H NMR.

Organoarsonium ylides, such as **19**, can also be employed in the preparation of α,β -unsaturated amides, such as **20** (Scheme 8).^[24,25,26] The yields are high, and in contrast to the phosphorus ylides, the mildly basic carbonate is used and the procedure is simple. Interestingly, there is an apparent requirement for traces of water for optimum results in the coupling reaction. Similar to the phosphorus series, the organoarsines are prepared in high yield by reaction of triphenylarsine with α -bromoacetamides.

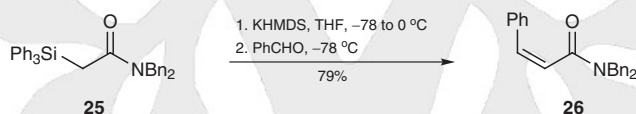
Scheme 8 Synthesis of Amides via Organoarsonium Bromides^[26]

R ¹	Reaction Time (h)	Yield (%)	Ref
Ph	19	96	[26]
4-ClC ₆ H ₄	12	95	[26]
4-O ₂ NC ₆ H ₄	7	99	[26]
(CH ₂) ₄ Me	12	95	[26]
(CH ₂) ₈ Me	11	97	[26]
4-MeOC ₆ H ₄	21	60	[26]
CH=CHMe	15	57	[26]
CH=CHPh	21	61	[26]

The phosphonium salt **21** containing two alkyl substituents can be deprotonated twice at two different α sites. The resulting phosphonium diylide **22**, which is more nucleophilic than classical monoylides, readily attacks weakly electrophilic cyclic carbamates resulting in a pseudo acylation process after ring opening. Following a proton transfer, the resulting stabilized ylide **23** can then react with an aldehyde in the standard Wittig fashion yielding α,β -unsaturated amide **24** bearing an *N*-hydroxyethyl functional group (Scheme 9).^[27] The configuration of the double bond in these reactions is almost exclusively *E*.

Scheme 9 Synthesis of an Amide via a Lithium Diphenylphosphonium Diylide^[27]

The Peterson reaction between α -(triarylsilyl)acetamides and predominately aromatic aldehydes can be used to prepare α,β -unsaturated amides with good *Z* selectivity. For example, the reaction between *N,N*-dibenzyl-2-(triphenylsilyl)acetamide (**25**) and benzaldehyde proceeds to give amide **26** in good yield and with over 97% *Z* selectivity (Scheme 10).^[28] Potassium hexamethyldisilazanide must be used as base, because a large counteraction effect is noted. (Trimethylsilyl)acetamide provides lower *Z/E* selectivities, and interestingly, better selectivities are observed with electron-rich amides and aldehydes. This is the only reliable method found for the preparation of enamides with the double bond in the unusual *Z* configuration, although the partial reduction of ynamides could also be envisaged as an entry into such compounds.

Scheme 10 Synthesis of an Amide via the Peterson Reaction of an α -(Triarylsilyl)acetamide^[28]

(2*E*,4*R*)-4-[(1*R*,5*R*)-5-Ethyl-3,3-dimethylcyclohexyl]-*N*-methoxy-*N*-methylpent-2-enamide (16).^[21]

To a soln of α -chloroacetamide **13** (20.7 g, 150 mmol) in MeCN (200 mL) was added Ph_3P (40.2 g, 153 mmol). The soln was refluxed for 15 h, cooled to rt, and concentrated under reduced pressure. The resulting viscous residue was dissolved in CH_2Cl_2 (500 mL) and washed with 2 M KOH (2×200 mL) and brine (200 mL). The aqueous layers were extracted with CH_2Cl_2 (200 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated to provide a thick oil that solidified on standing. The residue was recrystallized twice (hexane/EtOAc 1:1) to provide phosphoranylidene amide **14** as pale yellow crystals; yield: 45.8 g (84%); mp 183 – 185 °C. A soln of aldehyde **15** (4.90 g, 24.5 mmol) and phosphoranylidene amide **14** (18.2 g, 50 mmol) in CH_2Cl_2 (35 mL) was stirred at 25 °C for 12 h, then concentrated and chromatographed (hexane/EtOAc 3:1) to afford the α,β -unsaturated amide **16**; yield: 6.68 g (95%).

***N*-Methoxy-*N*-methylnon-2-enamide [18, $\text{R}^1 = (\text{CH}_2)_5\text{Me}$; $\text{R}^2 = \text{H}$]; Typical Procedure:**^[23]

α -Chloroacetamide **13** (20.0 g, 145 mmol) was heated for 18 h at 100 °C with $\text{P}(\text{OEt})_3$ (24.2 g, 145 mmol). Vacuum distillation (124 °C/ 0.8 Torr) afforded α -phosphorylacetamide **17**; yield: 31 g (88%). α -Phosphorylacetamide **17** (2.2 mmol) was reacted with NaH (2.6 mmol) in Et_2O (15 mL) at 0 °C for 30 min, followed by addition of an aldehyde or ketone (2.0 mmol) and warming to ambient temperature to provide the title compound; yield: 94%. Experimental details for the workup were not provided.

Amides 20; General Procedure:^[25]

Arsonium bromide **19** (0.324 g, 0.65 mmol), the aldehyde (0.50 mmol), K₂CO₃ (0.090 g, 0.65 mmol), MeCN, and H₂O (40 μ L) were stirred at 22 °C for 10.5 h. The mixture was passed through a short column of silica gel to remove most of the Ph₃AsO and inorganic salts. The desired products were isolated in excellent yield after chromatography on silica gel (petroleum ether/EtOAc 3:2). No *Z*-isomers were detected by ¹H NMR spectroscopy.

***N*-(2-Hydroxyethyl)-*N*-methyl-3-phenylacrylamide (24):**^[27]

To a suspension of dimethyldiphosphonium iodide (**21**; 1.71 g, 5 mmol) in THF (100 mL) was added 1.6 M BuLi in hexane (6.25 mL, 10 mmol) dropwise below –50 °C. The resulting colorless suspension was maintained for 15 min at –50 °C, allowed to warm slowly to 0 °C, and maintained for 1 h. At ca. –20 °C, the solid disappeared. 3-Methyl-1,3-oxazolidin-2-one (0.47 mL, 5.5 mmol) in THF (10 mL) was added dropwise at rt and the mixture was refluxed for 14 h, resulting in a beige solid. The mixture was cooled to rt, PhCHO (0.53 g, 5 mmol) was added, and stirring was continued for 12 h. The mixture was hydrolyzed with 0.5 M HCl, the THF was removed under reduced pressure, and the residue was extracted into CH₂Cl₂. The organic layer was dried (Na₂SO₄), concentrated, and the product was purified by chromatography (alumina); yield: 0.97 g (95%); mp 77–78 °C.

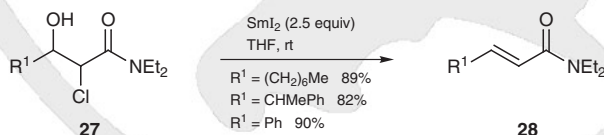
(2*Z*)-*N,N*-Dibenzyl-3-phenylacrylamide (26):^[28]

To a soln of *N,N*-dibenzyl-2-(triphenylsilyl)acetamide (**25**; 206 mg, 0.415 mmol) in THF (4 mL) cooled to –78 °C was added 0.5 M KHMDs in toluene (0.98 mL, 0.49 mmol). After stirring for 30 min at 0 °C, the soln was cooled to –78 °C. PhCHO (39 mg, 0.368 mmol) in THF (2.5 mL) was added, and stirring was continued for 3 h. The soln was quenched with H₂O, and the mixture was extracted with Et₂O. After workup and chromatographic purification by preparative TLC (silica gel, hexane/EtOAc 5:1), the product was obtained as a viscous oil; yield: 106 mg (79%).

21.6.1.3

**Method 3:
Elimination Reactions**

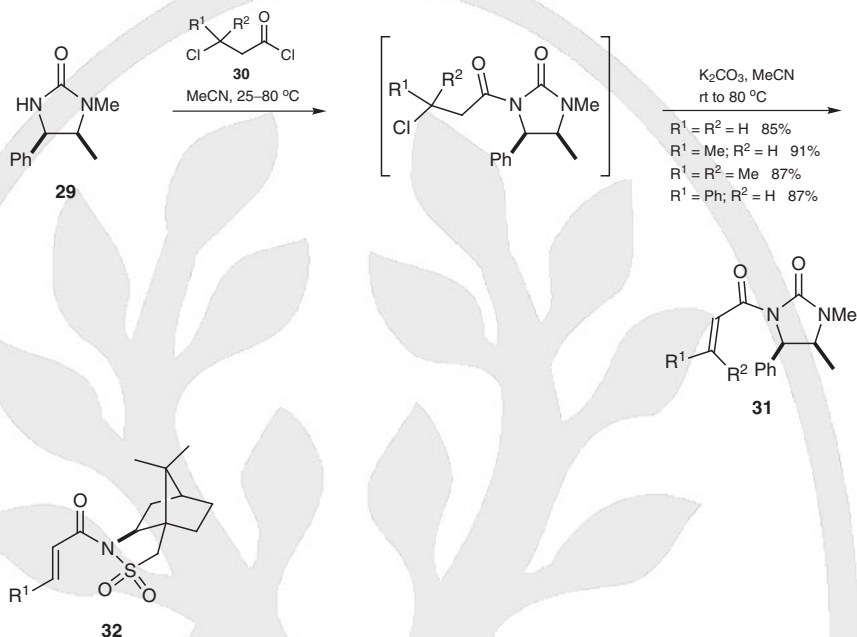
Elimination reactions of suitably substituted α -, β -, α,β -, β,γ -, and γ,δ -amides are capable of yielding unsaturated and polyunsaturated amides. Samarium(II) iodide can be employed to generate *E*- α,β -unsaturated amides by β -elimination of readily available 2-chloro-3-hydroxy amides. For example, by treating 2-chloro-3-hydroxy amide **27** with samarium(II) iodide in tetrahydrofuran at room temperature, the amides **28** are obtained after a few minutes (Scheme 11).^[29] Only preliminary results are presented, but isolated yields between 82–90% are obtained with *E* selectivities over 98%.

Scheme 11 Reaction of Samarium(II) Iodide with 2-Chloro-3-hydroxy Amides^[29]

In a process similar to the *N*-acylation of bornane-2,10-sultam,^[30] a mild acylation/elimination procedure was developed for the synthesis of 1-acylimidazolidin-2-ones. Treatment of the starting imidazolidin-2-one **29** with 3-chloroalkanoyl chlorides **30** followed by in situ elimination using potassium carbonate affords the α,β -unsaturated amides **31** in 85–91% yields and with ee's over 99.9% (Scheme 12).^[31] The method is applicable to 3-alkyl and 3-aryl substituted 3-chloroalkanoyl chlorides, affording the products with *E* geome-

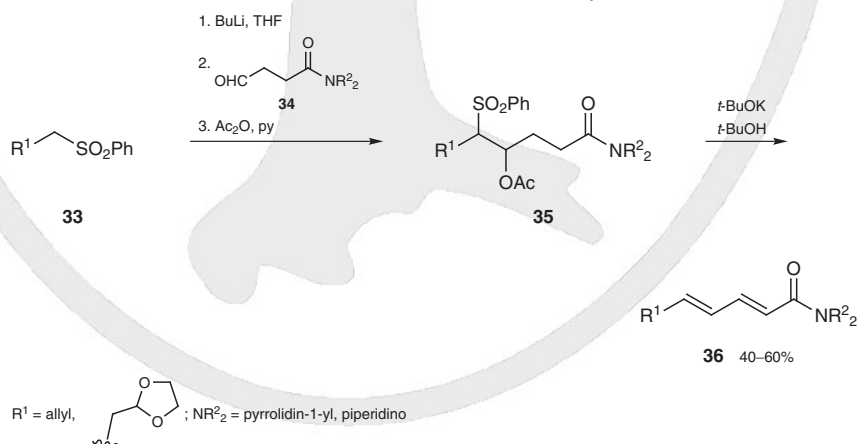
try. This method is also shown to be effective with Oppolzer's bornane-2,10-sultam auxiliary to provide **32** in comparable yields, but the Evans oxazolidin-2-one is unreactive.

Scheme 12 Acylation and Elimination of 3-Chloroalkanoyl Chlorides^[31]



The preparation of *2E,4E*-dienamides via the double elimination of β -acetoxy sulfones is reported, but only vague experimental details are provided.^[32,33] The yields are 40–60% but the required isolation and purification of the acetoxy sulfone intermediates is a major drawback. Using this methodology, sulfones **33** can be converted into β -acetoxy sulfones **35** after treatment with butyllithium followed by aldehydes **34**. Subsequent double elimination by the addition of potassium *tert*-butoxide provides the *2E,4E*-dienamides **36** (Scheme 13).

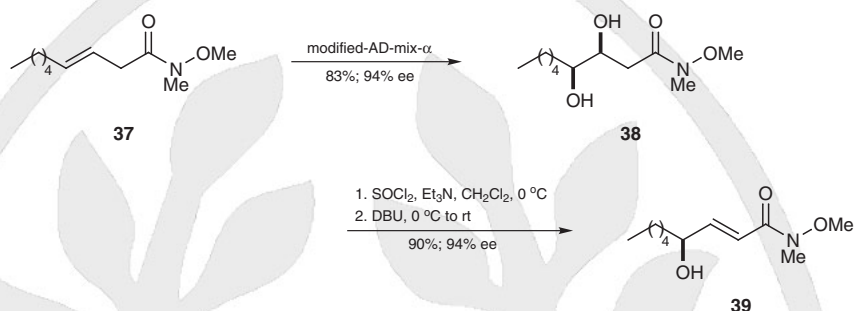
Scheme 13 *2E,4E*-Dienamides via the Double Elimination of β -Acetoxy Sulfones^[32,33]



The synthesis of γ -hydroxy- α,β -unsaturated amides with high enantiomeric purity via an asymmetric dihydroxylation and elimination process has been reported.^[34] Thus, treatment of β,γ -unsaturated amide **37**, with Modified-AD-mix- α and methanesulfonamide in

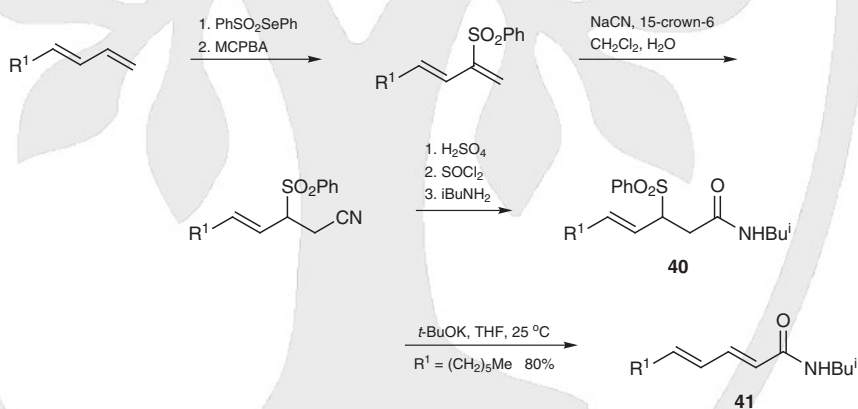
tert-butyl alcohol and water affords an 83% yield of diol **38** with 94% ee. Subsequent treatment with thionyl chloride and triethylamine in dichloromethane, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene, smoothly generates amide **39** in 90% yield (Scheme 14). Unfortunately, no experimental details were provided.

Scheme 14 Synthesis of a γ -Hydroxy- α,β -Unsaturated Amide^[34]

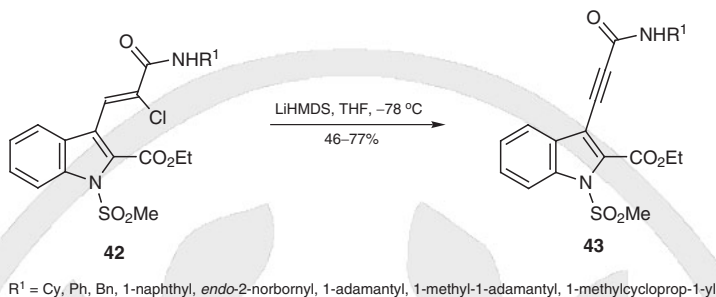


Another useful approach utilizes terminal diene starting compounds, which can undergo a selenosulfonylation and oxidation sequence to give vinylic sulfones. Michael addition of cyanide gives the β -sulfonyl nitriles but base-induced elimination of benzenesulfonic acid is nonselective, affording a 1:1 mixture of *2E,4E*- and *2Z,4E*-isomers. Greater selectivities in the elimination are realized when the nitriles are converted into the sterically more demanding amides **40** via hydrolysis, activation as the acid chlorides, and amidation (Scheme 15).^[35] The α,β -unsaturated amides **41** are obtained with *2E,4E* selectivities of over 98% and in 34–36% overall yields from the terminal dienes.

Scheme 15 Elimination of Benzenesulfonic Acid from β -Sulfonyl Amides^[35]



Elimination of vinyl chlorides provides a general entry to ynamides. For example, the reaction of vinyl carbamoyl chlorides **42** with lithium hexamethyldisilazide provides the ynamides **43** in moderate to good yields (Scheme 16).^[36] The vinyl carbamoyl chlorides are readily available via Horner–Emmons coupling of the *tert*-butyl chlorophosphonoacetate with the appropriate aldehyde followed by activation of the freed carboxylate as the 2-pyridyl thioester, and reaction with an amine.

Scheme 16 Elimination Reactions of Vinyl Carbamoyl Chlorides^[36]**1-Acylimidazolidin-2-ones 31; General Procedure:**^[25]

To a suspension of imidazolidin-2-one **29** (5.0 g, 26 mmol) in MeCN (50 mL) was added the acid chloride **30** (39.7 mmol) in one portion at 25 °C. The mixture was heated to 80 °C for 4–6 h under N₂ and cooled to rt. K₂CO₃ (3.6 g, 26.3 mmol) was added portionwise over 10 min and the mixture was heated to 80 °C for 2–4 h, and cooled to rt. The inorganic residues were removed via filtration and the filtrate was concentrated under reduced pressure. The organic residue was partitioned between CH₂Cl₂ and H₂O, and the organic phase was washed with sat. Na₂CO₃ and sat. NaCl, dried (MgSO₄), and concentrated. The crude product was purified by recrystallization (EtOH/H₂O 9:1, 5 mL·g⁻¹ substrate) at 0 °C or flash chromatography (silica gel, EtOAc/hexane 1:10); yield: 85–91%.

2E,4E-Dienamides 36; General Procedure:^[33]

Sulfone **33** was treated with BuLi (1.2 equiv) in THF at –30 °C for 1 h. Aldehyde **34** was added dropwise at –78 °C to this soln, and the reaction was continued at this temperature for 0.5 h. The crude β-hydroxy sulfone thus obtained was treated with Ac₂O and pyridine to provide the corresponding β-acetoxy sulfone **35** after column chromatography (silica gel). A soln of the acetate **35** (2.0 mmol) in *t*-BuOH (10 mL) was treated with *t*-BuOK (6.0 mmol) at rt for 12 h. Isolation of the pure products was performed by column chromatography (neutral alumina); yield: 40–60%.

(2E,4E)-N-Isobutylundeca-2,4-dienamide [41, R¹ = (CH₂)₅Me]; Typical Procedure:^[35]

t-BuOK (42 mg, 0.37 mmol) was added to a stirred soln of amide **40** [R¹ = (CH₂)₅Me; 140 mg, 0.37 mmol] in THF (5 mL) at 25 °C. A precipitate formed immediately, and stirring was continued for 30 min. H₂O (5 mL) was added and the mixture was extracted with several portions of Et₂O. The organic phase was washed with H₂O and brine, dried (MgSO₄), and concentrated under reduced pressure to afford the product as yellow-white crystals; yield: 70 mg (80%).

3-(Indol-3-yl)prop-2-ynamides 43; General Procedure:^[36]

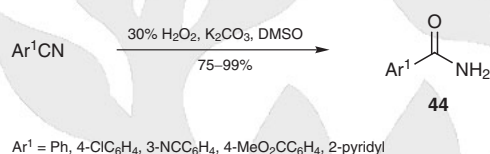
The vinyl chloride **42** (0.92 mmol) in THF (10.3 mL) was cooled to –78 °C and LiHMDS (3 mmol) was added dropwise. The mixture was stirred at this temperature for 5 h then warmed to 10 °C over 3 h. A sat. soln of NH₄Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel); yield: 46–77%.

21.6.1.4

Method 4: Hydrolysis of Nitriles

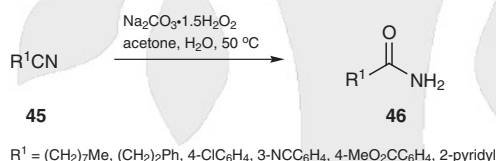
Hydrations of the corresponding nitriles can be effectively employed for the synthesis of N-unsubstituted amides. Although both acidic and basic conditions can be used for this transformation, the classical inorganic acidic hydrolyses^[37–39] are considered of more preparative value, because under basic conditions the product amides are at least as easily hydrolyzed as the nitriles themselves. Although suitable for the preparation of aliphatic amides, a basic process using aqueous hydrogen peroxide and potassium carbonate is especially well suited to the preparation of benzamides **44** (Scheme 17), with yields in the 75–99% range using a variety of substrates.^[40] This is similar to the original procedure described by Radziszewski in 1885.^[41]

Scheme 17 Hydrolysis of Nitriles Using Aqueous Hydrogen Peroxide and Potassium Carbonate^[40]



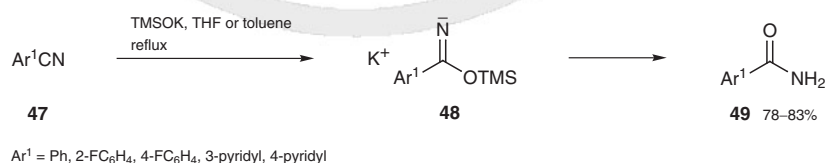
Sodium percarbonate can also be used for the noncatalyzed hydration of nitriles, a method particularly applicable to the synthesis of aryl and hetaryl amides.^[42] Sodium percarbonate, an addition compound of hydrogen peroxide and sodium carbonate, is used on an industrial scale,^[43] and is a stable and inexpensive reagent that releases 1.5 equivalents of hydrogen peroxide on dissolution in water. It cleanly hydrolyzes a variety of alkyl, aryl, and hetaryl nitriles, such as **45**, to the corresponding N-unsubstituted amides, such as **46**, in excellent yield (Scheme 18), but fails for the known recalcitrant *ortho*-substituted aromatic nitriles.

Scheme 18 Hydrolysis of Nitriles Using Aqueous Sodium Percarbonate^[42]



Potassium trimethylsilanolate can be used as a hydroxide anion equivalent to convert nitriles, e.g. **47**, into amides, e.g. **49**, in good yield under anhydrous conditions (Scheme 19).^[44] As with most of the hydrolytic procedures, it is most suited to the preparation of benzamides and hetaryl amides. The procedure is convenient and has the preparative advantage that the intermediate salt, e.g. **48**, precipitates, preventing overreaction and facilitating purification. The purified salt is then converted into the amide by treatment with water and the product is isolated by extraction. This method has the added advantage that it is compatible with aryl fluorides, and gives an 80% yield for the synthesis of 2-fluorobenzamide. In the cases studied, the sodium and lithium bases gave decidedly inferior results.

Scheme 19 Hydrolysis of Nitriles Using Potassium Trimethylsilanolate in the Absence of Water^[44]



4-Chlorobenzamide (44, Ar¹ = 4-ClC₆H₄); Typical Procedure:^[40]

To a stirred soln of 4-chlorobenzonitrile (1.37 g, 10 mmol) in DMSO (3.0 mL), cooled in an ice bath, were added 30% H₂O₂ (1.2 mL, 10.6 mmol) and anhyd K₂CO₃ (0.2 g, 1.45 mmol). The mixture was allowed to warm to rt (a strong exothermic effect was observed). After 5 min, distilled H₂O (50 mL) was added, cooling was applied, and the product was isolated by filtration; yield: 1.39 g (91%).

Aromatic Amides 46 Using Aqueous Sodium Percarbonate; General Procedure:^[42]

Na₂CO₃•1.5H₂O₂ (20 mmol) was added to a soln of nitrile **45** (10 mmol) in a mixture of acetone (ca. 30 mL) and H₂O (20 mL). The mixture was heated to 50 °C and maintained at that temperature for 0.75–6 h. After cooling to ambient temperature, the acetone was removed under reduced pressure. Depending on the solubility of the amide, the products were isolated by partition with either EtOAc or CH₂Cl₂, or were precipitated with additional H₂O.

Aromatic Amides 49 Using Potassium Trimethylsilanolate; General Procedure:^[44]

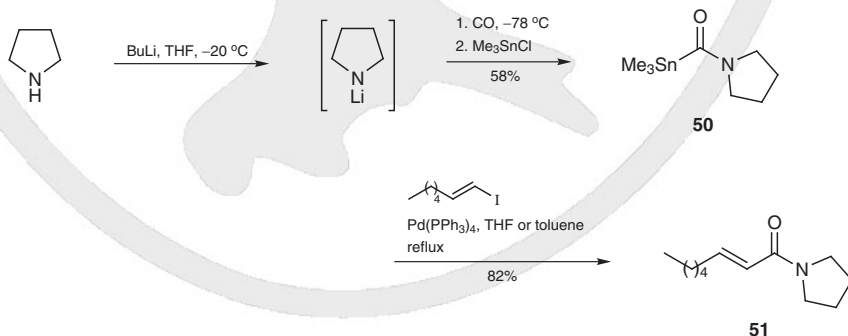
TMSOK (2 mmol) and nitrile **47** (1 mmol) were dissolved in either anhyd THF or toluene (5 mL). The mixture was refluxed until the nitrile was consumed. The mixture was cooled and the solid precipitate was collected by filtration, washed with anhyd solvent, and then poured into H₂O to hydrolyze the salts. The aqueous layer was extracted with EtOAc, and the organic extracts were dried (MgSO₄) and concentrated; yield: 78–83%.

21.6.1.5

**Method 5:
Transition-Metal-Catalyzed Couplings**

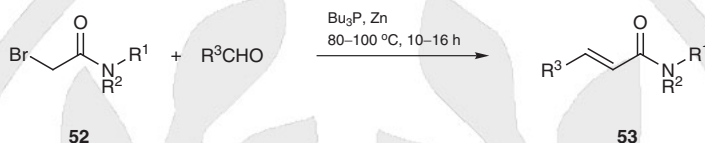
Carbonylation of the lithium salts of secondary amines results in the generation of a carbamoyllithium species, which upon quenching with chlorotrialkylstannanes affords carbamoyltrialkylstannanes, such as **50**. These species undergo palladium-catalyzed cross-coupling reactions with aryl, alkenyl, and hetaryl bromides or iodides to yield unsaturated amides, such as **51** (Scheme 20).^[45] Carbamoyltriphenylstannanes afford, in addition to the expected products, byproducts resulting from phenyl migration. Yields (49–83%) and reaction times (40–80 min) were optimized for the carbamoyltrimethylstannane series due to ease of removal of iodotrimethylstannane. However, the higher toxicity of the more volatile trimethylstannane reagent is definitely a limitation of the practical value of the method.

Scheme 20 Palladium-Catalyzed Cross-Coupling of a Carbamoyltrimethylstannane with a Vinyl Iodide^[45]



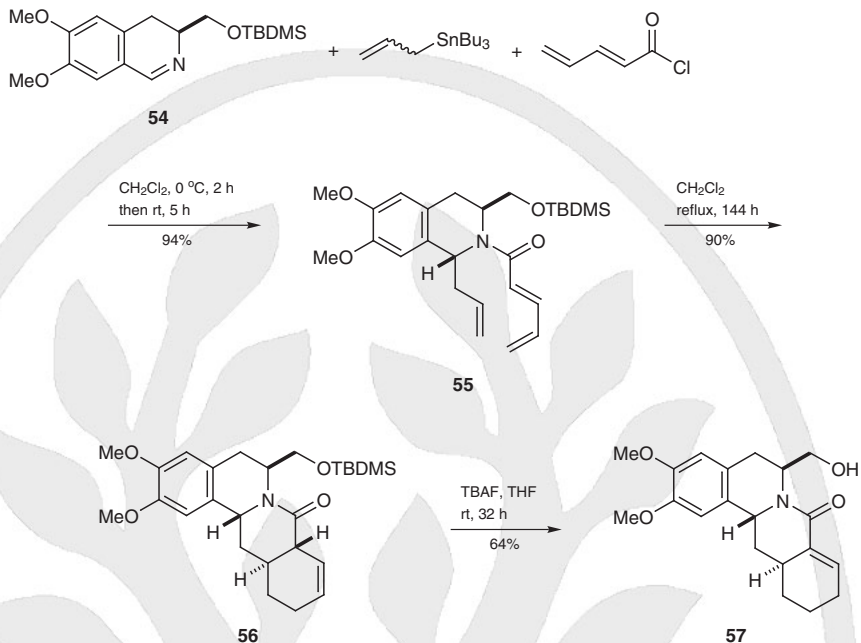
The preparation of α,β -unsaturated amides **53** from aldehydes and α -bromoacetamides **52** using zinc catalysis has been reported (Scheme 21).^[46] The products are obtained exclusively with *E* selectivity. Whereas the zinc-catalyzed procedure appears preparatively useful, the corresponding palladium-mediated coupling^[47] suffers from a high catalyst loading, e.g. 25 mol% tetrakis(triphenylphosphine)palladium is required. Only *N,N*-disubstituted amide substrates are employed in the procedure.

Scheme 21 Zinc-Catalyzed Coupling of α -Bromoacetamides with Aldehydes^[46]

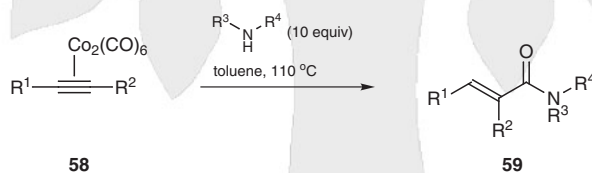


NR ¹ R ²	R ³	Yield (%)	Ref
piperidino	Ph	70	[46]
piperidino	4-ClC ₆ H ₄	72	[46]
piperidino	4-BrC ₆ H ₄	79	[46]
piperidino	4-FC ₆ H ₄	75	[46]
piperidino	4-O ₂ NC ₆ H ₄	80	[46]
piperidino	(CH ₂) ₅ Me	70	[46]
NEt ₂	Ph	86	[46]
NEt ₂	4-ClC ₆ H ₄	81	[46]
NEt ₂	2-furyl	80	[46]
NEt ₂	4-Tol	81	[46]
NEt ₂	iBu	76	[46]

Tin-mediated three-component couplings of the 3,4-dihydroisoquinoline **54** can be employed to generate the intramolecular Diels–Alder substrate **55** for the synthesis of *allo*- and pseudo-7,8-dimethoxyberbane systems (Scheme 22).^[48] The double bond of the adduct **56** is cleanly isomerized back into conjugation to complete the synthesis of α,β -unsaturated amide **57**.

Scheme 22 A Tin-Mediated Three-Component Coupling^[48]

Hydrocarbamylation of cobalt–alkyne complexes **58** with primary amines provides α,β -unsaturated amides **59** in yields ranging from 62–82% (Scheme 23).^[49] The reaction does not proceed when aniline is used as the amine, suggesting that electron density on the nitrogen atom is important. The secondary amine diethylamine can also be used, though a more moderate yield of 47% is obtained. The experimental details are incomplete, but the best yields are obtained using 10 equivalents of amine at 110 °C in toluene.

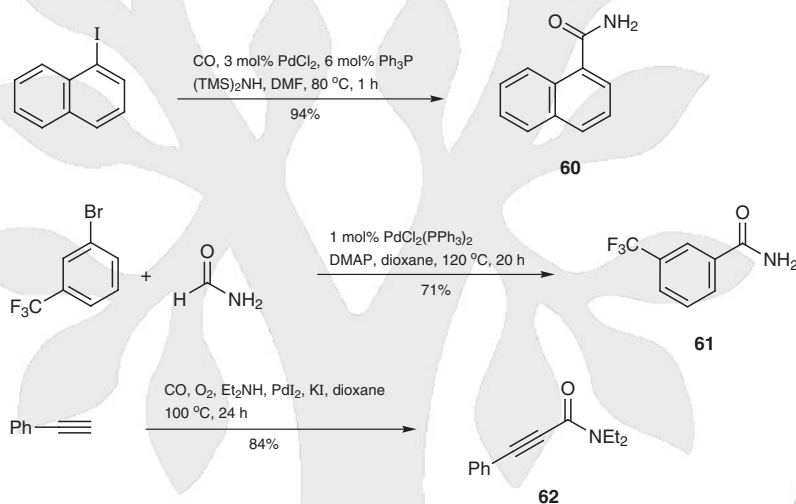
Scheme 23 Hydrocarbamylation of Alkynes^[49]

R ¹	R ²	R ³	R ⁴	Yield (%)	Ref
Ph	H	H	Bn	82	[49]
Ph	H	H	CHMePh	74	[49]
Bu	H	H	Bn	68	[49]
Bu	H	H	CHMePh	68	[49]
Pr	Pr	H	Bn	72	[49]
Pr	Pr	H	CHMePh	62	[49]

Palladium-catalyzed carbonylations of sp^2 -carbon halides and trifluoromethanesulfonates in the presence of primary or secondary amines have been used extensively to prepare N-mono- or N,N-disubstituted aromatic and α,β -unsaturated amides.^[50] The scope of this transformation has been extended to include the preparation of N-unsubstituted amides by employing either hexamethyldisilazane^[51] or formamide^[52] as an ammonia equivalent, as ammonia itself is reported not to participate in the reaction,^[51] presumably

due to its low nucleophilicity. The hexamethyldisilazane method, although lacking in atom economy, appears more general because alkenes are also described as suitable substrates. It is conducted with iodides and trifluoromethanesulfonates under much milder conditions (1–6 h at 80 °C) than the formamide method (20 h at 120 °C), but both are preparatively useful and provide good to excellent yields with a variety of substrates. The hexamethyldisilazane method generally uses 3–5 mol% palladium(II) chloride with triphenylphosphine as the ligand in dimethylformamide, as demonstrated by the synthesis of 1-naphthamide (**60**) from 1-iodonaphthalene (Scheme 24).^[51] In the formamide procedure only aryl bromides are reported as substrates and a full equivalent of an acylation catalyst is required, with 4-(dimethylamino)pyridine or imidazole being the catalysts of choice. Using this procedure, 3-(trifluoromethyl)benzamide (**61**) was obtained in 71% yield (Scheme 24).^[52] Dichlorobis(triphenylphosphine)palladium(II) is the carbonylation catalyst preferred using the method. Decomposition of the intermediate imide is thought to be the slow step of the process. In addition, palladium(II) iodide can be used in the carbonylation of phenylacetylene to obtain *N,N*-diethyl-3-phenylprop-2-ynamide (**62**) as shown in Scheme 24.^[53]

Scheme 24 Palladium-Catalyzed Carbonylations^[51–53]



1-Oct-2-enoylpyrrolidine (**51**); General Procedure:^[45]

CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

Under a N₂ atmosphere, a 100-mL, round-bottomed flask was charged with freshly distilled THF (20 mL), pyrrolidine (10 mmol), and BuLi (10 mmol) whilst the temperature was maintained at –10 °C. The resulting soln was stirred for 10 min and then cooled to –78 °C, whereupon a slow stream of CO (10 mL·min^{–1}) was bubbled through the soln at atmospheric pressure for 30 min. The resulting yellow soln was quenched with Me₃SnCl (11 mmol) either as a neat liquid or as a soln in THF (10 mL), and stirred for a further 2 h. The soln was allowed to warm to rt and added to Et₂O (40 mL). The organic layer was washed with aq KF (3 × 20 mL) and distilled H₂O (5 × 30 mL). The Et₂O layer was dried (MgSO₄) and concentrated. Purification of the oil by column chromatography or recrystallization provided 1-[(trimethylstannyl)carbonyl]pyrrolidine (**50**); yield: 58%.

A dry 100-mL, round-bottomed flask was purged with N₂ and charged with 1-iodohept-1-ene (1.0 mmol), freshly distilled THF or toluene (20 mL), and Pd(PPh₃)₄

(0.05 mmol). In a separate flask a soln of the stannane **50** (1.0 mmol) in dry THF or toluene (20 mL) was prepared under a N₂ atmosphere. This was added slowly, under N₂ at rt, to the former soln and gently refluxed until the reaction was complete (TLC). For reactions run in THF, the mixture was diluted with Et₂O (40 mL), washed with 30% aq KF and distilled H₂O (5 × 20 mL), and dried (MgSO₄). The organic layer was concentrated under reduced pressure to leave the crude products generally as oils. These were purified by flash chromatography (Kieselgel 60, petroleum ether/Et₂O). For reactions run in toluene, the toluene was removed under reduced pressure and the crude product was dissolved in Et₂O (40 mL), filtered, and then worked up as described above.

Amides 53; General Procedure:^[46]

An aldehyde (2.5 mmol), Bu₃P (2.5 mmol), Zn powder (2.5 mmol), and amide **52** were stirred and heated at 80–100 °C under N₂. After the aldehyde was consumed, the mixture was chromatographed (silica gel, petroleum ether/EtOAc 3:1) to give the product; yield: 70–86%.

(6S,12aS,13aR)-6-(Hydroxymethyl)-2,3-dimethoxy-5,6,10,11,12,12a,13,13a-octahydro-8H-isoquinolo[3,2-a]isoquinolin-8-one (**57**):^[48]

To a soln of (2S)-3,4-dihydroisoquinoline **54** (335 mg, 1.0 mmol) and allyltributylstannane (334 mg, 1.0 mmol) in CH₂Cl₂ was added penta-2,4-dienoyl chloride (0.10 mL, 1.0 mmol) dropwise at 0 °C, and the mixture was stirred at this temperature for 2 h and at rt for 5 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel) to give triene **55**; yield: 432 mg (94%). A soln of freshly prepared **55** (0.181 g, 0.395 mmol) and 2,6-di-*tert*-butylphenol (5 mg) in 1,2-dichloroethane (40 mL) was refluxed for 144 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel) to give amide **56**; yield: 164 mg (90%). To a soln of **56** (151 mg, 0.33 mmol) in THF (5 mL) was added a 1.0 M soln of TBAF in THF (0.99 mL, 0.99 mmol) at rt and the mixture was stirred for 32 h. To the mixture was slowly added H₂O (15 mL) and the mixture was stirred for 30 min. The organic materials were extracted (EtOAc) and dried (MgSO₄). The solvent was removed under reduced pressure and the residue was chromatographed (silica gel) to give **57**; yield: 73 mg (64%).

1-Naphthamide (**60**):^[51]

CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

A mixture of 1-iodonaphthalene (254 mg, 1 mmol), (TMS)₂NH (0.83 mL, 4 mmol), PdCl₂ (5 mg, 0.03 mmol), and Ph₃P (16 mg, 0.06 mmol) in dry DMF (3 mL) was purged with CO for 5 min and then stirred under a CO balloon at 80 °C for 1 h. After cooling to rt, MeOH (0.5 mL) was added and stirring was continued for 10 min. The mixture was then diluted with 1 M H₂SO₄ (20 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed successively with sat. aq NaHCO₃ (20 mL) and brine (2 × 20 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The product was purified by chromatography (silica gel, CH₂Cl₂/EtOAc 4:1); yield: 161 mg (94%).

3-(Trifluoromethyl)benzamide (**61**):^[52]

CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

An autoclave was charged with 1-bromo-3-(trifluoromethyl)benzene (8.01 g, 35.6 mmol), DMAP (4.74 g, 38.0 mmol), formamide (3.12 g, 69.1 mmol), PdCl₂(PPh₃)₂ (243 mg, 0.35 mmol), and dioxane (25 mL). It was purged with N₂ (5.92 atm, 3 ×), charged with CO

(4.93 atm), and heated to 120 °C. After 20 h, it was cooled to rt and the solvent was concentrated under reduced pressure. The residue was partitioned between CH₂Cl₂ and H₂O, and the aqueous layer was extracted with CH₂Cl₂ (2 ×). The organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, EtOAc/hexane) to afford colorless crystals; yield: 4.8 g (71%).

***N,N*-Diethyl-3-phenylprop-2-ynamide (62); General Procedure:**^[53]

CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

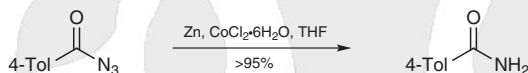
A 300-mL, stainless-steel autoclave was charged with PdI₂ (7.0 mg, 0.019 mmol), KI (32 mg, 0.19 mmol), and a soln of phenylacetylene (0.98 g, 9.6 mmol) and Et₂NH (0.70 g, 9.6 mmol) in dioxane (19 mL). The autoclave was pressurized with stirring at rt with CO (16 atm) and air (up to 20 atm) and then heated to 100 °C with stirring for 24 h. The solvent was removed under reduced pressure and the product was purified by chromatography (hexane/EtOAc 3:2); yield: 1.62 g (84%).

21.6.1.6

**Method 6:
Reduction of Aroyl Azides**

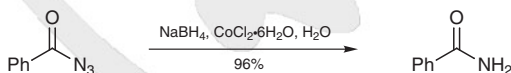
Many new reductive protocols for the preparation of benzamides from aroyl azides are available in the literature. Most of the reductions are performed using non-hydride-containing reagents, including samarium(II) iodide,^[54] iodotrimethylsilane,^[55] and systems involving iron/nickel(II) chloride,^[56] zinc/nickel(II) chloride,^[57] and zinc/cobalt(II) chloride.^[58] Some hydride-containing mixed reagents are also reported.^[59–61] A useful example of the nonhydride-containing reductions is shown in Scheme 25. The zinc/cobalt(II) chloride system tolerates a wide range of functionality, including nitro and halogen substituents.^[58]

Scheme 25 Reduction of an Aroyl Azide with Zinc and Cobalt(II) Chloride^[58]



Sulfonamides and benzamide itself were the only non-amine examples in a report on azide reductions using a cobalt(II) chloride/sodium borohydride system (Scheme 26).^[59] However, the reaction is performed in water, where at pH 7 the borohydride is more stable than in methanol, and less of an excess of the hydride is required compared to the procedures in methanol. Carboxylic acids, nitriles, alkenes, and nitro groups are all tolerated by the reagent, and the reactions are usually complete within 10 minutes or less. All of the reported yields are nearly quantitative.

Scheme 26 Reduction of an Aroyl Azide with Cobalt(II) Chloride and Sodium Borohydride^[59]

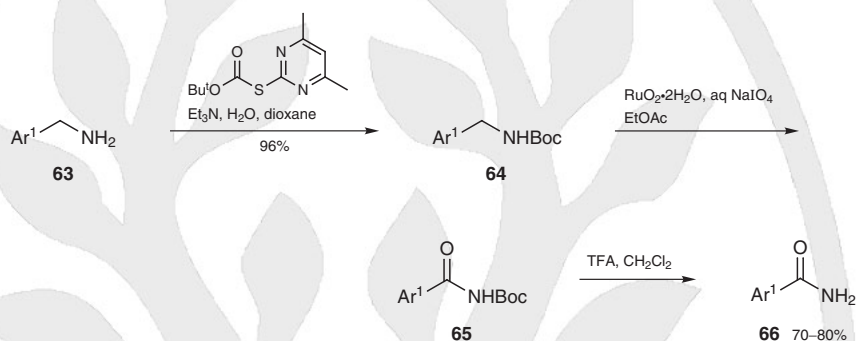


The sodium borohydride/copper sulfate system^[60] also tolerates a wide variety of functionality, but appears to be preparatively less useful, particularly on large scale, because solid sodium borohydride is added portionwise to affect the reaction. The reported yields are also lower than those given using the cobalt system. The sodium borohydride/nickel(II) chloride system does not tolerate nitro substituents.^[61]

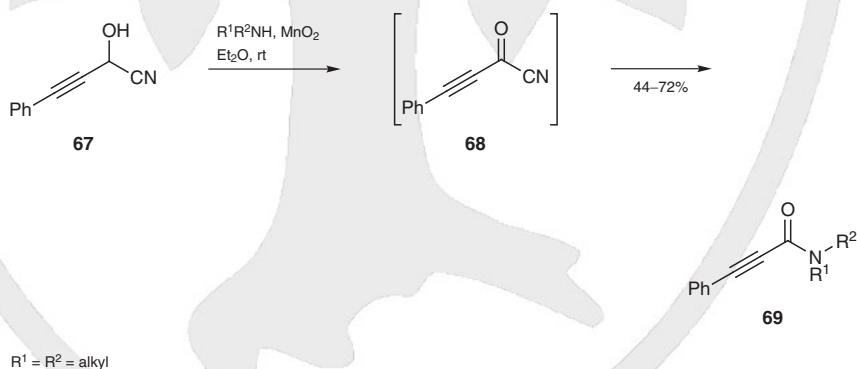
21.6.1.7

**Method 7:
Direct Amine Oxidations**

An interesting oxidative approach involving ruthenium(IV) oxide oxidation of protected amines bearing an α -methylene group is reported. This technique appears especially well suited to the preparation of benzamides. The amines **63** are converted into the protected amines **64**, which are oxidized to the mono-substituted amides **65**, followed by deprotection to give the N-unsubstituted amides **66** (Scheme 27).^[62] This three-step protocol affords benzamides in 70–80% yields and tolerates a wide range of functionality.

Scheme 27 Oxidation of Protected Amines Using Ruthenium(IV) Oxide^[62]

Propargylic cyanohydrins, such as **67**, are reported to undergo a facile oxidative amination, providing ynamides, such as **69**, in moderate to good yields (Scheme 28).^[63] Activated manganese(IV) oxide is the preferred reagent, but nickel(IV) and chromium(VI) reagents are also effective for the transformation, which is demonstrated to proceed through an unstable α -oxo species, such as **68**. N-Mono- and N,N-disubstituted ynamides are available via this methodology.

Scheme 28 Oxidation of Propargylic Cyanohydrins Using Manganese(IV) Oxide in the Presence of Amines^[63]**Amides 66; General Procedure:**^[62]

A soln of *O*-(*tert*-butyl) *S*-(4,6-dimethylpyrimidin-2-yl)thiocarbonate (60 mmol) in dioxane (30 mL) was slowly added to a soln of amine **63** (50 mmol) and Et₃N (55 mmol) in H₂O (30 mL) with stirring. After the mixture was stirred at rt for 6 h, the soln was made acidic with 6 M HCl while being cooled in an ice bath, and was then extracted with EtOAc (3 × 20 mL). The combined extracts were washed with H₂O (2 × 10 mL), dried (MgSO₄), and con-

centrated under reduced pressure to produce the crude product **64**, which was purified either by recrystallization or by vacuum distillation.

A soln of the protected amine **64** (10 mmol) in EtOAc (30 mL) was added to a mixture of $\text{RuO}_2 \cdot 2\text{H}_2\text{O}$ (150 mg, 1.13 mmol) and 10% aq NaIO_4 (80 mL). The mixture was vigorously stirred in a sealed flask at rt. After the starting material had disappeared (TLC), the layers were separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic soln was treated with *i*PrOH (2 mL) for 2–3 h and the black solids were removed by filtration. The filtrate was washed with H_2O (2×10 mL), dried (MgSO_4), and concentrated under reduced pressure to yield the crude product **65**, which was purified by recrystallization.

The protected amide **65** (20 mmol) was dissolved in a mixture of CH_2Cl_2 (15 mL) and TFA (15 mL). The mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The resulting residue was purified by recrystallization to afford the pure product **66**.

Ynamides 69; General Procedure:^[63]

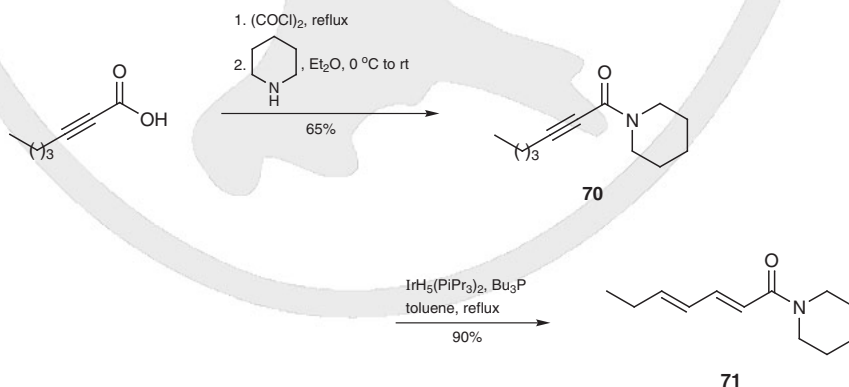
To a suspension of activated MnO_2 (8 g, 92 mmol) and amine (0.01 mol) in Et_2O (30 mL) at rt was added a soln of 2-hydroxy-4-phenylbut-3-ynenitrile (0.01 mol) in Et_2O (20 mL). The mixture was stirred at 20–25 °C for 2 h and filtered. The Et_2O soln was dried (MgSO_4) and concentrated under reduced pressure; yield: 44–72%.

21.6.1.8

Method 8: Stereoselective Isomerization of 2-Ynoic Amides

$\text{C}\equiv\text{C}$ bonds activated at the α -position with an electron-withdrawing group such as carbonyl afford dienones stereoselectively when treated with transition-metal complexes.^[64] This work has been extended to include α,β -ynoic esters and amides, e.g. **70**, which provide uniformly high yields of *E,E*-configured dienic amides, e.g. **71**, upon exposure to phosphineruthenium hydride or phosphineiridium hydride complexes in refluxing toluene (Scheme 29).^[65] The observed order of reactivity for this transformation is ketone > ester > amide. An external phosphine ligand is required to obtain synthetically useful yields. The iridium complex $[\text{IrH}_5(\text{P}i\text{Pr}_3)_2]$ has a higher catalytic activity than the ruthenium complex $[\text{RuH}_2(\text{PPh}_3)_4]$, which is attributed to the different phosphine ligands present in the catalyst. For this study, the fully characterized ynoic amides were prepared in good to excellent yield by activation of the parent acid with oxalyl chloride, followed by coupling with the appropriate amine.^[66]

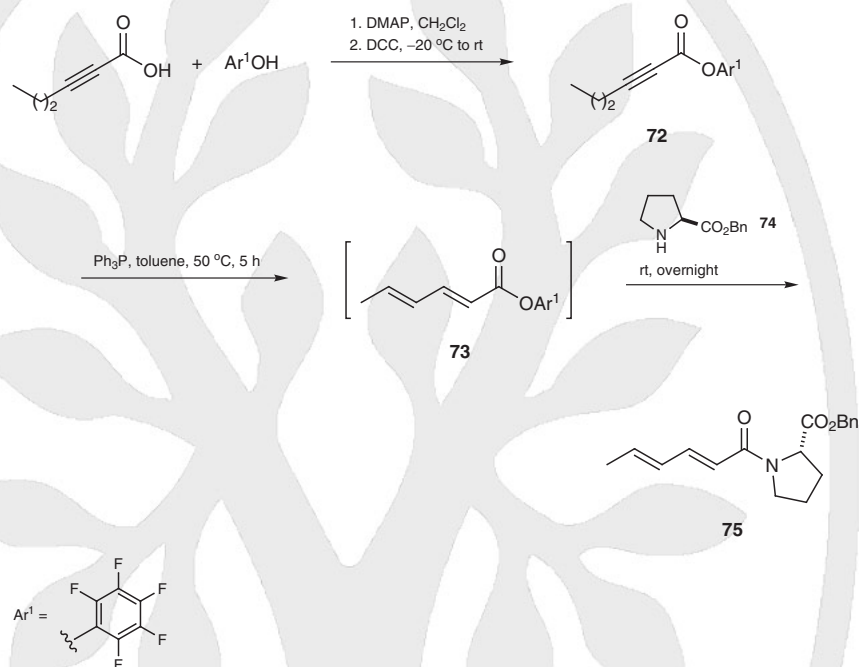
Scheme 29 A Dienic Amide from an Ynoic Amide^[65]



71

Pentafluorophenyl esters, e.g. **72**, can be isomerized to activated dienonic acids, e.g. **73**, by phosphines. This procedure allows a convenient entry into the α,β -unsaturated amides, e.g. amide **75**, by direct coupling of the activated esters with amines, e.g. **74**, in a one-pot procedure (Scheme 30).^[67] The yields of the almost exclusively formed *E,E*-configured dienic amides are high, and the esters are sufficiently reactive to allow the reactions to be conducted at room temperature, although the recommended procedure uses 5 mol% of triphenylphosphine at 50 °C.

Scheme 30 Synthesis of an *E,E*-Configured Dienic Amide from an Activated 2-Ynoic Acid Ester^[67]



1-[(2*E*,4*E*)-Hepta-2,4-dienoyl]piperidine (71**):**^[65]

A mixture of hept-2-ynoic acid (10 g, 79 mmol) and oxalyl chloride (29.6 g, 231 mmol) was refluxed for 40 min (the gas evolution ceased after 10 min). The excess oxalyl chloride was removed under reduced pressure and the residue was flash distilled to give hept-2-ynoyl chloride. A soln of piperidine (18.3 g, 215 mmol) and Et₂O (40 mL) was added dropwise to the acid chloride at 0 °C. After stirring for 1 h at rt, the mixture was diluted with Et₂O and washed with dil H₂SO₄, NaHCO₃, and H₂O. The Et₂O layer was dried (Na₂SO₄) and after removal of the solvent, the residue was distilled at reduced pressure to give the amide **70** as a colorless liquid; yield: 65%; bp 114–115 °C/0.05 Torr.

A soln of **70** (3 mmol), [IrH₅(PiPr₃)₂] (0.06 mmol), and Bu₃P (0.24 mmol) was refluxed in toluene for 40 h. After cooling and removal of the solvent, the red residue was purified by chromatography (silica gel) to give the product; yield: 90%; mp 91–92 °C.

Benzyl 1-[(2*E*,4*E*)-Hexa-2,4-dienoyl]-L-prolinate (75**); General Procedure:**^[67]

Hex-2-ynoic acid (1 mmol) and pentafluorophenol (1 mmol) were dissolved in CH₂Cl₂ (5 mL), and after addition of DMAP (0.1 mmol) the soln was cooled to –20 °C. A soln of DCC (0.1 mmol) in CH₂Cl₂ (1 mL) was added and the mixture was allowed to warm to rt overnight. After filtration and removal of the solvent, the residue was dissolved in toluene (5 mL). Ph₃P (0.05 mmol) was added and the soln was warmed to 50 °C for 5 h. After

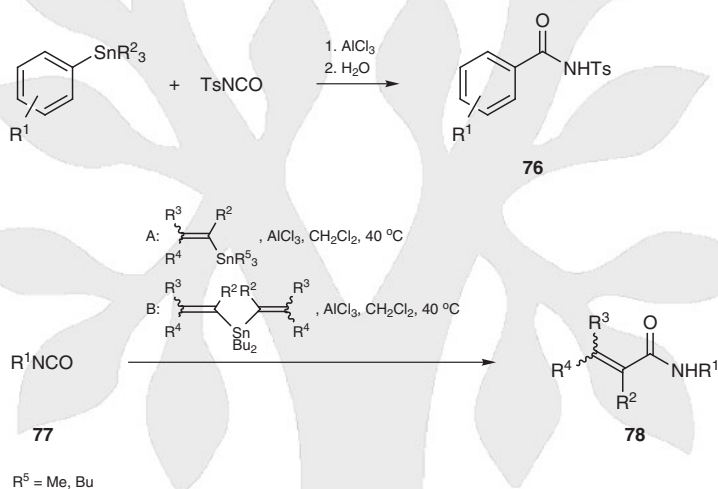
cooling to rt, the amine **74** (1.0–1.5 mmol) was added and the mixture was stirred at rt overnight. The obtained crude product was purified by flash chromatography or recrystallization.

21.6.1.9

Method 9: Electrophilic Substitution

It has long been known that Friedel–Crafts acylation of aromatic hydrocarbons with isocyanates yields *para*-substituted aryl amides.^[68] The acylation of aryltrialkylstannanes with tosyl isocyanate results in a facile *ipso* substitution leading to *N*-tosyl carboxamides **76** (Scheme 31).^[69] This work was later extended to include the reaction of isocyanates **77** with either alkenyltrialkylstannanes (Method A) or the less toxic dialkenyldibutylstannanes (Method B) affording excellent yields of α,β -unsaturated amides **78** (Scheme 31).^[70] The products, however, are obtained as *E/Z* mixtures with the amount of *E*-isomer increasing at longer reaction times. In general, though, the isomer ratios are serviceable. Similar procedures exist for terminal alkynes.^[71]

Scheme 31 α,β -Unsaturated Amides from Isocyanates and Aryl- or Vinylstannanes^[70]

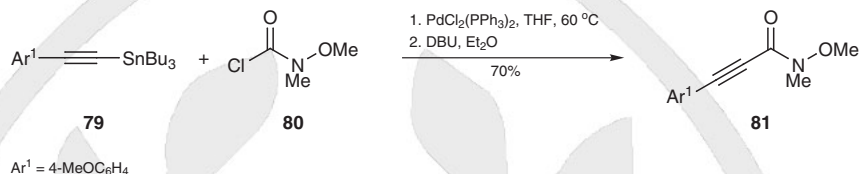


R ¹	R ²	R ³	R ⁴	Yield (%) ^a		Ref
				Method A	Method B	
Ph	H	H	Me	50	74	[70]
Ph	Me	H	Me	45	68	[70]
3-ClC ₆ H ₄	H	H	Me	74	78	[70]
3-ClC ₆ H ₄	Me	H	Me	78	73	[70]
3-ClC ₆ H ₄	Ph	H	H	78	–	[70]
Bu	H	H	Me	69	48	[70]
Bu	Me	H	Me	58	47	[70]
Bu	Ph	H	H	53	–	[70]
Ph	(CH ₂) ₅		H	–	50	[70]
3-ClC ₆ H ₄	(CH ₂) ₅		H	69	56	[70]
Bu	(CH ₂) ₅		H	53	44	[70]

^a R⁵ = Me, Bu; not specified.

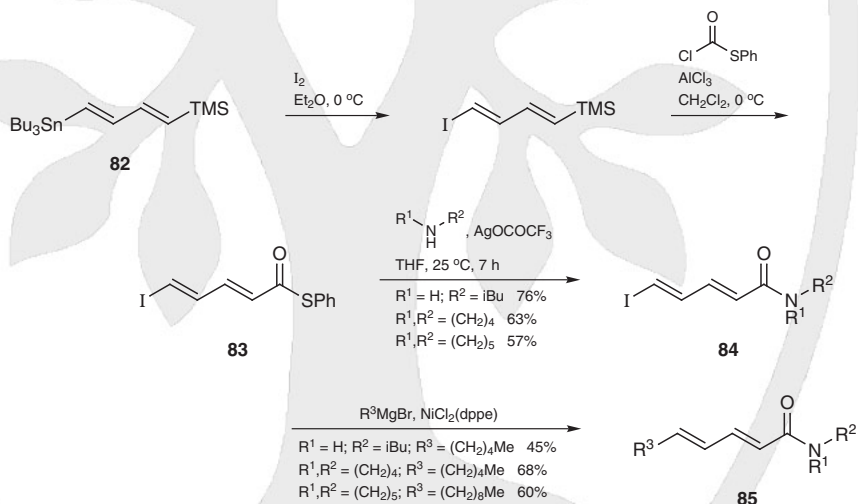
A host of unsaturated Weinreb amides have been prepared via palladium-catalyzed coupling of vinyl- and alkynylstannanes with methoxy(methyl)carbamoyl chloride (**80**). For example, the reaction of alkynylstannane **79** with **80** provides the Weinreb amide **81** in good yield (Scheme 32).^[71]

Scheme 32 Palladium-Catalyzed Coupling of Alkynylstannanes^[71]

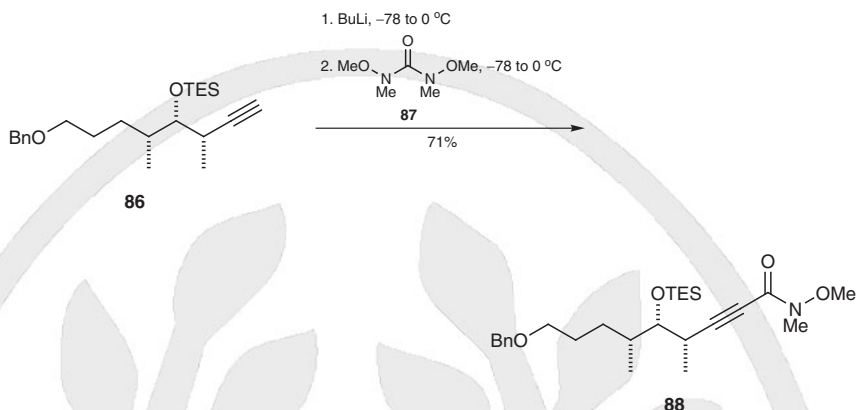
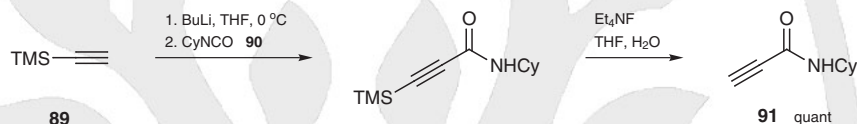


Sequential double selective electrophilic substitution of butadiene **82**,^[72] is an efficient entry into dienamides. Thus, treatment of **82** with iodine followed by electrophilic substitution of the trimethylsilyl group with *S*-phenyl chloridithiocarbonate yields the key thioester intermediate **83**. It is converted into iodo-substituted dienamides **84** by treatment with silver trifluoroacetate and the amine.^[73] Finally the alkyl group is appended in standard fashion to obtain the alkyl-substituted dienamides **85** (Scheme 33). This method has been used to prepare a series of dienamide natural products in 34–42% overall yield from **82**.

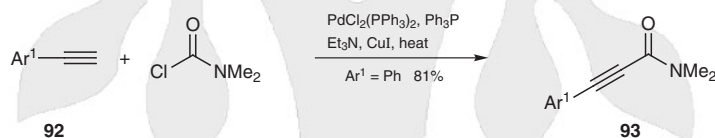
Scheme 33 Double Selective Substitution of 1-(Trimethylsilyl)-4-(tributylstannane)buta-1,3-diene^[72,73]



In a reaction with no real counterpart for the alkene series, alkynes, e.g. **86** and **89**, can be used to generate ynamides, e.g. **88** and **91**, upon reaction with butyllithium followed by activated carbonyls, e.g. amide **87** and isocyanate **90**, as shown in Schemes 34 and 35.^[74,75]

Scheme 34 Synthesis of an Alk-2-ynamide from an Acetylide and an Activated Carbonyl^[74]**Scheme 35** Synthesis of an Alk-2-ynamide from a Lithium Acetylide and an Isocyanate^[75]

Sonogashira-type couplings have also been employed successfully in the ynamide series. Thus, coupling of terminal acetylenes **92** with carbamoyl chlorides using palladium(II) chloride and copper(I) iodide catalysis in the presence of base provides acetylenic amides **93** (Scheme 36).^[76] The Grignard and lithium acetylide variants afford lower yields.

Scheme 36 Sonogashira Coupling of Terminal Acetylenes with Carbamoyl Chlorides^[76]

Amides **78**; General Procedure:^[70]

The isocyanate **77** (7.0 mmol) was added to AlCl₃ (7.0 mmol) in anhyd CH₂Cl₂ (20 mL) and the mixture was stirred for 30 min. After addition of the appropriate vinylstannane (7.0 mmol), the mixture was stirred at 40 °C for 12 h. The soln was then poured on ca. 50 g of ice and stirred for 30 min. Separation of the organic layer was then followed by extraction of the aqueous phase with CH₂Cl₂ (2 × 15 mL). When alkenyltrialkylstannane reagents were used, the combined organic layers were treated with sat. aq KF (10 mL), stirred vigorously for 3 h, and the precipitated trialkylfluorostannane was removed by filtration. The filtrate was extracted with CH₂Cl₂ (2 × 10 mL) and the combined organic layers were dried (MgSO₄) if necessary and concentrated under reduced pressure. The crude residue was purified by distillation or recrystallized from the appropriate solvent.

N-Methoxy-3-(4-methoxyphenyl)-*N*-methylprop-2-ynamide (**81**):^[71]

A mixture of PdCl₂(PPh₃)₂ (12.6 mg, 0.018 mmol), alkynylstannane **79** (238 mg, 0.6 mmol), and amide **80** (81.5 mg, 0.66 mmol) in THF (3 mL) was stirred at 60 °C for 6 h. After cooling, the solvent was removed under reduced pressure, the residue was diluted with Et₂O, and DBU (100 mg, 0.66 mmol) was added. The mixture was passed through a short pad of silica

gel to remove insoluble materials, and the eluent was subjected to preparative TLC (silica gel, EtOAc/hexane 1:3) to afford the pure product; yield: 93.4 mg (70%).

1-[(2*E*,4*E*)-5-Iodopenta-2,4-dienoyl]pyrrolidine [84, $R^1, R^2 = (CH_2)_4$]; Typical Procedure:^[73]

AgOCOCF₃ (0.20 g, 0.9 mmol) was added to a stirred soln of the thioester **83**, pyrrolidine (0.08 g, 1.1 mmol), and powdered 4-Å molecular sieves in THF (25 mL). The reaction was stirred at 25 °C for 7 h, and the solvent was concentrated under reduced pressure. The resulting solid was resuspended in Et₂O, and the mixture was filtered. The concentrated filtrate was purified by flash chromatography (petroleum ether/EtOAc 4:1) affording the title compound; yield: 63%.

(4*S*,5*S*,6*R*)-9-(Benzyloxy)-*N*-methoxy-*N*,4,5-trimethyl-5-(triethylsiloxy)non-2-ynamide (88):^[74]

To a soln of 2.1 M BuLi in hexane (5.56 mL, 11.8 mmol) in THF (20 mL) was added a soln of alkyne **86** (4.0 g, 10.8 mmol) in THF at –78 °C. The pale yellow mixture was warmed to 0 °C for 10 min, recooled to –78 °C, and the urea **87** (2.0 g, 13.5 mmol) was added. After warming to 0 °C for 1 h, the mixture was quenched with NH₄Cl, extracted with Et₂O, washed with brine, dried (MgSO₄), and concentrated. The residue was purified by chromatography (silica gel); yield: 3.6 g (71%).

***N*-Cyclohexylprop-2-ynamide (91):^[75]**

To a soln of ethynyl(trimethyl)silane (**89**; 0.98 g, 0.01 mol) in THF (20 mL) at 0 °C under N₂, was added dropwise 1.6 M BuLi in hexane (0.64 g, 0.01 mol). The mixture was stirred at 0 °C for 1 h and then a soln of the isocyanate **90** (0.01 mol) in THF (5 mL) was added dropwise. After stirring at 0 °C for 90 min, the mixture was quenched by the addition of sat. NH₄Cl. The organic phase was separated and the aqueous phase was washed with CH₂Cl₂. The organic phases were combined and the solvent was removed under reduced pressure. The residue was dissolved in THF (15 mL) containing H₂O (1 mL) and Et₄NF. After stirring at rt for 4 h, the solvent was removed under reduced pressure. The residue was filtered through a pad of silica gel using CHCl₃ to elute the pure product; yield: 1.50 g (quant).

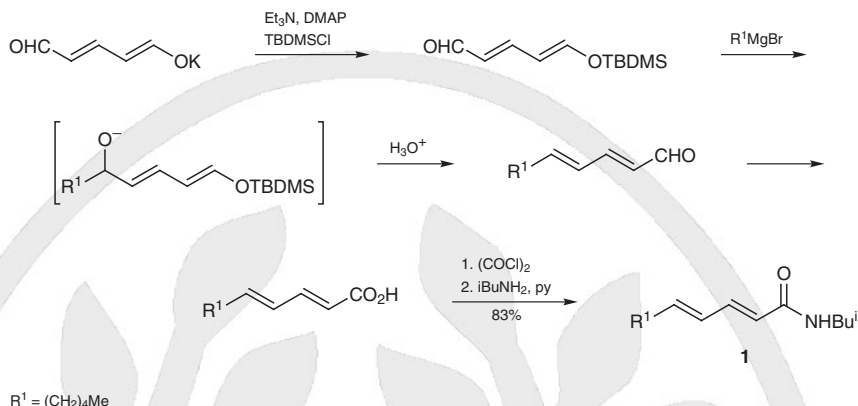
Ynamides 93; General Procedure:^[76]

Alkyne **92** (0.1 mol) and dimethylcarbamoyl chloride (10.7 g, 0.1 mol) were dissolved in Et₃N (100 mL). CuI (40 mg, 0.21 mmol), PdCl₂(PPh₃)₂ (52 mg, 0.07 mmol), and Ph₃P (52 mg, 0.2 mmol) were added and the mixture was degassed and heated under N₂ with stirring at 90 °C for 6 h. (For alkynes with boiling points of less than 90 °C, the mixture was heated to the alkyne boiling point for 4 h, then stirred at 90 °C for 2 h.) After cooling, the mixture was treated with MeOH (50 mL) and concentrated. The residue was taken up in Et₂O, washed with 5% aq HCl (2 ×), then H₂O, and dried (anhyd CaCl₂). The solvent was removed under reduced pressure and the residue was recrystallized [hexane/petroleum ether or toluene/benzene (**CAUTION: carcinogen**)] or vacuum distilled to give the products; yield: 43–81%.

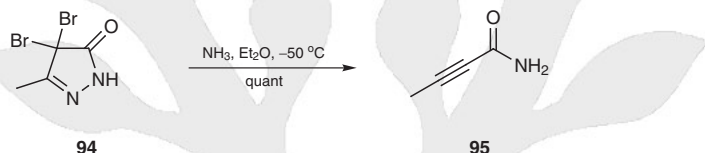
21.6.1.10

**Methods 10:
Additional Methods**

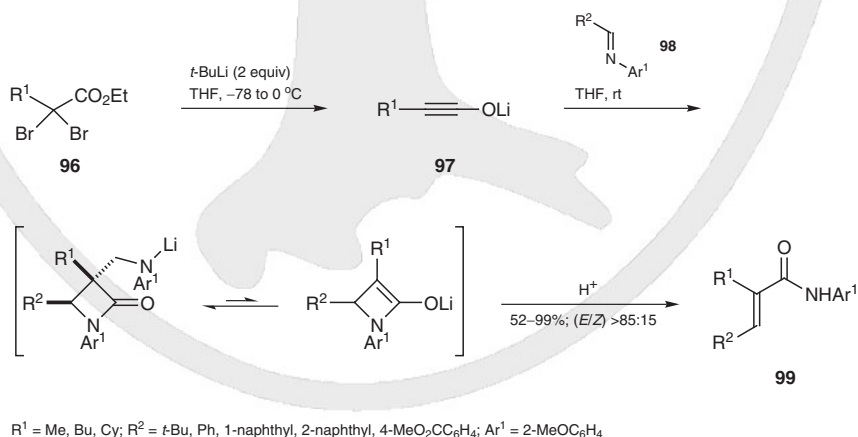
A five-carbon homologation process leading to 2*E*,4*E*-dienals from the readily available glutaconaldehyde salts^[77] has been applied to the synthesis of sarmentine and pellitorine (**1**).^[78] Overall, the process converts organometallic reagents into dienals in a one-pot alkylation/isomerization of the vinylsilane. The synthesis is completed by oxidation, activation, and amidation, which yields the natural products (Scheme 37).

Scheme 37 A 2*E*,4*E*-Dienal from Glutaconaldehyde Salts^[77,78]

Ring opening of 4,4-dibromo-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**94**) by treatment with ammonia provides but-2-ynamide (**95**) in quantitative yield (Scheme 38).^[79]

Scheme 38 Ring Opening of 4,4-Dibromo-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one^[79]

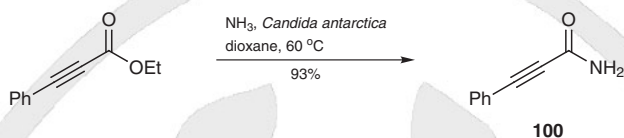
The treatment of 2,2-dibromoesters **96** with 2 equivalents of *tert*-butyllithium yields lithium ynolates **97**. Reaction of these ynolates with aldimines **98** affords α,β -unsaturated amides **99** with high *E* selectivity (Scheme 39).^[80] The 4-methoxyphenyl-substituted imines are not productive substrates, but the 2-methoxyphenyl-substituted imines, which are much better electrophiles for lithium ynolates due to chelation, provide the unsaturated amides in high yield and, in general, greater than 90:10 selectivity. The reaction is believed to proceed via a retro-Mannich pathway followed by ring opening of the β -lactam.

Scheme 39 α,β -Unsaturated Amides Via Lithium Ynolates^[80]

Immobilized lipases are widely used for the synthesis and hydrolysis of esters in both chiral and achiral manifolds. It is well known that ammonia under pressure reacts with α,β -unsaturated esters to yield the 1,4-adducts. In contrast, microbiological amidation of es-

ters with ammonia provides a convenient and high-yielding entry into primary enamides and ynamides as shown in Scheme 40 for the synthesis of 3-phenylprop-2-ynamide (**100**).^[81]

Scheme 40 Microbiological Amidation of an Ester^[81]



But-2-ynamide (95):^[79]

4,4-Dibromo-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**94**; 1.02 g, 4.0 mmol) was dissolved in Et_2O (20 mL) and cooled to -50°C . NH_3 (12.4 mmol) in Et_2O (5 mL) was added and the mixture was stirred for 4 h. H_2O (20 mL) was added, the layers were separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic phases were washed with aq NH_4Cl and dried to provide the crude product, which upon recrystallization afforded the pure product; yield: 330 mg (quant).

N-Arylalk-2-enamides 99; General Procedure:^[80]

To a soln of 2,2-dibromoester **96** (1.2 mmol) in THF (6 mL) was added a soln of *t*-BuLi in pentane (4.8 mmol) at -78°C . After 3 h, the mixture was warmed to 0°C and stirred for 0.5 h. To the thus formed soln of ynoate **97** was added a soln of imine **98** (1.0 mmol) in THF (2 mL) at rt. The resulting mixture was quenched with aq NaHCO_3 and extracted with EtOAc . The organic layer was washed with brine and dried (Na_2SO_4). After concentration, the products were isolated by chromatography (silica gel); yield: 52–99%.

3-Phenylprop-2-ynamide (100):^[81]

Ethyl 3-phenylprop-2-ynoate was dissolved in ca. 1.5% NH_3 in dioxane (10 mL) and the immobilized lipase *Candida antarctica* (480 mg) was added. The mixture was held at 60°C for 65 h and the enzyme was removed by filtration. Concentration of the filtrate provided the product and further purification was not necessary; yield: 93%.

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Product Class 7: β -Heteroatom-Substituted Alkanamides

S. Manyem and M. P. Sibi

General Introduction

Previously published information regarding this product class can be found in *Houben-Weyl*, Vol. VIII, pp 647–713 and Vol. E 5/2, pp 934–1134; however, there were no specific sections and classification in terms of β -substituents.

The skeletal features of β -heteroatom-substituted alkanamides and alkanimides are present in many of the pharmacologically and synthetically privileged structures.^[1,2] This section presents reliable methods for the construction of alkanamides with heteroatoms at the β -position. The very nature of this substitution pattern allows its construction through one of the most straightforward methods of introducing substituents at the β -position to an electron-withdrawing group, i.e. the conjugate addition (note: the term Michael addition historically refers to the addition of carbon nucleophiles). The methods similar to aldol or Claisen-type condensations also produce the product class discussed in this section; however, these methods are covered elsewhere in *Science of Synthesis*. The methods of aminohydroxylation and dihydroxylation can provide heteroatom substitution at both α - and β -centers, see *Science of Synthesis*, Vol. 1 [Compounds with Transition Metal–Carbon π -Bonds and Compounds of Groups 10–8 (Ni, Pd, Pb, Co, Rh, Ir, Fe, Ru, Os) (Section 1.9.4)] and Vol. 36 (Alcohols). The stereochemistry at the β -center can be established with reasonable control with either chiral reagents, auxiliaries, or catalysts, as is seen in many examples in this section.

These compounds are generally safe to handle in laboratory scale quantities using standard precautions. Special safety measures should be enforced for larger scale preparations and for specific products.

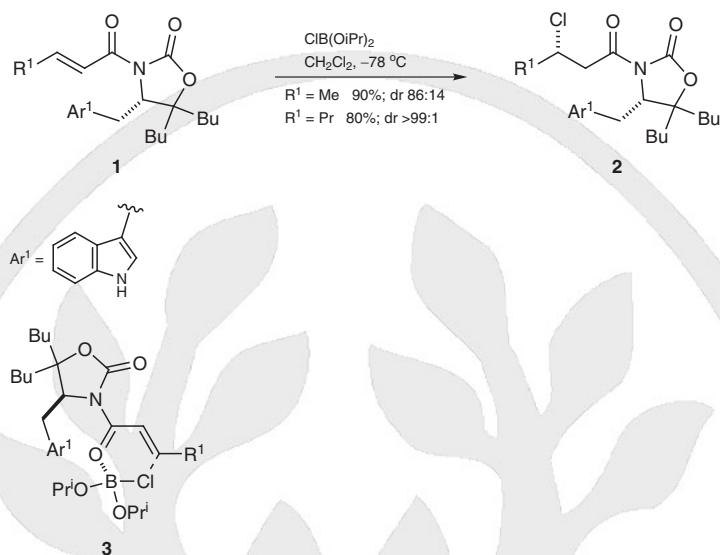
21.7.1 Product Subclass 1: β -Halogen-Substituted Alkanamides

This section describes one example of the introduction of chloride through the conjugate addition strategy. Most of the compounds in this subclass are prepared through the conventional methods of amide formation discussed in the other sections of this volume.

21.7.1.1 Synthesis of Product Subclass 1

21.7.1.1.1 Method 1: Addition of Chloride to Alkenimides

The addition of chloride to alkenimides has been achieved only through the internal transfer of the anions bound to a Lewis acid. Chloroborates [of the type $\text{ClB}(\text{OR}^1)_2$] have been used in reactions with imides **1** to give chlorides **2** (Scheme 1).^[3] This conjugate addition is chemically efficient and good diastereomeric ratios have been obtained when there are bulky alkyl substituents at the 5-position of the chiral auxiliary, the butyl group being optimal. The observed stereochemistry is explained with model **3** where the enoate group is twisted out of plane as shown. The borate reagent approaches from the face opposite to that of the indolyl moiety.

Scheme 1 1,4-Addition of Chloride to Alkenimides Using a Boron Reagent^[3]**(4S)-5,5-Dibutyl-3-[(3S)-3-chloroalkanoyl]-4-(1H-indol-3-ylmethyl)oxazolidin-2-ones 2;****General Procedure:**^[3]

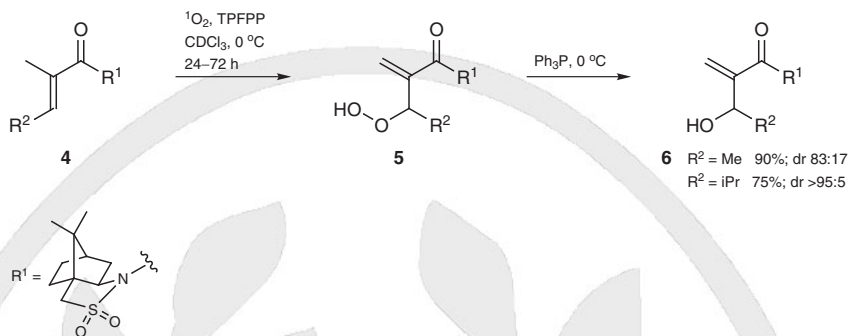
To a soln of **1** (0.5 mmol) in anhyd CH_2Cl_2 (10 mL) under an inert atmosphere at -78°C was added dropwise with stirring ClB(OiPr)_2 in anhyd CH_2Cl_2 . When the reaction was complete, H_2O and 0.05 M aq NaHCO_3 were added until the aqueous layer reached pH 7, and the two layers were separated. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified if necessary by chromatography (silica gel, cyclohexane/EtOAc 4:1).

21.7.2**Product Subclass 2:
 β -Oxygen-Substituted Alkanamides**

The products belonging to this subclass have traditionally been prepared through the aldol reaction. This factor combined with the nucleophilicity of the neutral oxygen reagents has impeded the development of conjugate addition with oxygen nucleophiles. Nevertheless, a few approaches are presented in this section.

21.7.2.1**Synthesis of Product Subclass 2****21.7.2.1.1****Method 1:
Diastereoselective Ene Reaction**

The ene reaction of alkenes with singlet oxygen installs the oxygen atom as a hydroperoxide which can be reduced to the hydroxy group using triphenylphosphine. The singlet oxygen is generated using a photosensitizer [TPFPP = 5,10,15,20-tetrakis(perfluorophenyl)porphine]. Using the Oppolzer sultam as the chiral auxiliary, an alkene **4** gives hydroperoxide **5** upon treatment with singlet oxygen, and alcohol **6** following reduction (Scheme 2).^[4] Good selectivity has been obtained for **4** ($\text{R}^2 = \text{Me}$) and an excellent diastereomeric ratio was obtained for **4** ($\text{R}^2 = \text{iPr}$).

Scheme 2 Ene Reaction of Alkenes with Singlet Oxygen^[4]

(1*S*,2*R*)-*N*-[(3*R*)-3-Hydroxy-2-methylenebutanoyl]bornane-10,2-sultam (6, $\text{R}^2 = \text{Me}$):^[4]

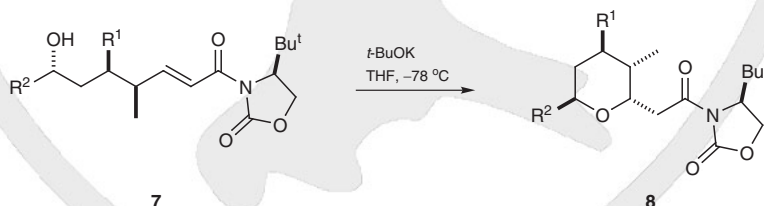
CAUTION: Hydroperoxides are potentially explosive. These substances were handled below 0 °C and immediately reduced *in situ* to the respective alcohols.

To a soln of the sultam **4** ($\text{R}^2 = \text{Me}$; 500 mg, 1.68 mmol) was added 5,10,15,20-tetrakis(per-fluorophenyl)porphine (TPFPP, ca. 2 mg) as sensitizer and the mixture was photooxygenated at 0 °C for 24 h. The hydroperoxide **5** ($\text{R}^2 = \text{Me}$) thus obtained was reduced with Ph_3P (1.00 g, 3.81 mmol) at 0 °C. After removal of the solvent, the crude product was purified by chromatography (silica gel, Et_2O /petroleum ether 2:3) to afford a 83:17 mixture of the diastereomeric alcohols *lk*-**6** and *ul*-**6** as a colorless powder; yield: 474 mg (90%).

21.7.2.1.2

Method 2: Intramolecular Conjugate Addition

The intramolecular conjugate addition of alkoxides in the 7-hydroxy-substituted enimes **7** provides an efficient route to tetrahydropyrans **8** (Scheme 3).^[5] The various substituents on the starting enime dictate the levels of selectivity obtained in this kinetically controlled conjugate addition of alkoxide. The varying levels of selectivity, dependent primarily on the γ - and δ -substituents, show that the effect of the chiral auxiliary is minimal, if present. The reactions are very fast even at -78°C and care must be taken for the substrates to be used rather quickly as they can undergo cyclization on storage.

Scheme 3 Intramolecular Addition of Alkoxides^[5]

R^1	R^2	dr	Yield (%)	Ref
H	H	5:1	70	[5]
Ph	H	10:1	65	[5]
Me	Me	>20:1	62	[5]
Me	$\text{CH}_2\text{CH}=\text{CH}_2$	>20:1	81	[5]

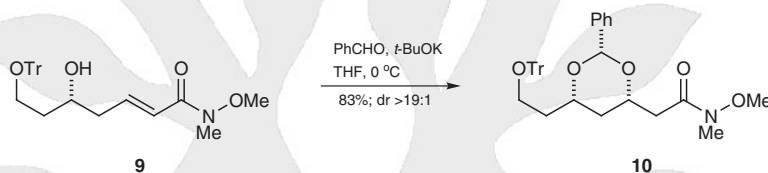
Tetrahydropyrans 8; General Procedure:^[5]

To a hydroxy-substituted enamide **7** (0.30 mmol) was added dry THF (2 mL) and *t*-BuOK (50 mg, 0.45 mmol) was subsequently added at -78°C . After stirring for 30 min at -78°C , sat. NH_4Cl soln was added and the layers were separated. The aqueous phase was extracted with Et_2O (2 \times). The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure. The crude product was purified by chromatography to obtain **8**.

21.7.2.1.3

Method 3:**Tandem Acetalization–Conjugate Addition**

A novel method for the introduction of the β -hydroxy group has been used toward the total synthesis of altohyrtin C.^[6] The addition of benzaldehyde to δ -hydroxy-substituted enamide **9** results in the formation of the acetal along with conjugate addition to provide **10** (Scheme 4). In essence, the stereochemistry at the β -carbon is established along with the protection of the 1,3-diol needed for the further steps. In this transformation, 10 mol% of potassium *tert*-butoxide is used: two additions of 5 mol% each of the potassium *tert*-butoxide is used to obtain the best yield. The reaction with a single addition of 10 mol% potassium *tert*-butoxide results in lower yields.

Scheme 4 Acetal Formation with Benzaldehyde and Intramolecular Conjugate Addition^[6]***N*-Methoxy-*N*-methyl-2-((2*S*,4*S*,6*S*)-2-phenyl-6-[2-(trityloxy)ethyl]-1,3-dioxan-4-yl)acetamide (**10**):**^[6]

To a soln of amide **9** (5.0 g, 11.23 mmol) in THF (112 mL) at 0°C was added freshly distilled PhCHO (1.25 mL, 12.35 mmol) followed by *t*-BuOK (0.051 g, 0.56 mmol). The resulting yellow soln was stirred for 15 min at 0°C . This sequence was repeated again. After 25 min, the mixture was quenched with pH 7 phosphate buffer (100 mL). The aqueous phase was separated and extracted with Et_2O (3 \times 100 mL). The combined extracts were washed with brine, dried (MgSO_4), and concentrated under reduced pressure. Purification of the residue by chromatography (silica gel, EtOAc /hexanes 3:7) gave **10** as a white solid; yield: 5.13 g (83%).

21.7.3

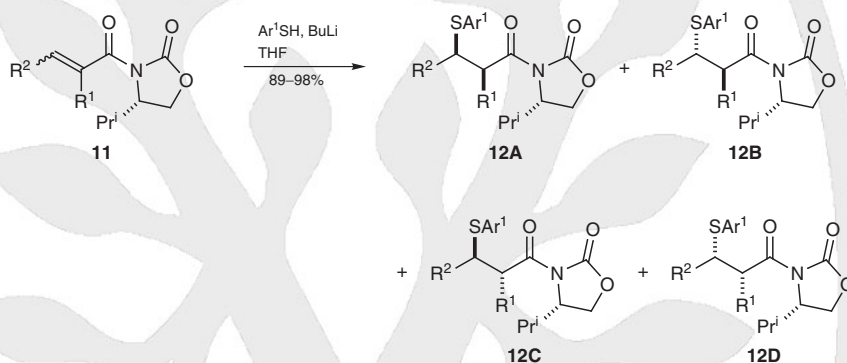
Product Subclass 3: **β -Sulfur-Substituted Alkanamides**

The β -sulfur-containing alkanamides are important compounds in pharmaceutical applications. For example, captopril, an angiotensin I-converting-enzyme (ACE) inhibitor, and (+)-*cis*-diltiazem, a vasodilating agent, both contain β -sulfanyl functionalities. The main route for their synthesis has been the conjugate addition of either metal thiolates or neutral thiols.

21.7.3.1 Synthesis of Product Subclass 3

21.7.3.1.1 Method 1:
Addition of Metal Thiolates

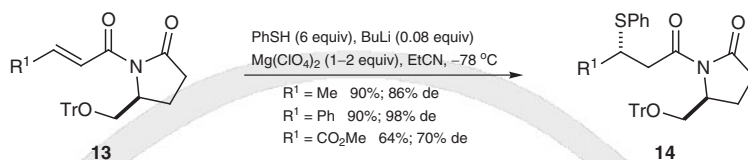
The addition of metal thiolates is one of the prevalent methods in the introduction of sulfanyl nucleophiles via conjugate addition. Lithium thiolates have been added to chiral imides **11** to obtain **12** in good yields and diastereomeric ratios (Scheme 5).^[7] The lithium arenethiolates are generated in situ using butyllithium and the diastereomeric ratios are dependent on the number of equivalents of butyllithium used. Both *E*- and *Z*-isomers of **11** have been used and the reaction is not always stereospecific especially in the presence of an ether functional group at the α -position (compare the last two examples in Scheme 5). This methodology has been used in the synthesis of various natural and bioactive products.^[8,9]

Scheme 5 Addition of Lithium Thiolates to Chiral Enimides^[7]

R ¹	R ²	Ar ¹	Config of 11	Ratio (Ar ¹ SH/Ar ¹ SLi)	Temp (°C)	Time (h)	12A ^a	12B ^a	12C	12D	Ref
Me	Me	Ph	<i>E</i>	10:0.1	–50	2	>89	<1	4	6	[7]
Me	Me	Ph	<i>Z</i>	10:0.1	–30 to –10	2	3	4	<1	>92	[7]
Me	Ph	Ph	<i>Z</i>	10:0.1	0	5	8	1	22	69	[7]
OMEM	4-MeOC ₆ H ₄	2-H ₂ NC ₆ H ₄	<i>Z</i>	1.5:3	–40	3	n.r.	n.r.	18	82	[7]
OMEM	4-MeOC ₆ H ₄	2-H ₂ NC ₆ H ₄	<i>E</i>	1.5:3	–40	3	n.r.	n.r.	30	70	[7]

^a n.r. = not reported.

The addition of lithium thiolates to other chiral imides has also been explored.^[10] 5-[(Tri-tyloxy)methyl]pyrrolidin-2-one is used as the chiral auxiliary. The ratio of the thiol to lithium thiolate has been optimized for the cinnamoyl derivative **13** (R¹ = Ph) (Scheme 6). Other β -substituents, either smaller than phenyl (R¹ = Me) or containing a donor atom (R¹ = CO₂Me) give moderate diastereomeric ratios. Magnesium perchlorate is used to force the bidentate coordination of the substrate to magnesium. In the absence of magnesium salts two different geometries for the substrate are possible and low selectivities are observed for the formation of **14**.

Scheme 6 Addition of Lithium Thiolates to Chiral Enimides^[10]

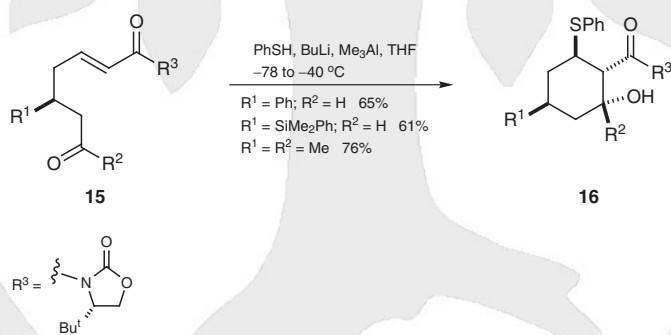
(5S)-1-[(3R)-3-Phenyl-3-(phenylsulfanyl)propanoyl]-5-[(trityloxy)methyl]pyrrolidin-2-one (14, $\text{R}^1 = \text{Ph}$); Typical Procedure:^[10]

To benzenethiol (0.3 mL, 2.9 mmol) was added 1.3 M BuLi in hexanes (0.03 mL, 0.04 mmol) at 0 °C. After the mixture was stirred for 10 min, propanenitrile (2 mL) was added. A soln of **13** ($\text{R}^1 = \text{Ph}$; 243 mg, 0.5 mmol) and $\text{Mg}(\text{ClO}_4)_2$ (112 mg, 0.5 mmol) in propanenitrile (3 mL) was added to the above soln at -78 °C. This soln was stirred at -78 °C for 1 h and then treated with sat. NH_4Cl (10 mL). The two layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 \times 20 mL). The combined extracts were washed with 10% KOH (2 \times 10 mL) and brine (2 \times 10 mL) and dried (Na_2SO_4). Concentration followed by column chromatography [benzene (**CAUTION: carcinogen**)] gave a diastereomeric mixture of **14** ($\text{R}^1 = \text{Ph}$); yield: 268 mg (90%).

21.7.3.1.1

Variation 1:**Addition of Aluminum Thiolates and Intramolecular Trapping with a Carbonyl Group**

The addition of an aluminum thiolate to a chiral imide **15** containing a terminal carbonyl group gives **16** (Scheme 7).^[11] The sequence involves an initial addition of the thiolate followed by the intramolecular trapping of the enolate by the ketone or aldehyde. The major diastereomer of **16** is shown and this was formed in excess of 90% (the other diastereomers could not be detected by NMR spectroscopy).

Scheme 7 Addition of Aluminum Thiolates to Chiral Enimides^[11]

(4S)-4-tert-Butyl-3-[[[(2R,4R,6R)-2-hydroxy-4-phenyl-6-(phenylsulfanyl)cyclohexyl]carbonyl]-oxazolidin-2-one (16, $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{H}$); Typical Procedure:^[11]

CAUTION: Neat trimethylaluminum is highly pyrophoric.

To benzenethiol (33 μL , 0.33 mmol) dissolved in THF (5 mL) was added 2.5 M BuLi in hexane (131 μL , 0.33 mmol) at 0 °C. After 5 min, 2 M Me_3Al in hexane (164 μL , 0.33 mmol) was added at 0 °C and after stirring for 1 h, the soln was cooled to -78 °C, and the 7-oxo-substituted enamide **15** ($\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{H}$; 107 mg, 0.31 mmol) in THF (1 mL) was added. After stirring for 1 h at -78 °C, the reaction was quenched with H_2O , and the aqueous phase was

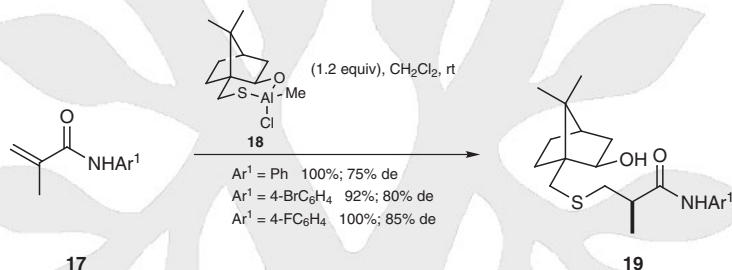
extracted twice with Et₂O. The combined organic extracts were dried (MgSO₄) and concentrated. The crude product was purified by chromatography (silica gel, Et₂O/pentane 1:1) to give a colorless solid; yield: 92 mg (65%).

21.7.3.1.1.2

Variation 2:**Addition of a Thiolate Derived from an Odorless Thiol**

Thiols have the notoriety of being malodorous depending on the molecular weight of the compound. In a diastereoselective conjugate addition of thiols, (–)-10-sulfanylisoborneol has been used as the source of a thiol group.^[12] This compound is practically odorless and, in addition, serves as a chiral thiol source. The addition of reagent **18**, an aluminate generated from dimethylaluminum chloride and (–)-10-sulfanylisoborneol, to methacrylamides **17** generates the products **19** containing an α -chiral center with good diastereomeric ratios (Scheme 8). The diastereomeric ratios are dependent on the nitrogen substituents. Electron-donating substituents on nitrogen result in lower diastereoselectivity. The products can be converted into the free thiols by treatment with boron trifluoride-diethyl ether complex followed by an excess of dodecane-1-thiol (which is also odorless).

Scheme 8 Addition of the Chloromethylaluminate Derivative of (–)-10-Sulfanylisoborneol^[12]



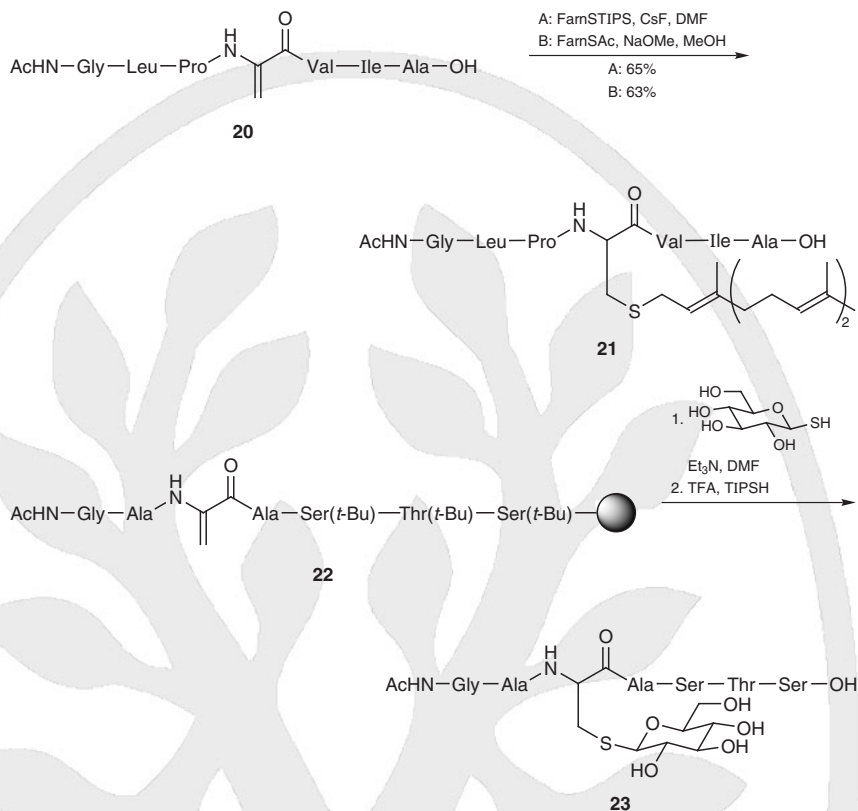
(2R)-3-[(2-Hydroxy-7,7-dimethylbicyclo[2.2.1]hept-1-yl)methylsulfanyl]-2-methyl-N-phenylpropanamide (19, Ar¹ = Ph); Typical Procedure:^[12]

To a soln of (–)-10-sulfanylisoborneol (32 mg, 0.17 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added dropwise 0.98 M Me₂AlCl in hexanes (0.17 mL, 0.17 mmol). After being stirred for 7 min, a soln of the amide **17** (Ar¹ = Ph; 0.14 mmol) in CH₂Cl₂ (1 mL) was added dropwise and the mixture was stirred at rt and monitored by TLC. The mixture was then poured into ice water, and the aqueous layer was extracted with CHCl₃ (3 × 50 mL). The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated. Chromatography of the residue (silica gel, hexane/EtOAc 20:1 to 3:1) gave **19** (Ar¹ = Ph); yield: 100%.

21.7.3.1.2

Method 2:**Addition of Sulfur Nucleophiles Derived from Thioesters or Silyl Thioethers**

A method for the in situ generation of sulfur nucleophiles under mild conditions has been reported for the synthesis of peptide conjugates (Scheme 9; Farn = farnesyl).^[13] The strategy is to prepare peptides containing dehydroalanine (Dha) and then to introduce the nucleophilic sulfur component. In this way, the *S*-farnesylated peptide **21** (from **20**) and thioglycopeptide **23** were prepared. Another key point is that with the unprotected β -thioglucose, the conjugate addition could be carried out in aqueous media in good yields. The procedure is also compatible with solid-phase synthesis as illustrated in the conversion of **22** into **23**. The overall yield in the solid-phase synthesis is 45% over nine steps.

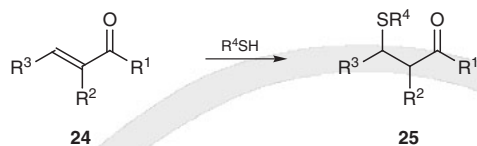
Scheme 9 Addition of In Situ Generated Thiolate Nucleophiles^[13]**Ac-Gly-Leu-Pro-Cys(Farn)-Val-Ile-Ala-OH (21):**^[13]

Method B: *S*-Farnesyl thioacetate (FarnSAC; 28 mg, 0.10 mmol) was dissolved in dry MeOH (1 mL) under an argon atmosphere. A 0.1 M NaOMe soln in MeOH (1 mL) was added, followed by a soln of Ac-Gly-Leu-Pro-Dha-Val-Ile-Ala-OH (**20**; 10 mg, 0.015 mmol) in dry MeOH (0.5 mL). The reaction was stirred at rt and was complete in 2.5 h as shown by HPLC. The reaction was quenched with 2 M HCl, and extracted with EtOAc. The organic layer was dried and concentrated. The solid residue was purified by HPLC to give the product; yield: 8.5 mg (63%).

21.7.3.1.3

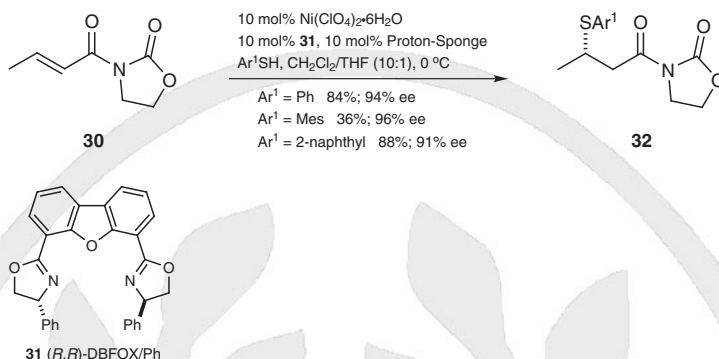
**Method 3:
Stereoselective Addition of Thiols**

The diastereoselective conjugate addition of thiols to α,β -unsaturated amides **24** has been carried out with a few chiral auxiliaries: camphorsultam unit **26**,^[14] 4-phenyloxazolidinone unit **28**,^[15] pyrazole unit **29**,^[16] and camphorpyrazolidinone unit **27**.^[17] Moderate to excellent diastereomeric ratios are obtained for the products **25** (Scheme 10). An interesting case of selectivity reversal is observed: titanium(IV) chloride (in dichloromethane) and tin(IV) chloride (in acetonitrile) give opposite diastereomers ($R^1 = \mathbf{27}$).^[17] Methacryloyl substrates give better diastereomeric ratios in the absence of Lewis acids ($R^1 = \mathbf{28}$). Similar effects are observed with template **27**.

Scheme 10 Diastereoselective Addition of Thiols to Chiral Enimides^[14–17]

R ¹	R ²	R ³	R ⁴	Lewis Acid	Solvent	Temp (°C)	Time (h)	dr	Yield (%)	Ref
 26	H	Me	2-MeO ₂ CC ₆ H ₄	TiCl ₄	CH ₂ Cl ₂	−78	3	99:1	67	[14]
	H	Ph	CH ₂ CO ₂ Et	TiCl ₄	CH ₂ Cl ₂	−78	24	87:13	72	[15]
 27	H	Me	(CH ₂) ₂ CO ₂ Et	TiCl ₄	CH ₂ Cl ₂	−30 to rt	72	>95:5 (S)	88	[17]
	H	Me	(CH ₂) ₂ CO ₂ Et	SnCl ₄	MeCN	−40	104	13:87 (R)	72	[17]
 28	Me	H	Bz	TiCl ₄	CH ₂ Cl ₂	−40 to rt	6	57:43	87	[14]
	Me	H	Bz	–	CH ₂ Cl ₂	0 to rt	6	97:3	84	[14]
 29	Me	H	Ph	–	THF	rt	1	2.5:1	100	[16]

Arenethiols have been added enantioselectively to the *N*-crotonyloxazolidinone **30** to give oxazolidinones **32** with nickel(II) and dibenzofuran-4,6-diyl-2,2'-bis(4-phenyl-4,5-dihydrooxazole) (DBFOX/Ph **31**, Scheme 11).^[18] The enantiomeric excesses are dependent on the reaction conditions. The use of a proton sponge [1,8-bis(dimethylamino)naphthalene, 10 mol%] helps in achieving high selectivity. The hydrated complexes are necessary in these reactions; the use of anhydrous complexes leads to racemic material.

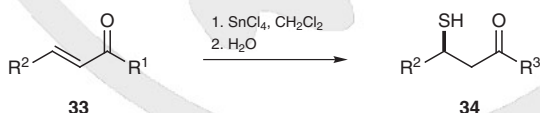
Scheme 11 Nickel(II)-Catalyzed Addition of Thiols^[18]**3-[(3S)-3-(Phenylsulfanyl)butanoyl]oxazolidin-2-one (32, $\text{Ar}^1 = \text{Ph}$); Typical Procedure:**^[18]

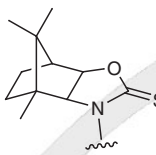
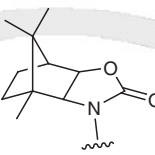
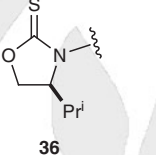
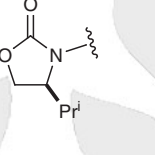
A mixture of **31** (32.5 mg, 0.071 mmol) and $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (25.9 mg, 0.071 mmol) in anhyd THF (4.4 mL) was stirred at rt for 30 min to give a greenish-blue soln. Oxazolidinone **30** (0.109 g, 0.709 mmol) and benzenethiol (0.878 mL, 0.780 mmol) were added in this order. The reaction was stirred at rt and monitored by TLC. After completion, sat. aq NH_4Cl was added and the mixture was extracted with THF (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed (silica gel, hexane/EtOAc 3:1) to give adduct **32** ($\text{R}^1 = \text{Ph}$); yield: 0.188 g (100%). The ee was determined using HPLC [Daicel OD-H, hexane/*i*PrOH 9:1; 1.0 mL·min⁻¹, $t_{\text{R}} = 36$ (R) and 44 min (S)].

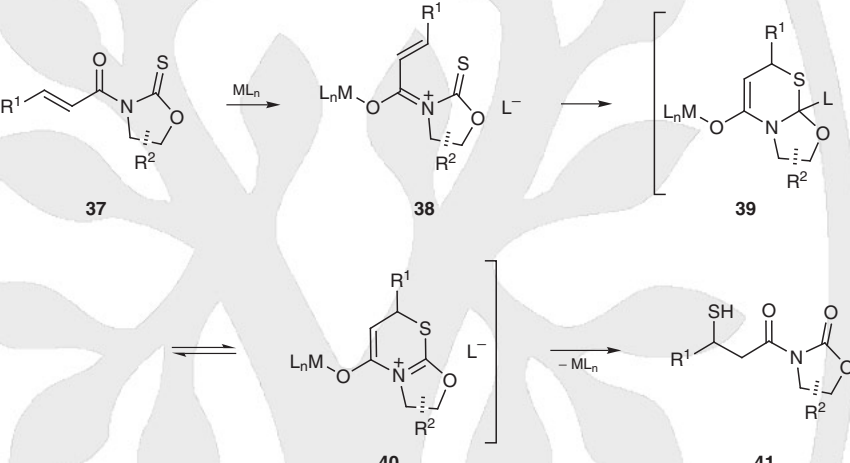
21.7.3.1.4

Method 4:**Intramolecular Transfer of Sulfur from a Thiocarbonyl Group**

The indirect introduction of an unprotected sulfanyl group has been made possible with the novel transfer of the sulfur atom from an oxazolidinethione chiral auxiliary to the β -position of an enamide (Scheme 12).^[19] Treatment of enamides **33** with 2 equivalents of tin(IV) chloride at low temperature results in the transfer of sulfur to give products **34**. The reaction is chemically efficient and provides high diastereoselectivities. In the case of β -aryl substrates, the reactions are warmed to room temperature for completion. The chiral auxiliary **35** is more effective in stereoinduction compared to **36** (compare the results for $\text{R}^2 = 4\text{-ClC}_6\text{H}_4$). This reaction is proposed to occur as shown in Scheme 12; complexation of the Lewis acid to **37** generates the eneiminidinium species **38**, which undergoes electrocyclic rearrangement to **39**. Hydrolysis of its tautomeric structure **40** provides the β -sulfanyl compound **41**. Once this transformation has been achieved, the chiral auxiliary is cleaved and can be converted into the oxazolidinethione using Lawesson's reagent.

Scheme 12 Transfer of Sulfur from Oxazolidinethiones^[19]

R ¹	R ²	R ³	Temp (°C)	dr	Yield (%)	Ref
 35	Me	 36	-78	>98:2	84	[19]
	Et		-78	>98:2	83	[19]
	4-ClC ₆ H ₄		-78 to rt	93:7	76	[19]
 37	Me	 38	-78	>98:2	72	[19]
	4-ClC ₆ H ₄		-78 to rt	75:25	70	[19]



(4S)-4-Isopropyl-3-[(3R)-3-sulfanylbutanoyl]oxazolidin-2-one [34, R² = Me; R³ = (4S)-4-Isopropyl-2-oxooxazolidin-3-yl].^[19]

To a soln of *N*-enoyl oxazolidine-2-thione **33** (R¹ = **36**, R² = Me; 1 mmol) in CH₂Cl₂ (20 mL) cooled to -78 °C was added SnCl₄ (0.24 mL, 2 mmol) dropwise via syringe. After 5–10 min of stirring at that temperature, a yellowish solid appeared, which redissolved on stirring (for R² = aryl, the mixture was warmed to rt), and the mixture was stirred at that temperature until completion. The mixture was then poured into a sat. soln of NaHCO₃ (100 mL). The layers were separated and the organic phase was washed with brine, dried (MgSO₄), and concentrated. The crude material was purified further by chromatography; yield: 72%.

**21.7.4 Product Subclass 4:
 β -Selenium-Substituted Alkanamides**

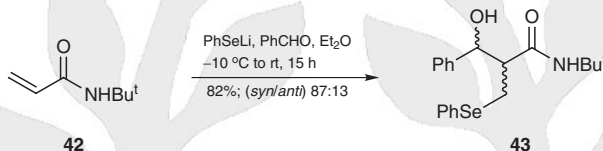
Selenium nucleophiles are often introduced in a 1,4-fashion, only to be oxidized and eliminated to the corresponding alkenes. Many products are normally not isolated or purified.

21.7.4.1 Synthesis of Product Subclass 4

21.7.4.1.1 Method 1:
Addition of Lithium Selenolates

The most common procedure for the addition of selenium is the use of lithium organoselenides. The addition of lithium phenylselenide to the amide **42** is followed by trapping of the metal enolate with benzaldehyde to give aldol-type products **43** in high *syn* selectivity (Scheme 13).^[20] These adducts can undergo oxidation followed by elimination of the selenoxide to provide the corresponding Baylis–Hilman adducts.

Scheme 13 Addition of a Lithium Selenolate to an Enamide^[20]



N-tert-Butyl-3-hydroxy-3-phenyl-2-[(phenylselenanyl)methyl]propanamide (*syn*-43**); Typical Procedure:**^[20]

A 1.5 M soln of MeLi in Et₂O (2 mL, 3 mmol) was added to a soln of diphenyl diselenide (0.937 g, 3 mmol) in Et₂O (4 mL) at rt until the yellow color of the diselenide disappeared. The colorless soln was maintained at rt for 1 h and then cooled to -10 °C. PhCHO (0.350 g, 3.3 mmol) was added and the resulting mixture was stirred for 15 min. To this mixture, N-(tert-butyl)acrylamide (**42**; 0.256 g, 2.01 mmol) was added and the mixture was allowed to warm to rt for 15 h. 1 M aq HCl (10 mL) was added and the resulting mixture was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, hexane then hexane/EtOAc 5:1) to give the product as a white solid; yield: 0.641 g (82%); mp 113 °C.

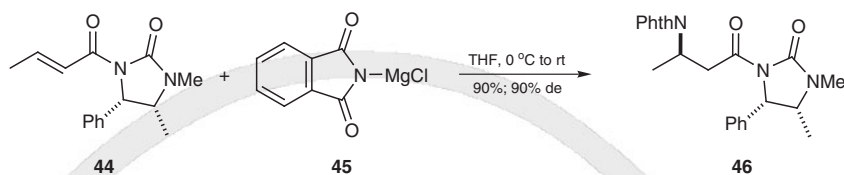
21.7.5 **Product Subclass 5:**
 β -Nitrogen-Substituted Alkanamides

This subclass of compounds is far the most well-known among the β -heteroatom-substituted alkanamides, and rightly so. β -Amino acids, higher homologues of α -amino acids, have been studied intensely due to their biological importance.^[2] Many approaches to this subclass have been investigated. The most common approach is the conjugate addition of a nitrogen nucleophile. Various sources of nitrogen nucleophiles are available depending on the synthetic needs.

21.7.5.1 Synthesis of Product Subclass 5

21.7.5.1.1 Method 1:
Addition of Phthalimide Salts to Alkenimides

Phthalimides can be easily converted into the free amines. Although phthalimide itself is a poor nucleophile, its metal salts can add in a 1,4-manner to alkenimides, e.g. **44**. Of the few metal salts explored, the magnesium salt **45** is the most effective in providing good yields and diastereomeric ratios, e.g. of product **46** (Scheme 14).^[21] The procedure requires 5 equivalents of the chloromagnesium phthalimide.

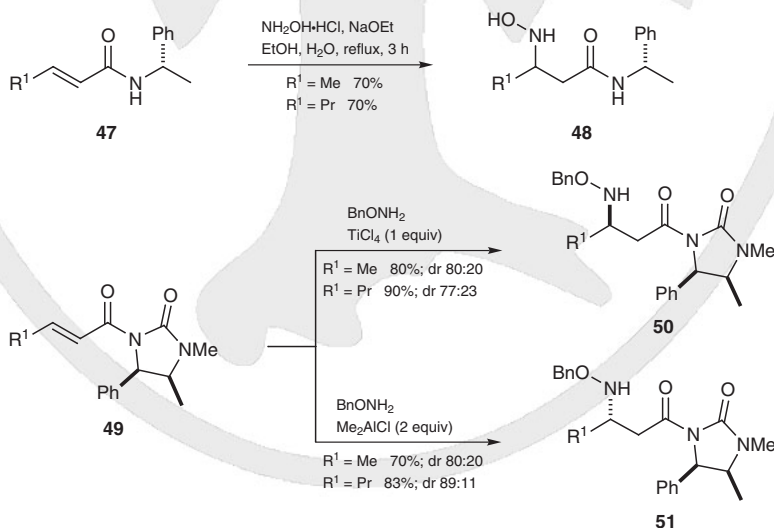
Scheme 14 1,4-Addition of a Phthalimide Salt to an Imide^[21]**(4R,5S)-3,4-Dimethyl-5-phenyl-1-[(3R)-3-phthalimidobutanoyl]imidazolidin-2-one (46):**^[21]

To a soln of phthalimide (0.56 g, 3.8 mmol) in dry THF was added 2 M iPrMgCl in THF (1.9 mL, 3.8 mmol) at 0 °C. The mixture was stirred for 30 min and then a soln of **44** (0.2 g, 0.76 mmol) in dry THF was added slowly. The mixture was warmed to rt, and stirred for 24 h. After completion, the reaction was quenched with 1 M aq NaHCO₃ and the aqueous phase was extracted with CH₂Cl₂. The organic layers were washed with H₂O, brine, dried (MgSO₄), and concentrated under reduced pressure. The dr was determined from the ¹H NMR spectrum and HPLC analysis. The isomers were purified by chromatography (silica gel) and recrystallized (EtOH); yield: 90%.

21.7.5.1.2

Method 2:**Addition of Hydroxylamines to Alkenamides**

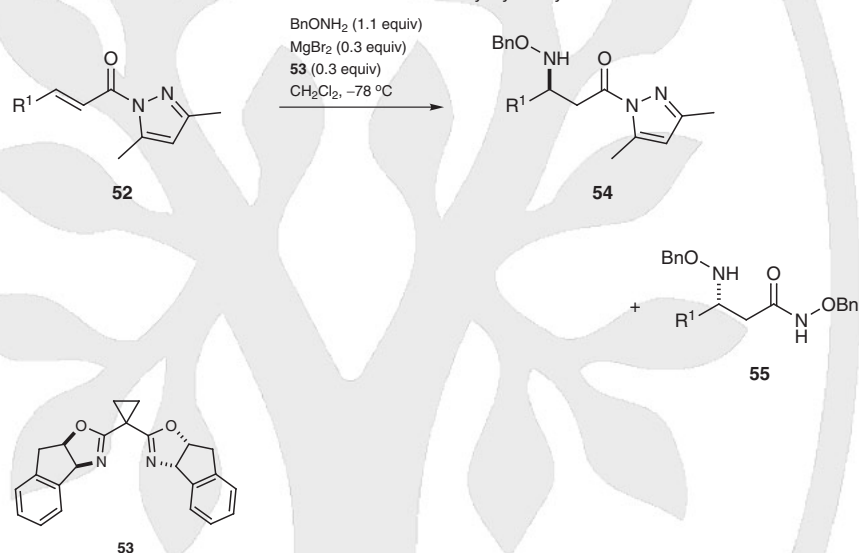
The second class of nitrogen nucleophiles is the hydroxylamines. Both free and protected hydroxylamines have been used in conjugate addition reactions. In one example the free hydroxylamine is generated from the hydrochloride salt by treatment with 1 equivalent of sodium ethoxide (**47** → **48**, Scheme 15).^[22] Addition of *O*-benzylhydroxylamine to imides is initially achieved in a diastereoselective fashion.^[23] Imides **49**, derived from (4*S*,5*R*)-4-methyl-5-phenylimidazolidin-2-one chiral auxiliary, give good diastereomeric ratios with Lewis acids; titanium(IV) chloride and dimethylaluminum chloride give opposite diastereomers **50** and **51**, respectively. The products can be converted into either β -amino acids or aziridines.

Scheme 15 Diastereoselective Addition of Hydroxylamines^[22,23]

Chiral Lewis acids can catalyze the addition of *O*-benzylhydroxylamine to α,β -unsaturated imides and there have been various attempts to devise an efficient system. A chiral Lewis

acid has been developed from titanium and 1,1'-bi-2-naphthol (BINOL).^[24] This catalyst is efficient in providing high conversions but only moderate enantiomeric excess (42%) has been achieved. A conjugate addition of *O*-benzylhydroxylamine with pyrazole templates **52** has been achieved in good yields and enantiomeric excesses up to 95% (Scheme 16).^[25] A combination of magnesium bromide–diethyl ether complex and chiral ligand **53** is essential for the high enantiomeric excesses. The high enantiomeric excesses obtained in these reactions with **52** ($R^1 = \text{Me}$) are a consequence of selective addition of amine (ca. 9:1) followed by a kinetic resolution wherein the minor enantiomer of **54** ($R^1 = \text{Me}$) is preferentially converted into **55** ($R^1 = \text{Me}$) by amidolysis. Substoichiometric amounts of the Lewis acid (30 mol%) give better yields (due to less amidolysis) and only a slight decrease in enantiomeric excess. Alkyl substituents at the β -position lead to good conversions whereas aryl substituents exhibit poor reactivity. The use of lanthanide Lewis acids such as yttrium(III) trifluoromethanesulfonate leads to the reversal of product stereochemistry.

Scheme 16 Enantioselective Addition of *O*-Benzylhydroxylamine^[25]



R^1	ee (%)	Yield (%) of 54	Ref
Me	92 (<i>R</i>)	80	[25]
Me ^a	59 (<i>S</i>)	67	[25]
Bn	95 (<i>R</i>)	80	[25]
iPr	87 (<i>R</i>)	76	[25]
Ph	83	24 ^b	[25]

^a 1 equiv $\text{Y}(\text{OTf})_3$ used.

^b 60% recovered starting material.

3-(Benzyloxyamino)-1-(3,5-dimethylpyrazol-1-yl)alkan-1-ones **54**; General Procedure:^[25]

Under an inert atmosphere, a mixture of $\text{MgBr}_2 \cdot \text{OEt}_2$ (0.05 mmol) and bis(dihydrooxazole) **53** (0.05 mmol) in CH_2Cl_2 (1 mL) was stirred at rt for 30 min. A 3,5-dimethylpyrazole derivative **52** (0.167 mmol) in CH_2Cl_2 (1 mL) was added, and the mixture was stirred for an additional 30 min at rt. The soln was cooled to -78°C and BnONH_2 (0.184 mmol) in CH_2Cl_2 (1 mL) was added. The reaction was monitored by TLC and, when complete, was quenched with H_2O and extracted with CH_2Cl_2 ($3 \times 10 \text{ mL}$). The combined organics were dried

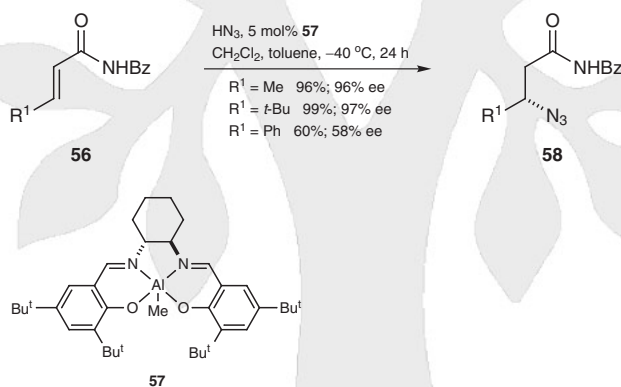
(MgSO₄) and concentrated. The product **54** was purified by chromatography. The ee was determined by HPLC. Note: If the reactions are incomplete, it is important to fully quench the Lewis acid, and care should be taken to remove solvents at low temperature during workup. This will ensure that addition at a higher temperature does not occur, which may lead to lowered selectivity.

21.7.5.1.3

Method 3:**Chiral Lewis Acid Catalyzed Addition of Hydrazoic Acid to Alkenimides**

The addition of azides to alkenamides generates the corresponding β -azido compounds. Hydrazoic acid can either be used directly or generated in situ with azidotrimethylsilane in the presence of a protic acid. These useful intermediates can be elaborated further to the corresponding β -amino acids by reduction or can be used as dipoles in dipolar cycloadditions. The additions are catalyzed either by Lewis acids through substrate activation or by Lewis bases.

The enantioselective addition of azide to acyclic imides **56** can be catalyzed using aluminum–salen catalysts.^[26] The catalysis occurs through the initial formation of an aluminum–azide bond. The stable form of the catalyst, **57**, could be used to generate the active catalyst. Various alkyl substituents in the β -position of **56** are tolerated and the enantiomeric excesses are above 95% for the β -azido products **58** (Scheme 17). β -Aryl substitution is not amenable for catalysis due to lower reactivities (the data in Scheme 17 for R¹ = Ph correspond to 10 mol% catalyst and reaction at room temperature).

Scheme 17 Aluminum–Salen Catalyzed Addition of Hydrazoic Acid^[26]***N*-[(3*R*)-3-Azidobutanoyl]benzamide (**58**, R¹ = Me); Typical Procedure.^[26]**

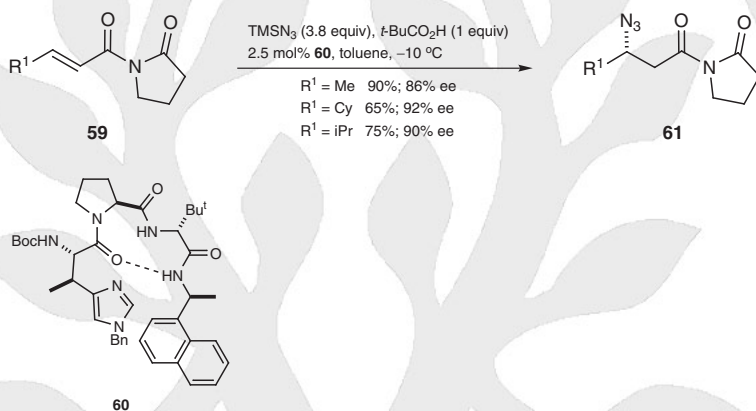
CAUTION: Hydrazoic acid is violently explosive and of variable sensitivity in concentrated or pure states. It is a severe irritant with effects on the central nervous system.

To a soln of imide **56** (R¹ = Me; 0.5 mmol) and salen complex (*S,S*)-**57** (5 mol%, 0.025 mmol) in CH₂Cl₂ (1 mL) at -78°C was added 3.3 M hydrazoic acid in toluene (1.0 mL, 3.3 mmol). The reaction was warmed to -40°C and allowed to stir for 24 h. The reaction was then warmed to rt and flushed with N₂ to remove the remaining hydrazoic acid. The crude mixture was diluted with CH₂Cl₂ and purified by chromatography (EtOAc/CH₂Cl₂ 1:19) to give pure product; yield: 96%; 96% ee (chiral HPLC).

21.7.5.1.3.1

Variation 1:**Enantioselective Addition of Azidotrimethylsilane to Alkenimides Using a Peptide Catalyst**

Various Lewis bases have been found to catalyze the addition of azidotrimethylsilane to alkenimides; *N*-methylimidazole and 1,8-diazabicyclo[5.4.0]undec-7-ene are effective in such conjugate additions.^[27] As an asymmetric variant, the peptide catalyst **60** with a β -turn structure has been developed (Scheme 18).^[28,29] This catalyst can be used in very low loadings (2.5 mol%) to give the azido amides **61**. Substrates bearing a pyrrolidinone unit, e.g. **59**, are better due to their higher reactivity and good enantiomeric excesses are obtained for various β -substituents.

Scheme 18 1,4-Addition of Azidotrimethylsilane Catalyzed by a Peptide^[29]**1-[3-Azidoalkanoyl]pyrrolidin-2-ones **61**; General Procedure:^[29]**

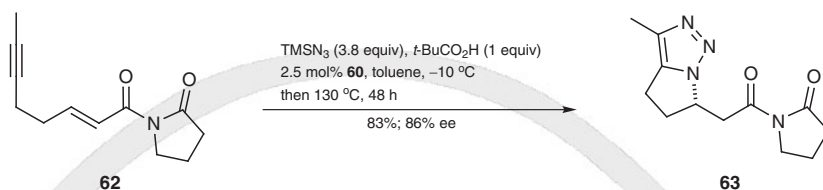
CAUTION: Contact of metal azides with acids liberates the highly toxic and explosive hydrazoic acid. Most of the azides described in this section are stable up to 130°C as determined by the differential scanning calorimetry (DSC) data.

To a soln of an unsaturated imide **59** (0.141 mmol) in anhyd toluene (0.35 mL) was added TMSN_3 (0.536 mmol) at -10°C . $t\text{-BuCO}_2\text{H}$ (0.141 mmol) was then added in one portion, followed by peptide catalyst **60** (2.5 mg, 2.5 mol%). The reaction vial was capped, and the mixture was stirred at -10°C for 24 h. The mixture was then diluted with Et_2O (10 mL) and washed with sat. NaHCO_3 soln (10 mL), followed by a 10% aq citric acid soln (10 mL). The organic layer was dried (Na_2SO_4) and concentrated to give the desired azido imide **61**.

21.7.5.1.3.2

Variation 2:**Addition of Azide to Alkenimides Followed by Intramolecular Cycloaddition**

The recognition of azides as efficient dipoles has allowed the further manipulation of products, e.g. **61** (see Scheme 18), through either intra- or intermolecular cycloadditions. In both cases, there is no erosion of enantiomeric excesses of the product azides. An example of intramolecular addition is shown in Scheme 19.^[29] Using **62**, which can undergo both conjugate addition by azide followed by cyclization with the alkyne moiety, triazole **63** is obtained in good yield.

Scheme 19 1,4-Addition of Azidotrimethylsilane and Intramolecular Cycloaddition^[29]

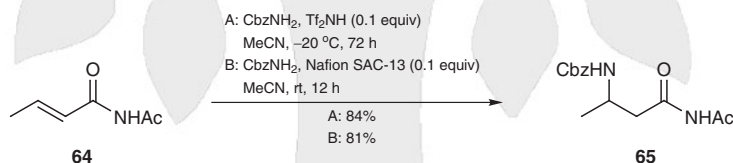
1-((6*S*)-3-Methyl-5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazol-6-yl)acetyl}pyrrolidin-2-one (63**); Typical Procedure:^[29]**

The procedure is similar to that given in Section 21.7.5.1.3.1 (for the preparation of the azide) followed by the cyclization as follows: A soln of the azide (0.14 mmol) in anhyd toluene (4.0 mL) was heated at 130 °C for 48 h in a sealed tube. The mixture was cooled to rt and concentrated to an oil, which was purified by chromatography (silica gel, MeOH/CH₂Cl₂ 1:49) to afford triazole **63**; yield: 83%; 86% ee.

21.7.5.1.4

Method 4:
Addition of Carbamates to Alkenamides

Carbamates can be added in a 1,4-fashion to alkenamide **64** using weakly acidic Brønsted acids through the activation of the alkenamide to give carbamic esters **65**. Various acids have been studied and it has been found that bis(trifluoromethylsulfonyl)amine is the most efficient (Scheme 20; Method A).^[30] Based on this discovery, it has been demonstrated that the reaction can be carried out with a solid catalyst.^[31] Amberlyst-15 and Nafion can be used whereas Dowex-50W is not effective. The catalyst can be used repeatedly although regeneration of the catalyst with aqueous acid is necessary after each reaction run.

Scheme 20 1,4-Addition of a Carbamate^[30,31]

Benzyl 3-(Acetylamino)-1-methyl-3-oxopropylcarbamate (65**):^[31]**

Method B: To a soln of amide **64** (0.25 mmol) and CbzNH₂ (0.375 mmol, 1.5 equiv) dissolved in MeCN (0.5 mL) was added Nafion SAC-13 (15 mg, 60 g·mol⁻¹) at rt and the mixture was stirred. The reaction was monitored by TLC and the product was isolated by preparative TLC after filtering off the catalyst; yield: 81%.

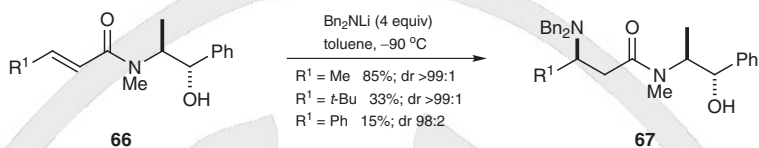
21.7.5.1.5

Method 5:
Addition of Lithium Amides

Amine nucleophiles are unreactive although they can be deprotonated and the corresponding lithium amides give conjugate addition products in good yield. The addition of lithium dibenzylamide to alkenamides **66** derived from (+)-pseudoephedrine and alkenoic acids has been reported (Scheme 21).^[32] The additions are efficient but the isolated yields are low at -78 °C. Hence the lower temperature of -90 °C has been adopted. The products **67** are obtained in high diastereomeric ratios for most cases. In the case of the cinnamoyl derivative, the diastereoselectivity is increased in the presence of 4 equivalent

lents of *N,N,N',N'*-tetramethylethylenediamine (data not shown) but this effect was not consistent with other amides.

Scheme 21 1,4-Addition of a Lithium Amide^[32]



(3*R*)-3-(Dibenzylamino)-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylbutanamide (67, $\text{R}^1 = \text{Me}$); Typical Procedure:^[32]

A soln of BuLi (4 mmol) was added to a soln of dibenzylamine (4 mmol) in anhyd toluene (40 mL) at -78°C and the mixture was stirred at this temperature for 30 min. This mixture was slowly added within 2 h to a cooled (-90°C) soln of the imide **66** ($\text{R}^1 = \text{Me}$; 1 mmol) in anhyd toluene (20 mL). The reaction was stirred further for 20 h at -90°C after which it was quenched with a sat. NH_4Cl soln (30 mL). The mixture was extracted with CH_2Cl_2 (3×15 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc 1:1) of the residue gave the amide **67** ($\text{R}^1 = \text{Me}$); yield: 85%; dr >99:1.

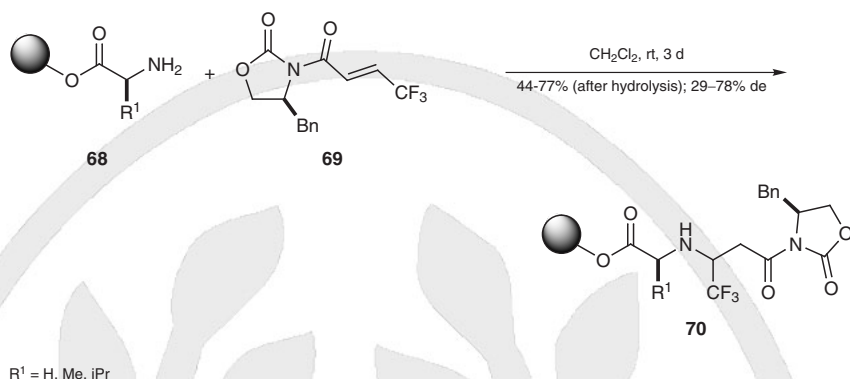
21.7.5.1.6

Method 6:

Addition of Amino Esters to Alkenamides

The most straightforward route for the β -amino-substituted alkenamides would be the addition of ammonia. This has been achieved under high-pressure conditions in the presence of ammonium chloride.^[33] Amines provide convenient handles for the introduction of the nitrogen substituent through conjugate addition. They are not strong nucleophiles and require activation of the substrates either through Lewis acids or through strong electron-withdrawing β -substituents.

Addition of α -amino esters to the β -(trifluoromethyl)acrylamide derivative **69** has been achieved.^[34] The amino esters can be used either as the free base or as their hydrochloride salts in the presence of 2,4,6-collidine. A solid-phase methodology using the same protocol has also been developed (shown in Scheme 22 with H-Val-Wang resin **68**).^[35] Typically, the reactions take 16–88 hours. The products **70** are obtained in good chemical yields and 29–78% de depending on the amino acid substituents. The diastereomeric excesses in these reactions are practically determined by the steric bulk on the amine reagent. This is due to the *s-trans* conformation adopted by the alkenamide **69** in the absence of Lewis acids. A similar procedure has also been extended to the solid- and solution-phase syntheses of hydroxamates.^[36]

Scheme 22 1,4-Addition of Amino Esters^[35]

Resin-Bound (2*S*)-2-((3-((4*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-3-oxo-1-(trifluoromethyl)propyl)amino)-3-methylbutanoic Acid (70**, $\text{R}^1 = \text{iPr}$):^[35]**

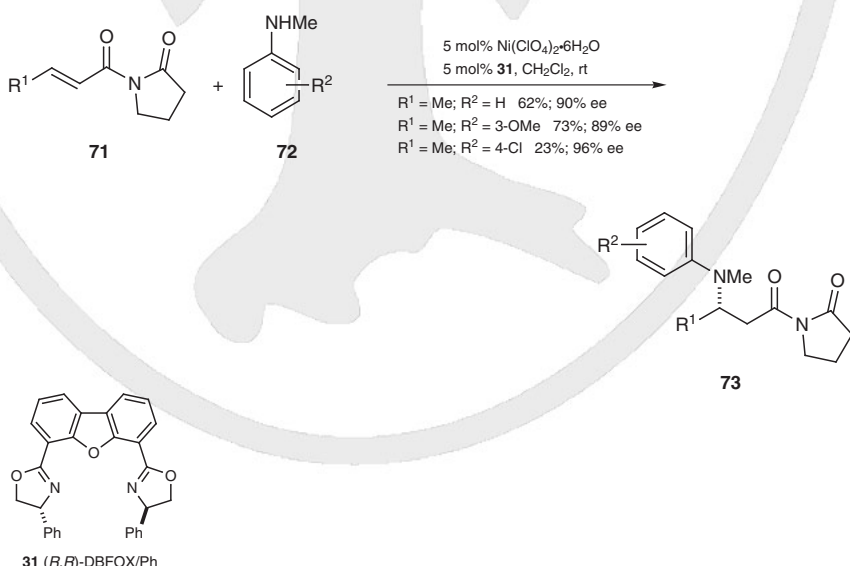
A solid-phase reaction vessel was charged with H-Val-Wang resin **68** ($1.15 \text{ mmol} \cdot \text{g}^{-1}$; 1.15 equiv), oxazolidinone **69** (1.03 g, 3.45 equiv), and CH_2Cl_2 (24.4 mL) and shaken for 3 d at rt. The soln was drained and concentrated under reduced pressure to recover the unreacted reagent **69** (0.69 g, 2.30 equiv). The resin **70** was washed with CH_2Cl_2 (5–20 mL) and dried under reduced pressure to a constant weight.

21.7.5.1.6.1

Variation 1:

Enantioselective Addition of Amines Using Dibenzofuran-4,6-diyl-2,2'-bis(4-phenyl-4,5-dihydrooxazole)–Nickel Catalyst

A successful example of the addition of amines is through chiral Lewis acid catalysis. Various *N*-methylanilines **72** could be added to alkenimide **71** ($\text{R}^1 = \text{Me}$) with good yield and moderate to good enantiomeric excess (Scheme 23).^[37] Low yields of **73** are obtained for **71** ($\text{R}^1 = \text{Pr}$) and low enantiomeric excesses are obtained for the imide **71** ($\text{R}^1 = \text{CO}_2\text{Et}$).

Scheme 23 Addition of Aromatic Amines Using a Chiral Nickel–Lewis Acid Catalyst^[37]

1-((3*S*)-3-[Methyl(phenyl)amino]butanoyl)pyrrolidin-2-one (73, $R^1 = \text{Me}$; $R^2 = \text{H}$); Typical Procedure:^[37]

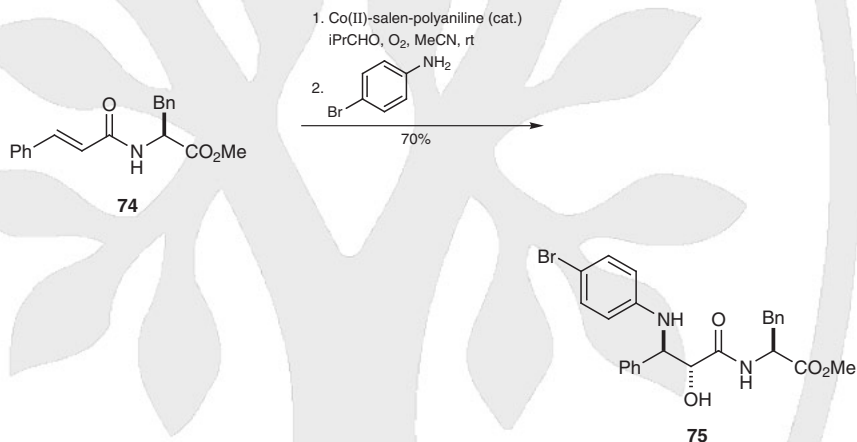
To a flame-dried Schlenk tube was added $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (4.6 mg, 0.0125 mmol) and (*R,R*)-**31** (6.4 mg, 1.1 equiv). The mixture was dried under reduced pressure for 1 h and freshly distilled anhyd CH_2Cl_2 (1.0 mL) was added and the soln was stirred for 0.5 h. Subsequently, **71** ($R^1 = \text{Me}$; 38.8 mg, 0.25 mmol) and **72** ($R^2 = \text{H}$; 135 mL, 1.25 mmol) were added and the mixture was stirred for 40 h. The product was obtained by flash chromatography (silica gel, Et_2O /pentane 1:1) as a pale yellow oil; yield: 62%; 90% ee (HPLC).

21.7.5.1.6.2

Variation 2:**Aminohydroxylation Using a Solid-Supported Catalyst**

The ring opening of epoxides with amines provides amino alcohols. A one-pot procedure of epoxidation of alkenamide **74** followed by ring opening with aniline nucleophiles, e.g. to give **75**, using solid-phase catalysts has been demonstrated (Scheme 24).^[38] Various alkenamides have been evaluated as starting materials and the yields in this reaction range from 30–70%. The catalyst can be reused without much loss in activity.

Scheme 24 Epoxidation–Ring Opening of Amides Catalyzed by a Polyaniline-Supported Cobalt(II)–Salen Complex^[38]



Methyl N-((2*R*,3*R*)-3-[(4-Bromophenyl)amino]-2-hydroxy-3-phenylpropanoyl)-L-phenylalaninate (75):^[38]

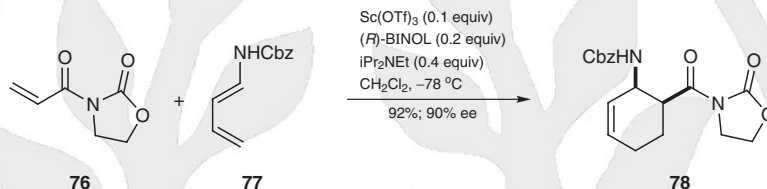
The polyaniline-supported Co(II)–salen was prepared by stirring an equal mixture (w/w) of polyemeraldine base and Co(II)–salen in MeCN at rt for 36 h. Filtration and washing with MeCN and AcOH followed by drying at 110–120 °C afforded a crystalline solid which showed the presence of cobalt in UV–vis spectra. To amide **74** (5 mmol) dissolved in MeCN (25 mL), 2-methylpropanal (15 mmol) was added and the resulting mixture was stirred in the presence of the supported catalyst (~25 mg) under an O_2 atmosphere (balloon) at rt (16–22 h). The reaction was monitored by TLC and when complete, the oxygen balloon was removed and 4-bromoaniline (5 mmol) and Co catalyst (~10 mg) were added to the mixture. After stirring for an additional 6 to 8 h at 25 °C the solvent was removed to yield a residue which was washed with CCl_4 (**CAUTION: toxic**) to afford the corresponding β -phenylisoserine derivative as a solid in >90% purity (HPLC); yield: 70%.

21.7.5.1.7

Method 7:**Diels–Alder Reaction of Buta-1,3-dien-1-amines with Alkenimides**

An interesting and simple approach for cyclic β -amino-substituted imides is through the enantioselective Diels–Alder reaction. It has been shown that the chiral Lewis acid obtained from scandium(III) trifluoromethanesulfonate and 1,1'-binaphthol (BINOL) catalyzes the reaction of **76** with the dienamine **77** generating the cyclic amino compound **78** in 92% yield and 90% ee (Scheme 25).^[39]

Scheme 25 Diels–Alder Reaction of a Buta-1,3-dien-1-amine with an Acryloyloxazolidinone^[39]



Benzyl (1*R*,6*S*)-6-[(2-Oxooxazolidin-3-yl)carbonyl]cyclohex-2-en-1-ylcarbamate (78**):**^[39]

To a mixture of $\text{Sc}(\text{OTf})_3$ (443 mg, 0.9 mmol), (R) -BINOL (309 mg, 1.08 mmol), and 4-Å molecular sieves (1.17 g) was added $i\text{Pr}_2\text{NEt}$ (279 mg, 376 mL, 2.16 mmol) in CH_2Cl_2 (18 mL) at -78°C . The mixture was stirred for 30 min at -78°C , and then a soln of **76** (1.27 g, 9.00 mmol) in CH_2Cl_2 (9 mL) and a soln of **77** (1.83 g, 9.00 mmol) in CH_2Cl_2 (9 mL) were added successively via a cannula. The resulting soln was slowly warmed to 0°C , stirred at 0°C for 24 h, quenched with H_2O , and extracted with EtOAc . The combined organic layers were washed with brine, dried (MgSO_4), and concentrated. The residue was purified by chromatography (silica gel, EtOAc /hexanes 3:7) to give **78** as a white crystalline solid; yield: 2.85 g (92%); 90% ee. The *exo*-product was also obtained as a colorless oil; yield: 174 mg (6%).

21.7.6

Product Subclass 6: **β -Phosphorus-Substituted Alkanamides**

β -Phosphorus-containing alkanamides are of some pharmacological importance due to their similarity to γ -aminobutyric acid (GABA). The phosphinyl compounds are often used as ligands for organometallic processes. Hence, there has been some interest in their synthesis. Phosphorus nucleophiles can be classified according to their oxidation states and their interconversion is possible.

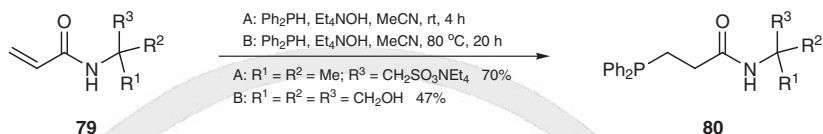
21.7.6.1

Synthesis of Product Subclass 6

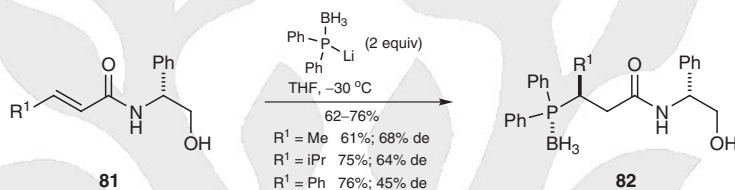
21.7.6.1.1

Method 1:**Addition of Secondary Phosphines**

The addition of secondary phosphines by itself to α,β -unsaturated systems is cumbersome due to the problems associated with polymerization and the oxidation of the phosphine. The reaction can be accelerated in the presence of an aqueous base. When acrylamides **79** with different substituents at the amide nitrogen are subjected to diphenylphosphine in acetonitrile with a catalytic amount of tetraethylammonium hydroxide, products **80** are obtained in reasonable yields (Scheme 26).^[40] Di-*tert*-butylphenol was added in small amounts to prevent polymerization.

Scheme 26 Addition of Secondary Phosphines^[40]

The addition can also be carried out with a borane–phosphine complex; the nucleophilicity lost due to complexation can be regained through deprotonation with butyllithium. An example of the diastereoselective addition in the preparation of β -phosphorus-substituted alkanamides **82** is shown in Scheme 27.^[41] Moderate diastereoselectivities for the phosphine addition have been achieved using amides derived from chiral amino alcohols. Optimal diastereomeric ratios are obtained with alkenamides **81** when a chiral auxiliary derived from phenylglycinol is used.

Scheme 27 Addition of Borane–Phosphine Complex^[41]

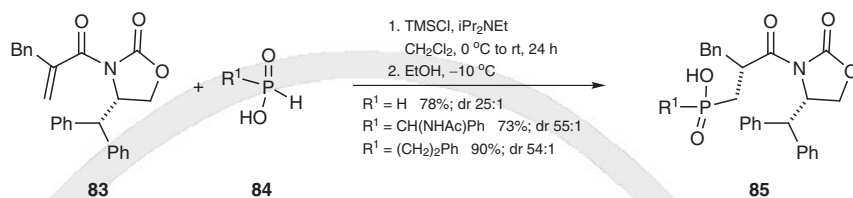
[(1R)-3-[(R)-2-Hydroxy-1-phenylethyl]amino]-3-oxo-1-phenylpropyl]diphenylphosphine-Borane Complex (82, $\text{R}^1 = \text{Ph}$); Typical Procedure:^[41]

A soln of BuLi in hexane (1.6 mL, 2.5 mmol) was added to a soln of $\text{Ph}_2\text{PH} \cdot \text{BH}_3$ (0.5 g, 2.5 mmol) in anhyd THF (10 mL) under an inert atmosphere at –78 °C and the soln was warmed to 0 °C. After stirring for 0.5 h at 0 °C, the mixture was cooled to –30 °C, and a soln of amide **81** ($\text{R}^1 = \text{Ph}$; 0.33 g, 1.25 mmol) in THF (1 mL) was added. After stirring for 4 h at –30 °C, H_2O (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (MgSO_4) and concentrated. The crude mixture was purified by chromatography (silica gel, EtOAc/cyclohexane 1:1); yield: 0.44 g (76%); 45% de.

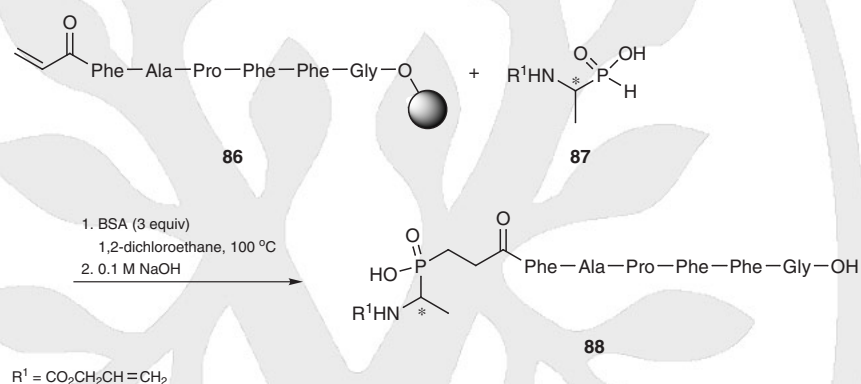
21.7.6.1.2

Method 2:
Addition of Phosphinates

β -Phosphinyl amides have attracted attention due to the structural feature they provide to the peptide backbone and hence are used to make peptidomimetics. Phosphinates, containing a P–H bond, can be activated for 1,4-addition using a base. The nucleophile can be generated in situ using either *N,O*-bis(trimethylsilyl)acetamide or a combination of chlorotrimethylsilane and an amine base. This methodology has been shown to be viable for the addition of phosphinates **84** to **83**, derived from (*S*)-(-)-4-(diphenylmethyl)oxazolidin-2-one (Sibi auxiliary), with excellent diastereomeric ratios (Scheme 28).^[42] After the addition of the phosphinate, the silyl enolate generated is diastereoselectively quenched at –10 °C with ethanol. Lowering the temperature further does not enhance the diastereomeric ratios and leads to lower yields of the products **85**.

Scheme 28 Addition of Phosphinates^[42]

This methodology has been applied to solid-phase peptide synthesis in one example.^[43] The combination of phosphinic acid **87** and 3 equivalents of *N,O*-bis(trimethylsilyl)acetamide at elevated temperature with the acrylamide **86** followed by the cleavage of the resin gives the corresponding phosphinic peptide **88** in a quantitative conversion (Scheme 29). The product on the resin was taken through further to synthesize a phosphinic undecapeptide.

Scheme 29 1,4-Addition of a Phosphate in Solid-Phase Peptide Synthesis^[43]

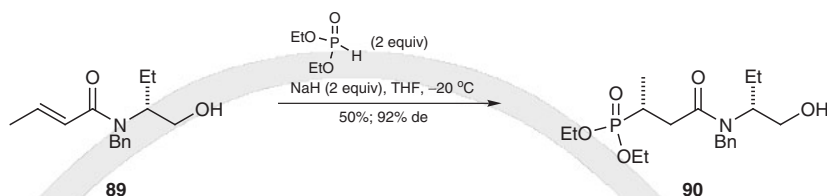
(2*R*)-2-Benzyl-3-[(4*S*)-4-(diphenylmethyl)-2-oxooxazolidin-3-yl]-3-oxopropylphosphinic Acid (85**, $\text{R}^1 = \text{H}$); Typical Procedure:**^[42]

To a soln of phosphinic acid (0.081 mmol) in anhyd CH_2Cl_2 (1 mL) at 0°C were added $i\text{Pr}_2\text{NEt}$ (63 μL , 0.36 mmol) and TMSCl (46 μL , 2.43 mmol) under an argon atmosphere. The mixture was stirred for 3 h at rt and cooled to 0°C and (*S*)-3-(2-benzylprop-2-enoyl)-4-(diphenylmethyl)oxazolidin-2-one (**83**; 0.097 mmol) was added dropwise. The soln was warmed up slowly and stirred at rt for 24 h. The mixture was again cooled to -10°C and quenched with abs EtOH (66 μL). After 30 min, the product was isolated and the ratio of the two isomers was determined with LC/MS and HPLC; yield: 78%; dr 25:1.

21.7.6.1.3

Method 3:**Diastereoselective Addition of a Phosphite**

The addition of diethyl phosphite to various unsaturated amides has been carried out in a diastereoselective fashion.^[44] The phosphite reagent is activated with sodium hydride. In most of the cases low yields are obtained due to possible side reactions. The diastereomeric ratios obtained are excellent for the preparation of **90** using **89** containing a chiral auxiliary (Scheme 30).

Scheme 30 Addition of Diethyl Phosphite^[44]

(3*R*)-*N*-Benzyl-3-(diethoxyphosphoryl)-*N*-[(1*R*)-1-(hydroxymethyl)propyl]butanamide (90); Typical Procedure:^[44]

Diethyl phosphite (1.16 mL, 9 mmol) was added to a suspension of NaH (0.206 g, 8.6 mmol) in anhyd THF (20 mL) under argon at rt. After stirring for 1 h, the mixture was cooled to -20 °C and a soln of amide **89** (1 g, 4.29 mmol) in THF (10 mL) was added. After stirring for 5 h at -20 °C, H₂O (10 mL) was added and the product was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (MgSO₄) and concentrated. The crude mixture was purified by chromatography (silica gel, EtOAc/MeOH 19:1) to provide **90**; yield: 0.8 g (50%).

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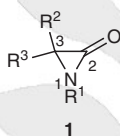
Product Class 8: α -Lactams

R. V. Hoffman and V. Cesare

General Introduction

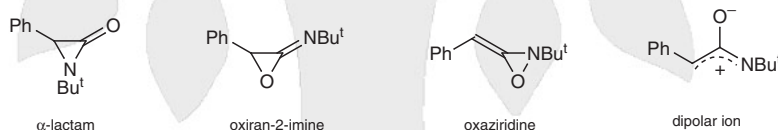
α -Lactams (aziridinones) **1** are three-membered rings containing the amide function. Their general structure and the numbering of the ring atoms are shown in Scheme 1. Although α -lactams are not naturally occurring compounds, at the time of writing over 50 stable ones, including five spiro- and two bis- α -lactams, have been synthesized, isolated, and characterized.

Scheme 1 General Structure of an α -Lactam^[1]



The first preparation of a stable α -lactam, 1-*tert*-butyl-3-phenylaziridinone, was reported^[1] in 1962. Its structure was distinguished from several alternative possibilities, which include the oxiranimine, the oxaziridine, and the open dipolar structure shown in Scheme 2.^[2] This report was soon followed by the preparation and various reactions of a second α -lactam, 1-*tert*-butyl-3,3-dimethylaziridinone.^[3]

Scheme 2 Structural Isomers of α -Lactams^[2]



The first comprehensive review^[4] of the chemistry of α -lactams was published in 1968 and this still serves as the foundation for the study of α -lactams. Further information on this product class can be found in *Houben-Weyl*, Vol. E 16b, pp 1–19 and in other reviews from 1980^[5] and 2000.^[6] Significant progress has been made concerning the synthesis of α -lactams and a better understanding of their chemical reactivity has been achieved.

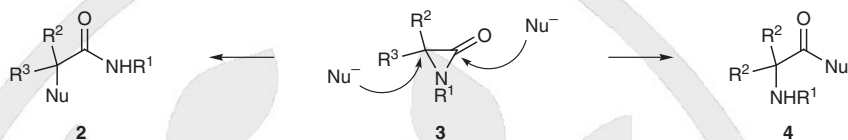
Nearly all α -lactams which are sufficiently stable to be isolated are solids with melting points over 100 °C. The one notable exception is 1,3-di-*tert*-butylaziridinone,^[7] which is a liquid. All α -lactams are readily soluble in polar and nonpolar organic solvents.

Some α -lactams are remarkably stable and can be stored indefinitely at room temperature in a desiccator. Recrystallization from boiling heptane or the use of chromatography (silica gel with a hexane/ethyl acetate mobile phase) has been used to purify several of the stable α -lactams without decomposition.

The α -lactam ring contains about 41 kcal·mol^{−1} of strain energy^[8,9] which profoundly influences its structure and reactivity. Both crystallographically^[10] and computationally determined^[8,9] structures reveal that α -lactams contain a C=O bond and a pyramidal nitrogen. This suggests that, unlike normal lactams, there is in α -lactams minimal resonance interaction between the nitrogen lone pair and the carbonyl group.

A second consequence of the ring strain in α -lactams **3** is their facile reaction with nucleophiles to yield ring-opened products. Nucleophiles add readily to either the C2 carbonyl carbon or to the C3 ring carbon to produce 2-aminocarboxylic acid derivatives **4** or 2-substituted amides **2**, respectively (Scheme 3).

Scheme 3 Products of C2 and C3 Attack of Nucleophiles on α -Lactams^[4]



α -Lactams can be easily identified by their characteristic infrared carbonyl stretching frequency at approximately $1840\text{--}1850\text{ cm}^{-1}$. If one of the substituents at C3 is hydrogen and the other substituent is an alkyl group, then the signal for the C3 proton in the ^1H NMR spectrum is between δ 2.00 and 2.75. The ^{13}C NMR signal for the carbonyl carbon is between δ 154 and 162. A characteristic ion appearing in the electron ionization mass spectrum^[11] of α -lactams is the $\text{M}^+ - 28$ ion due to the loss of carbon monoxide.

α -Lactams can be broadly classified as isolable or nonisolable depending on their stability, and particularly their resistance to nucleophilic attack. The stability of α -lactams has been shown to be dependent on the substituents at the N1 and C3 positions.^[4] All stable, isolable α -lactams have a tertiary alkyl group (e.g., *tert*-butyl, 1-adamantyl, or trityl) attached to nitrogen. In addition, there should be at least one tertiary alkyl or aryl group at C3. Three α -lactams^[3,12,13] with a geminal dimethyl group at C3 have been synthesized, but these are relatively less stable. Bulky groups at the N1 and C3 positions appear to shield the ring from nucleophilic attack, thus kinetically stabilizing these α -lactams toward nucleophilic ring opening.^[4,7,14] There has been one report of a stable α -lactam, 1-(2-adamantyl)-3-(1-adamantyl)aziridinone,^[15] which contains a bulky secondary alkyl group attached to the ring nitrogen, but all attempts to duplicate this synthesis have been unsuccessful. No experimental detail was given in the literature^[15] and all attempts to isolate α -lactams containing the 2-adamantyl moiety at the N1 position were unsuccessful in the author's laboratory, although they were detected by IR in the reaction mixture for a short time.

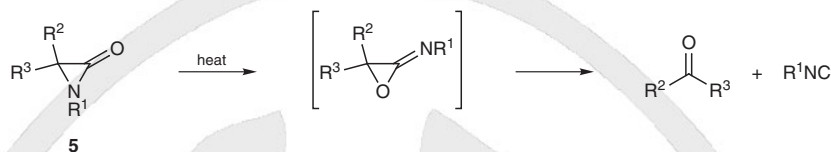
Although steric factors appear to play a dominant role in the kinetic stabilization of α -lactams, it has been suggested that electronic effects also play a role in α -lactam stability. It has been proposed^[7] that a dipolar ion (Scheme 2) might be involved in the decomposition of α -lactams. Substituents which stabilize this intermediate by conjugation thereby destabilize the α -lactam and make its preparation more difficult. For example, electronic effects have been invoked to explain^[4] why the synthesis of 1-*tert*-butyl-3,3-diphenylaziridinone is more difficult than that of 1-*tert*-butyl-3,3-dimethylaziridinone. The two phenyl groups stabilize the acyclic intermediate by delocalization and make the preparation of the α -lactam more difficult.

The thermal stability of α -lactams, first investigated in 1964,^[3] can easily be determined. The protocol currently used is to reflux the α -lactam in a series of alkane solvents of increasing boiling points. Eventually a sufficiently high temperature is achieved for ring opening to occur.^[16] Some extraordinarily heat-stable α -lactams, such as 1,3-di-*tert*-butylaziridinone,^[7] 1-*tert*-butyl-3-tritylaziridinone,^[13] and 1-(1-adamantyl)-3-tritylaziridinone^[13] have been reported.

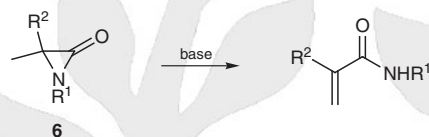
Upon sufficient heating in non-nucleophilic solvents, α -lactams **5** fragment to the corresponding isocyanide and aldehyde or ketone via a proposed oxiranimine intermediate^[17] (Scheme 4). While the conditions required for complete thermal decomposition cannot be predicted on the basis of structure, the products obtained from any given α -lactam **6** can be accurately predicted. It should be noted that if an α -lactam contains β -hydro-

gens, such as in 1-*tert*-butyl-3,3-dimethylaziridinone (**6**, $R^1 = t\text{-Bu}$; $R^2 = \text{Me}$), a base-catalyzed isomerization to the α,β -unsaturated amide can occur as well (Scheme 5).^[18]

Scheme 4 Thermal Decomposition of α -Lactams^[17]



Scheme 5 Base-Catalyzed Isomerization of α -Lactams^[18]



α -Lactams which lack bulky substituents at N1 and C3 lack steric stabilization toward nucleophilic attack and are generally nonisolable. Nevertheless, many α -lactams can be generated and reacted in situ with various nucleophiles without the need for isolation.

21.8.1 Synthesis of Product Class 8

Currently, there are two methods used to synthesize α -lactams: cyclization by dehydrohalogenation of α -halo amides and cycloelimination of *N*-sulfonyloxy-substituted amides.

21.8.1.1 Method 1: Dehydrohalogenation of α -Halo Amides

All of the reported stable α -lactams **8** have been synthesized by the dehydrohalogenation of α -halo amides **7** (Scheme 6). One of three bases (Table 1) (sodium *tert*-butoxide, potassium hydroxide, or sodium hydride) is currently used to effect dehydrohalogenation and reaction progress is easily monitored by the disappearance of the amide carbonyl band ($\sim 1680\text{ cm}^{-1}$) of the starting α -halo amide and the appearance of the α -lactam carbonyl band ($\sim 1840\text{ cm}^{-1}$) in the IR spectrum.

Table 1 compares the reaction times and yields for the synthesis of four stable α -lactams: 1,3-di-*tert*-butylaziridinone, 3-(1-adamantyl)-1-*tert*-butylaziridinone, 1-(1-adamantyl)-3-*tert*-butylaziridinone, and 3-*tert*-butyl-1-tritylaziridinone using the three different variations (bases) described in Sections 21.8.1.1.1–21.8.1.1.3 for the dehydrohalogenation of α -halo amides.

Scheme 6 The Synthesis of α -Lactams via Dehydrohalogenation of α -Halo Amides^[3,19,20]

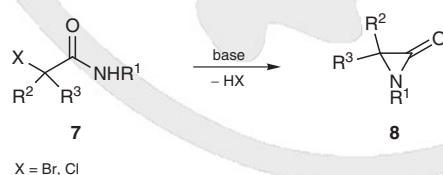


Table 1 Comparison of the Three Variations (Different Bases) Used for α -Lactam Synthesis^[7,14,16,19,20,21]

α -Lactam	Base	Time (h)	Yield (%)	Ref
1-(1-adamantyl)-3- <i>tert</i> -butylaziridinone	NaH	2	96	[19]
	<i>t</i> -BuOK	n.r. ^a	65	[14]
	KOH	12	89	[20]
3- <i>tert</i> -butyl-1-tritylaziridinone	NaH	1	96	[19]
	NaOt-Bu	2.5	93	[16]
1,3-di- <i>tert</i> -butylaziridinone	NaH	4	98	[19]
	<i>t</i> -BuOK	0.25	68	[7]
	KOH	12	80	[20]
3-(1-adamantyl)-1- <i>tert</i> -butylaziridinone	NaH	0.5	98	[19]
	<i>t</i> -BuOK	0.42	56	[21]
	KOH	12	94	[20]

^an.r. = not reported.

Although a few α -chloro amides^[19,22] have been utilized, α -bromo amides^[3,7,13,14] are most frequently employed as the precursor. The synthesis of the α -bromo amide precursor is easily accomplished in three steps, starting from the appropriate carboxylic acid. The most frequently used procedure is to first convert a carboxylic acid into its acid chloride by means of thionyl chloride and then to α -brominate using *N*-bromosuccinimide.^[23] The α -bromo acid chloride is then reacted with a primary amine by either of two methods.^[24,25]

It should be noted that (benzyloxy)carbonyl α -amino acids, when treated with a dehydrating agent such as thionyl chloride and subsequent addition of triethylamine, had reportedly^[26] been used for the synthesis of the corresponding 3-substituted [1-(benzyloxy)carbonyl]aziridinones. However, this report was later shown^[27] to be incorrect.

21.8.1.1.1 Variation 1: Using the *tert*-Butoxide Ion

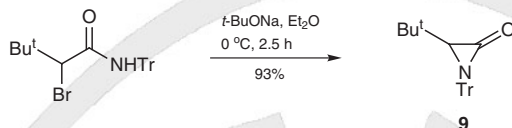
Potassium *tert*-butoxide, the first base used to dehydrohalogenate an α -bromo amide to obtain the corresponding α -lactam,^[3] was the base of choice for nearly all of the early α -lactam syntheses. However, later reports^[16] show that sodium *tert*-butoxide should be preferred over potassium *tert*-butoxide because the former, while a strong enough base to effect smooth and fast dehydrohalogenation, is much less hygroscopic, and therefore easier to handle. Diethyl ether^[3,7,16,22] is the solvent of choice when using the *tert*-butoxide ion and the reaction is performed at -20°C , 0°C , or room temperature, depending on the stability of the α -lactam being synthesized. The reaction is usually complete in less than 1 hour, a major advantage when using this base.

α -Lactam yields are generally good when using *tert*-butoxide, although the possibility of unwanted side reactions^[3,4] resulting from the nucleophilicity of the *tert*-butoxide ion or the *tert*-butyl alcohol byproduct has been reported. In addition, during the synthesis of 3,3-dimethylsubstituted α -lactams, the unwanted base-catalyzed rearrangement^[3,18] of the α -lactam to the more stable α,β -unsaturated amide can occur (see Scheme 5).

Some examples of α -lactams that have been synthesized by this method are 3-*tert*-butyl-1-tritylaziridinone (**9**) (Scheme 7),^[16] 1,3-di-*tert*-butylaziridinone,^[7] and 3-(1-adamantyl)-

1-tritylaziridinone.^[13] In addition, this method has been used to synthesize the chiral α -lactam (R)-1,3-di-*tert*-butylaziridinone.^[28]

Scheme 7 Synthesis of 3-*tert*-Butyl-1-tritylaziridinone Using *tert*-Butoxide Ion^[16]



3-*tert*-Butyl-1-tritylaziridinone (9); Typical Procedure:^[16]

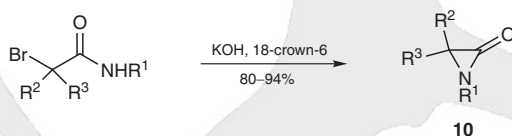
2-Bromo-3,3-dimethyl-*N*-tritylbutanamide (1.00 g, 0.0023 mol) was dissolved in dry Et₂O (100 mL) and cooled to 0 °C in an ice bath. NaOt-Bu (0.66 g, 0.0069 mol) was added to the soln in one portion, and the resulting suspension was stirred for 2.5 h. The mixture was then washed with distilled H₂O (100 mL). The organic layer was dried (Na₂SO₄) and the Et₂O removed on a rotary evaporator under reduced pressure. The residual crude α -lactam was dissolved in hexane (5 mL) and cooled to –23 °C for 3 d. Pure product **9** precipitated as a white crystalline solid and was collected; yield: 0.75 g (93%); mp 103–104 °C; IR (CCl₄) $\tilde{\nu}_{\text{max}}$: 1840 cm^{–1} (α -lactam C=O); ¹H NMR (CDCl₃, δ): 0.90 (s, 9H, *t*-Bu), 2.14 (s, 1H, CH), 7.28–7.46 (m, 15H, Tr).

21.8.1.1.2

**Variation 2:
Using Potassium Hydroxide and 18-Crown-6**

Dehydrohalogenation of α -haloamides using solid potassium hydroxide and a catalytic amount of the phase-transfer catalyst 18-crown-6, first introduced in 1982,^[20] provides a highly efficient and simple method for obtaining many stable α -lactams. α -Lactams **10** are obtained in good to excellent yields (54–94%)^[20,29] from the corresponding α -bromo amides (Scheme 8). The most commonly reported reaction conditions utilize reaction times of 12 hours at room temperature in benzene. 1,3-Di-*tert*-butylaziridinone, 3-(1-adamantyl)-1-*tert*-butylaziridinone, 1-(1-adamantyl)-3-*tert*-butylaziridinone, and 1,3-di(1-adamantyl)aziridinone have all been synthesized in high yield^[20] by this method. Significantly lower yields and longer reaction times are reported^[20] when various quaternary ammonium salt phase-transfer catalysts are used with 50% aqueous sodium hydroxide and dichloromethane.

Scheme 8 Synthesis of Aziridinones Using Potassium Hydroxide and 18-Crown-6^[20]



It should be noted that when extended reaction times are required to cyclize the α -bromo amide, the potassium hydroxide hydrolyzes some of the α -lactam that forms.^[30] In addition, water, a byproduct of this reaction, can coagulate the potassium hydroxide, thereby possibly extending the reaction times. It appears that this method is also unsuitable for the synthesis of some phenyl-substituted α -lactams.^[16,31]

Aziridinones 10; General Procedure:^[20]

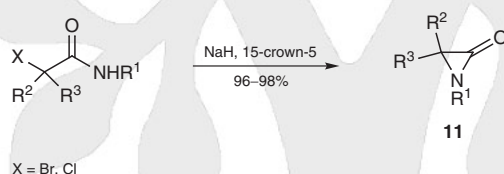
Powdered KOH (800 mg, 14.2 mmol) was added to a soln of an α -bromo amide (3 mmol) and 18-crown-6 (0.45 mmol) in anhyd benzene (30 mL) (**CAUTION: carcinogen**). After stirring for 12 h at rt, the suspension was filtered, washed with H₂O (3 \times 20 mL), dried (Na₂SO₄), and concentrated to dryness. The crude product was recrystallized (heptane) or distilled to afford the pure α -lactam. For specific yields, see Table 1, Section 21.8.1.1.

21.8.1.1.3

Variation 3:**Using Sodium Hydride and 15-Crown-5**

The use of sodium hydride for the synthesis of α -lactams was first attempted in the 1950s and 1960s.^[32–38] In no case, however, could an α -lactam be isolated or detected as an intermediate because the incorrect substituent (a phenyl group at position 1) and reaction conditions (heating in benzene) had been chosen. Nevertheless, the formation of the isolated products could be explained through a common α -lactam intermediate.

The high-yield syntheses of several stable α -lactams **11** using sodium hydride with a catalytic amount of 15-crown-5 has been reported (Scheme 9).^[19] Dichloromethane is the preferred solvent; lower yields are obtained if hexane, benzene, or tetrahydrofuran is employed as the solvent. Advantages of this method include short reaction times, easy work-up (the byproducts are hydrogen gas and sodium bromide), high yields, and the ability to synthesize α -lactams containing a phenyl substituent. In addition, in the case of 1-*tert*-butyl-3,3-dimethylaziridinone, sodium hydride does not catalyze the isomerization of this α -lactam to *N*-*tert*-butylmethacrylamide, which has been observed^[3,18] when potassium *tert*-butoxide is used.

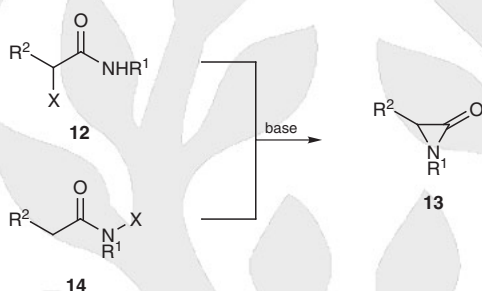
Scheme 9 Synthesis of Aziridinones Using Sodium Hydride and 15-Crown-5^[19]**Aziridinones 11; General Procedure:**^[19]

A 60% dispersion of NaH in mineral oil (6.0 mmol) and 15-crown-5 (0.5 mmol) in CH₂Cl₂ (50 mL) was stirred for 20 min. The α -halo amide (2.0 mmol) was then added and the mixture stirred for an additional 0.5–3 h, depending on the α -lactam being synthesized. The progress of the reaction is monitored by IR (the disappearance of the α -halo amide carbonyl band at \sim 1680 cm^{–1} and the appearance of the α -lactam carbonyl band at \sim 1840 cm^{–1}). The mixture was then washed with distilled H₂O (3 \times 50 mL) and dried (Na₂SO₄), and the CH₂Cl₂ was removed under reduced pressure. The resulting crude α -lactam was taken up in hexane (50 mL) and washed with distilled H₂O (3 \times 50 mL) to remove the 15-crown-5, dried (Na₂SO₄), and the hexane was removed under reduced pressure to afford pure α -lactam **11**. For specific yields, see Table 1, Section 21.8.1.1.

21.8.1.2

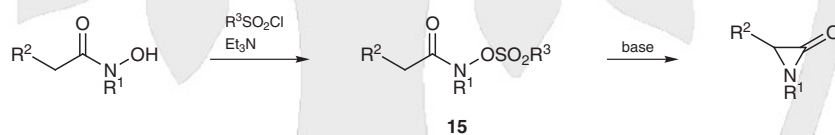
Method 2:
Cycloelimination of *N*-Sulfonyloxy Amides

As described in Section 21.8.1.1, base-promoted 1,3-elimination in secondary α -halo amides **12** is a common way to produce α -lactams **13**. In such cases the acidic proton is on the amide nitrogen and the halide leaving group is on the α -carbon (Scheme 10). An alternative strategy for base-promoted 1,3-elimination is to utilize an α -proton of an amide as the acidic proton and have a leaving group attached to the amide nitrogen, as in compound **14** (Scheme 10).

Scheme 10 Alternative Strategies for the Preparation of α -Lactams^[1]


The first isolated α -lactam, 1-*tert*-butyl-3-phenylaziridinone, was prepared from an *N*-chloro amide utilizing this alternative strategy.^[1] In general, however, the use of *N*-halo amides as elimination substrates for the preparation of α -lactams by this route is unsatisfactory because yields are low and the preparation of the *N*-halo amides themselves is problematic.

The use of *N*-sulfonyloxy amides **15** as elimination substrates is a much better approach since they are easily prepared from hydroxamic acids and high yields of the α -lactam are produced upon treatment with bases (Scheme 11).

Scheme 11 Preparation of α -Lactams via *N*-Sulfonyloxy Amides^[39,40]


Although one α -lactam has been isolated by this method,^[39] the method is particularly useful for nonisolable α -lactams which are not sterically stabilized. The α -lactam, generated by the reaction of the *N*-sulfonyloxy amide with a base, reacts in situ with nucleophiles present in the mixture. A variety of sulfonyloxy leaving groups have been used including arenesulfonate,^[39,41] methanesulfonate,^[42] and trifluoromethanesulfonate,^[43] but by far the most useful synthetically is the methanesulfonate group.^[40]

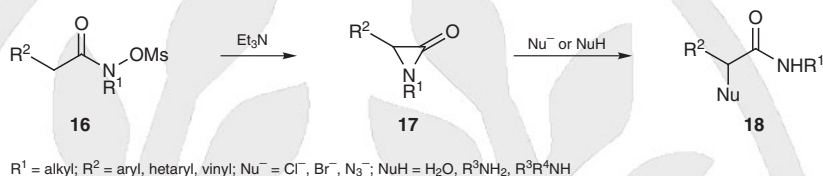
21.8.1.2.1

Variation 1:
Using Amines as Bases

Treatment of an *N*-mesyloxy amide **16** with triethylamine or diisopropylethylamine in the presence of various nucleophiles produces 2-substituted amides **18**. In order to be successful, a conjugating substituent at the α -position is required to acidify the α -proton. Ar-

omatic, heteroaromatic, and vinyl groups all serve well in this regard.^[40] Primary and secondary alkyl substituents on nitrogen are well-tolerated, however the nitrogen substituent cannot be an aromatic ring. A variety of nucleophiles can thus be incorporated efficiently at the α -position of amides (Scheme 12). In cases where the nucleophile is basic (e.g., N_3^- or amines), then the nucleophile is also used as the base to promote formation of the α -lactam **17**.^[44]

Scheme 12 Conversion of *N*-Mesyloxy Amides into 2-Substituted Amides via α -Lactams^[40,44]



2-Bromo-*N*-cyclohexyl-2-phenylacetamide (18, $\text{R}^1 = \text{Cy}$; $\text{R}^2 = \text{Ph}$; $\text{Nu} = \text{Br}$); Typical Procedure:^[40]

Amine base and bromide nucleophile: A soln of Et_3N (222 mg, 2.2 mmol) in CH_2Cl_2 (15 mL) was added over a period of 45 min to a soln of *N*-cyclohexyl-*N*-mesyloxy-2-phenylacetamide (**16**, $\text{R}^1 = \text{Cy}$; $\text{R}^2 = \text{Ph}$; 592 mg, 2 mmol) and LiBr (1.74 g, 20 mmol) in CH_2Cl_2 (35 mL). The resulting mixture was stirred at rt for 4–8 h until TLC analysis (hexane/ EtOAc 3:2) showed the starting material to have disappeared. The solvent was removed and the residue was dissolved in EtOAc (60 mL), washed with H_2O (4×20 mL), 1 M HCl (15 mL), and brine (20 mL), and dried (MgSO_4). After removal of the solvent the residue (592 mg, 100%) was recrystallized (hexane/ CH_2Cl_2) to give **18** ($\text{R}^1 = \text{Cy}$; $\text{R}^2 = \text{Ph}$; $\text{Nu} = \text{Br}$) as a white solid; yield: 578 mg (97%) mp 134–135 °C; ^1H NMR (δ): 5.42 (s, 1H, CHBr); IR $\tilde{\nu}_{\text{max}}$: 1681 cm^{-1} .

2-Hydroxy-*N*-methyl-2-phenylacetamide (18, $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Ph}$; $\text{Nu} = \text{OH}$); Typical Procedure:^[40]

Amine base and water nucleophile: A soln of Et_3N (212 mg, 2.1 mmol) in MeCN (24 mL) was added over a period of 9 h (syringe pump) to a soln of *N*-mesyloxy-*N*-methyl-2-phenylacetamide (**16**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$; 486 mg, 2 mmol) in $\text{MeCN}/\text{H}_2\text{O}$ (1:1, 24 mL) at rt, and the mixture was stirred overnight. The solvent was removed and the residue was diluted with EtOAc (60 mL), which was washed with H_2O (4×20 mL), 1 M HCl (15 mL), brine (20 mL), and dried (MgSO_4). After removal of the solvent the crude product (260 mg, 78%) was recrystallized [benzene (**CAUTION: carcinogen**)] to give a white solid; yield: 185 mg (55%); mp 93–94 °C [lit^[45] mp 94–95 °C].

***N*-Methyl-2-phenyl-2-piperidinoacetamide, (18, $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Ph}$; $\text{Nu} = \text{Piperidino}$); Typical Procedure:**^[44]

Amine as both base and nucleophile: A soln of piperidine (374 mg, 4.4 mmol) in CH_2Cl_2 (15 mL) was added to an ice-cooled soln of *N*-mesyloxy-*N*-methyl-2-phenylacetamide (**16**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$; 486 mg, 2 mmol) in CH_2Cl_2 (25 mL) over a period of 30 min. The mixture was then stirred at 0 °C for 1 h and then at rt until the starting material was absent as determined by TLC (hexane/ EtOAc 3:2). The solvent was removed and the residue was treated with 1 M NaOH (15 mL) and extracted with EtOAc (50 mL). The organic layer was washed with H_2O (2×10 mL) and dried (MgSO_4). After removal of the solvent the crude product (300 mg, 68%) was purified by flash chromatography (silica gel, hexane/ EtOAc 3:2) to give

the title compound as an oil; yield 280 mg (60%); ^1H NMR (δ): 2.35 (s, 3H, NCH_3), 4.43 (s, 1H, $\alpha\text{-CH}$); IR $\tilde{\nu}_{\text{max}}$: 1645 cm^{-1} .

21.8.1.2.2

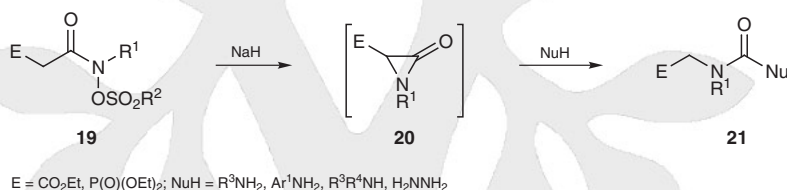
Variation 2: Using Sodium Hydride as Base

Nucleophiles such as hydrazines or arylamines are insufficiently basic to convert *N*-mesyloxy amides **19** ($\text{R}^2 = \text{Me}$) into α -lactams **20**. However, the use of tertiary amine bases such as triethylamine or diisopropylethylamine to generate the α -lactam in the presence of these relatively weak nucleophiles is also problematic because these bases, albeit tertiary and hindered, can also react as nucleophiles with the α -lactam.^[46]

Employing a non-nucleophilic base such as sodium hydride to generate the α -lactam **20** can minimize these difficulties, since it is basic enough to form the α -lactam but is insufficiently soluble to compete as a nucleophile (Scheme 13).^[47] This method works particularly well for *N*-mesyloxy amides with electron-withdrawing groups at the α -position. Only 1 equivalent of the capturing nucleophile is required and a wide range of amines and hydrazines can be used. Because the reaction mixture is heterogeneous, the reaction times are between 7 and 15 hours, but can be shortened considerably by sonication.^[47]

The nucleophile attacks the carbonyl carbon and 2,3-ring opening occurs to give a urea derivative, e.g. **21**, when electron-withdrawing substituents are attached to the α -position.

Scheme 13 Conversion of *N*-Sulfonyloxy Amides into Urea Derivatives via α -Lactams Using Sodium Hydride as Base^[47]



Ethyl *N*-Methyl-*N*-(morpholinocarbonyl)glycinate (**21**, $\text{E} = \text{CO}_2\text{Et}$; $\text{R}^1 = \text{Me}$; $\text{Nu} = \text{Morpholino}$); Typical Procedure:^[47]

A soln of ethyl *N*-mesyloxy-*N*-methylmalonamide (**19**, $\text{E} = \text{CO}_2\text{Et}$; $\text{R}^1 = \text{R}^2 = \text{Me}$; 0.71 g, 2.96 mmol) in THF (20 mL) was added dropwise over 30 min to a stirred suspension of NaH (3.26 mmol) in THF (20 mL) at 0 °C. A soln of morpholine (0.28 g, 3.26 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h and then at rt for 10 h until TLC (hexane/EtOAc 1:1) indicated the starting material was absent. The solvent was removed by rotary evaporation and the residue was taken up in EtOAc (75 mL), washed with 1 M HCl (2×10 mL) and H_2O (2×20 mL), and dried (MgSO_4). The solvent was removed and the title compound was purified by flash chromatography (silica gel, hexane/EtOAc 3:2) to give an oil; yield: 73%; IR $\tilde{\nu}_{\text{max}}$: 1747, 1649 cm^{-1} .

Diethyl ((Benzyl[(2-benzylhydrazino)carbonyl]amino)methyl)phosphonate [**21**,

$\text{E} = \text{P}(\text{O})(\text{OEt})_2$; $\text{R}^1 = \text{Bn}$; $\text{Nu} = \text{NHNHBn}$]; Typical Procedure:^[47]

A soln of *N*-benzyl-*N*-mesyloxydiethylphosphonoacetamide [**19**, $\text{E} = \text{P}(\text{O})(\text{OEt})_2$; $\text{R}^1 = \text{Bn}$; $\text{R}^2 = \text{Me}$; 0.81 g, 2.13 mmol] in THF (20 mL) was added dropwise to a stirred suspension of NaH (94 mg, 2.34 mmol) in THF (20 mL) at 0 °C. A soln of BnNHNH_2 (313 mg, 2.56 mmol) in THF (20 mL) was then added over a period of 20 min. The reaction flask was immersed in

an ultrasonic bath (125 W) filled with ice water and sonicated at 0 °C for 2 h. The solvent was removed and the residue was taken into EtOAc (50 mL), washed with H₂O (10 mL), and dried (MgSO₄). The solvent was removed and the product was purified by flash chromatography (silica gel, hexane/EtOAc 2:3) to give the title compound as an oil; yield: 67%; ¹H NMR (δ): 3.80 (d, J = 9.8 Hz, 2H); IR $\tilde{\nu}_{\text{max}}$: 1645 cm⁻¹.

21.8.2 Applications of Product Class 8 in Organic Synthesis

21.8.2.1 Method 1: Incorporation of Nucleophiles

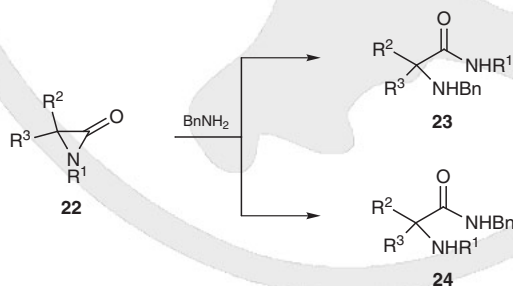
Due to their ring strain, α -lactams are generally very reactive toward nucleophiles and ring opening is observed. As shown in Scheme 3 (Section 21.8), nucleophiles add readily to either the C2 carbonyl carbon or to the C3 ring carbon. Addition to the C2 carbon usually results in 1—2 bond cleavage and production of 2-aminocarboxylic acid derivatives while addition to the C3 carbon results in 1—3 bond cleavage and production of 2-substituted amides. In order to be synthetically useful, the regiochemistry of nucleophilic addition must be controlled.

Two generalizations^[4] have served as the starting point for further efforts to understand the factors which influence the regioselectivity of α -lactam ring opening by nucleophiles and the mechanisms involved. The first is that the nucleophile attacks the C2 and C3 carbons competitively. For example, the groups of Quast,^[28,48] Maran,^[49] and D'Angelis^[50,51] have used the stereospecific incorporation of nucleophiles at C3 as evidence that nucleophilic attack at C3 competes with nucleophilic addition to C2.

The second generalization is that protic nucleophiles (e.g., water, alcohols, thiols, and amines) attack the C3 ring carbon to produce 2-substituted amides, while nonprotic, ionic nucleophiles (e.g., alkoxide ions) attack the C2 carbon to form 2-aminocarboxylic acid derivatives. A later report^[9] notes that in virtually all cases where C3 addition is predominant, the reaction mixture is protic, which agrees with the earlier report.^[4] Reagents, such as lithium aluminum hydride^[52] and organometallic reagents,^[53] also attack the C2 position with C2—N ring cleavage. Although a few exceptions to this general rule have been noted,^[29] it has been used nearly exclusively to explain regioselectivity in the reactions of α -lactams with nucleophiles.

However, several studies have recently been reported which bring this general rule into question.^[54–57] For example, the reaction between some α -lactams **22** and benzylamine (Scheme 14) leads to α -benzylamino amides **23** (C3 attack), while others give only an *N*-benzylamide **24** (C2 attack) as the major product.^[55]

Scheme 14 Reaction of α -Lactams with Benzylamine^[55]



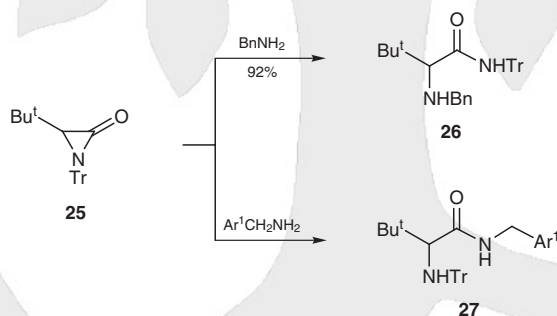
A survey^[54] of the reactions of a large number of proton-bearing and non-proton-bearing nucleophiles with 1,3-di-*tert*-butylaziridinone shows a significant number of exceptions to this general rule. In particular, several amines were found to give both C2 and C3 products depending on their nucleophilicity and steric bulk. Finally, another notable exception^[13] is the addition of the aprotic nucleophile, sodium methoxide, to 3,3-dimethyl-1-tritylaziridinone, which gives 2-methoxy-2-methyl-*N*-tritylpropanamide, a result of C3 attack.

Further studies have clarified the factors that influence the regioselectivity of α -lactam ring opening by nucleophiles. A summary^[55] of the reaction of 16 stable α -lactams with benzylamine reaches the following conclusions: (i) 3,3-dimethyl-substituted α -lactams, which are relatively less stable yet isolable α -lactams, consistently yield *N*-alkyl- α -benzylamino amides (C3 attack and 1—3 bond cleavage), irrespective of the nature of the *N*-substituent; (ii) *N*-trityl-substituted α -lactams, irrespective of their relative stability, also give α -benzylamino-*N*-trityl amides (C3 attack), either as the sole or major product, again reflecting C3—N bond cleavage; (iii) all other stable α -lactams, which have been reacted with benzylamine, give *N*-benzyl amides (C2 attack), arising from C2—N bond cleavage.

Thus, the steric bulk of substituents on an α -lactam exert a critical influence on the regioselectivity of their nucleophilic ring-opening reactions.

The ring-opening reactions of several α -lactams with substituted benzylamines and other primary amines has been reported,^[56] and conclude that the basicity of the amine is an important additional factor influencing regioselectivity. Weakly basic amines tend to lead to C3—N bond cleavage while reaction with more basic primary amines leads to C2—N bond cleavage. For example, when 3-*tert*-butyl-1-tritylaziridinone (**25**) is reacted with benzylamine (pK_b 4.70), the α -benzylamino-*N*-trityl amide **26** is isolated as the sole product (C3 attack), in 92% yield. However, substitution of the benzylamine in the *para* position with a strong (NMe_2) (pK_b 4.10) or moderately strong (OMe) (pK_b 4.55) electron-donor group engenders product reversal (C2 attack), e.g. to give **27** as shown in Scheme 15.

Scheme 15 Reaction of 3-*tert*-Butyl-1-tritylaziridinone with Benzylamine and 4-Substituted Benzylamines^[56]

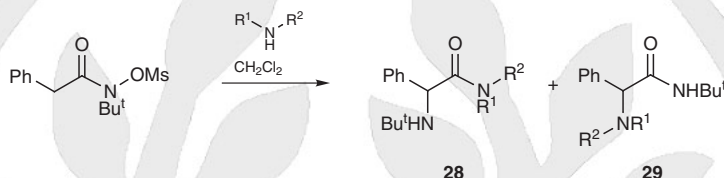


Since basicity is strongly correlated with nucleophilicity for nucleophiles of similar structure and steric bulk, these results emphasize the importance of nucleophilicity on the regioselectivity of ring opening. Good nucleophiles tend to attack C2 while poorer nucleophiles tend to attack C3.

The studies reported by Lengyel^[55] and Cesare^[56] were conducted with stable, isolated α -lactams. Hoffman and coworkers^[57] explored the in situ formation and subsequent reaction of 1-*tert*-butyl-3-phenylaziridinone with 11 different amines. *N*-*tert*-Butyl-*N*-mesyloxy-2-phenylacetamide is reacted with 2 equivalents of the amine (Section 21.8.1.2.1). The

first equivalent of the amine base causes 1,3-elimination to produce 1-*tert*-butyl-3-phenylaziridinone, which then reacts with the second equivalent of the amine nucleophile to give C2 and/or C3 products **28** and **29**, respectively (Scheme 16). It has also been concluded that good amine nucleophiles such as primary amines (e.g., isopropylamine) and cyclic secondary amines (e.g., piperidine) give primarily the C2 product. Sterically bulky amines, which are poorer nucleophiles [i.e., *tert*-butyl(methyl)amine], give mostly the C3 product.

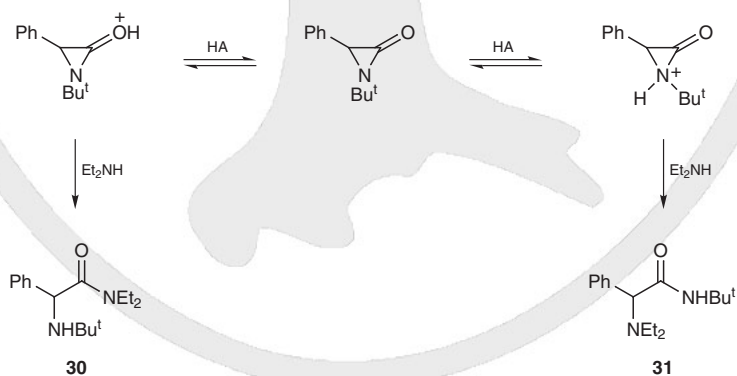
Scheme 16 The Reaction of 1-*tert*-Butyl-3-phenylaziridinone with Various Amines^[57]



The same publication^[57] compares the reaction of diethylamine with 1-*tert*-butyl-3-phenylaziridinone, which is either generated and reacted in situ from *N*-*tert*-butyl-*N*-mesyloxy-2-phenylacetamide or isolated as a stable compound and then reacted. The effects of temperature, amine concentration, and ammonium salt concentration have been studied and the following conclusions reached: (i) factors that favor C2 product formation are lower reaction temperatures and an increase in nucleophile concentration. In addition, both the overall rate of reaction and the amount of C2 product increase in the presence of a weak acid such as the ammonium methanesulfonate salt; (ii) the factor that favors C3 product formation is higher reaction temperatures and the reaction rate is dramatically increased by an acid catalyst and protic solvents. It has also been shown that whether or not the nucleophile bears a proton is irrelevant in determining the reaction outcome. It is the nucleophilicity of the nucleophile which is the major determinant.

Based on these observations, it has been proposed that there are two different pathways for the formation of the C2 and C3 products in protic media, and that both pathways are subject to some type of acid catalysis.^[57] The proposed mechanism (Scheme 17) shows that O-protonation leads to C2 attack (e.g., to give **30**) while N-protonation leads to C3 attack (e.g., to give **31**).

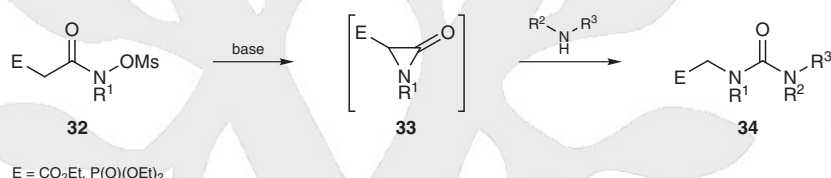
Scheme 17 Proposed Mechanisms of Nucleophilic Ring-Opening Reactions of α -Lactams^[57]



While a great deal of progress has been made in understanding the factors which control regioselectivity in the reactions of alkyl- and aryl-substituted α -lactams with nucleophiles, the fact remains that it is not possible to predict the regiochemistry with certainty in many cases. The most predictable results have been obtained with α -lactams which are not sterically stabilized and are generated in situ from *N*-mesyloxy amides. These results can be summarized as follows: (i) the use of unhindered primary and secondary amines both as base and nucleophile results in the product of C2 attack (Section 21.8.1.2.1); (ii) the use of hindered tertiary amines as bases (1.1 equiv) and poor nucleophiles such as halides, water, or alcohols results in the products of C3 attack (Section 21.8.1.2.1); (iii) placement of an electron-withdrawing group at C3 of an α -lactam simplifies the chemistry markedly.^[58] The electron-withdrawing group has three effects. Firstly, it acidifies the α -protons so that α -lactam formation from amide **32** is facilitated. Secondly, it activates the carbonyl group so that only C2 addition is observed with amine nucleophiles, regardless of their nucleophilicity. Thirdly, it causes 2—3 bond cleavage upon ring opening of **33** (Scheme 18). This provides an excellent way to prepare unsymmetrical ureas **34**. The amine can be used as both the base and nucleophile.

Alternatively, sodium hydride can be used as the base and the amine as the nucleophile (Section 21.8.1.2.1). In this way even weakly basic amines such as arylamines can be smoothly incorporated. If primary amines are used as the nucleophile, the ring-opening products can be cyclized to hydantoins using sodium hydride.^[47]

Scheme 18 The Synthesis of Unsymmetrical Ureas via α -Lactams^[58]



The use of hydrazines as nucleophiles can give two different heterocyclic products when the electron-withdrawing group is ethoxycarbonyl.^[59] If a monosubstituted hydrazine is chosen so that the terminal nitrogen of the hydrazine acts as the nucleophilic atom,^[46] base-induced ring closure occurs to give an *N*-aminohydantoin (see Section 21.8.2.1.1).

If a hydrazine is chosen so that the internal nitrogen of the hydrazine acts as the nucleophilic atom,^[46] base-induced ring closure occurs to give a 1,2,4-triazine-3,6-dione (see Section 21.8.2.1.2).

2-(Benzylamino)-2-phenyl-*N*-tritylacetamide (**23**, R¹ = Tr; R² = Ph; R³ = H); Typical Procedure:^[55]

Crude 3-phenyl-1-tritylaziridinone (**22**, R¹ = Tr; R² = Ph; R³ = H; 0.15 g, 0.399 mmol) was dissolved in THF (6 mL) and a soln of BnNH₂ (0.171 g, 1.60 mmol, 4 equiv) in THF (2 mL) was added. The mixture stirred at rt for 2 h. Excess solvent was removed under reduced pressure to afford a white solid, which was flash chromatographed (silica gel, hexane/EtOAc 4:1) to afford the pure product; yield: 53%; mp 119–121 °C; ¹H NMR (DMSO-*d*₆, δ): 3.61 (dd, *J* = 13.75, 5.67 Hz, 1H), 3.68 (dd, *J* = 13.75, 5.69 Hz, 1H, benzylic H); ¹³C NMR (DMSO-*d*₆, δ): 50.97 (benzylic C); IR (CCl₄) $\tilde{\nu}_{\text{max}}$: 1696 (amide C=O) cm⁻¹; MS: *m/z* 196 (PhCH=NHBn)⁺ (structure proving ion).

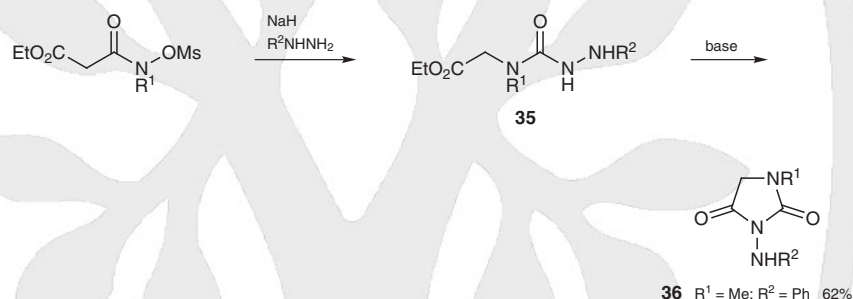
N-Benzyl-3,3-dimethyl-2-(tritylamino)butanamide (24, $R^1 = \text{Tr}$; $R^2 = t\text{-Bu}$; $R^3 = \text{H}$); Typical Procedure:^[55]

3-*tert*-Butyl-1-tritylaziridinone (**22**, $R^1 = \text{Tr}$; $R^2 = t\text{-Bu}$; $R^3 = \text{H}$; 0.10 g, 0.28 mmol) was dissolved in THF (3 mL) and a soln of BnNH_2 (0.12 g, 1.13 mmol, 4 equiv) in THF (1 mL) was added. The mixture stirred at rt for 5 d. Excess solvent and BnNH_2 were removed under reduced pressure to afford the crude product (0.13 g). Flash chromatography (silica gel, hexane/EtOAc 4:1) afforded pure product; yield: 0.11 g (85%); mp 151–154 °C; ^1H NMR (CDCl_3 , δ): 3.33 (d, $J = 14.34$ Hz, 1H), 4.12 (m, 1H, benzylic H); ^{13}C NMR (CDCl_3 , δ): 43.79 (benzylic C); IR (CCl_4) $\tilde{\nu}_{\text{max}}$: 1671 cm^{-1} ; MS: m/z 328, $(\text{TrCH}=\text{NH}t\text{-Bu})^+$ (structure proving ion).

21.8.2.1.1

**Variation 1:
Synthesis of *N*-Aminohydantoins**

If hydrazine is substituted with a sterically bulky (e.g., *t*-Bu) or conjugating (e.g., aromatic, alkoxy carbonyl) group or if the hydrazine is 1,1-disubstituted, the terminal nitrogen functions as the nucleophilic atom and *N*-aminohydantoins **36** result from base-induced cyclization of the intermediate capture product **35** (Scheme 19).^[46] Either tertiary amine bases or sodium hydride can be used to induce α -lactam formation.

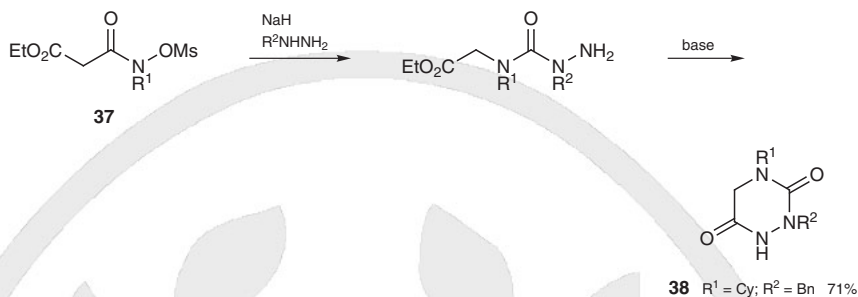
Scheme 19 The Synthesis of *N*-Aminohydantoins Using Hydrazine Nucleophiles^[46]**3-Methyl-1-(phenylamino)hydantoin (36, $R^1 = \text{Me}$; $R^2 = \text{Ph}$); Typical Procedure:**^[46,59]

Phenylhydrazine (4.5 mmol) and ethyl *N*-mesyloxy-*N*-methylmalonamide (4.17 mmol) were dissolved in CH_2Cl_2 (20 mL). A soln of Et_3N (4.25 mmol) in CH_2Cl_2 (48 mL) was added by syringe pump over a period of 10 h and the mixture was stirred further overnight. The solvent was removed and the residue was dissolved in EtOAc (60 mL). The mixture was washed with H_2O (4×20 mL) and brine (20 mL), and dried (MgSO_4). After solvent removal, the product was purified by flash chromatography (silica gel, EtOAc/hexanes 1:1) to give **36** ($R^1 = \text{Me}$; $R^2 = \text{Ph}$) as a colorless solid; yield: 62%; mp 150–152 °C; ^1H NMR (δ): 3.94 (s, 2H, CH_2); IR $\tilde{\nu}_{\text{max}}$: 1787, 1731 cm^{-1} .

21.8.2.1.2

**Variation 2:
Synthesis of 1,2,4-Triazine-3,6-diones**

If hydrazine is substituted with an alkyl group or if the hydrazine is 1,2-disubstituted, the internal nitrogen functions as the nucleophilic atom and 1,2,4-triazine-3,6-diones **38** result from base-induced cyclization of the intermediate capture product formed from *N*-mesyloxy amide **37** (Scheme 20).^[46]

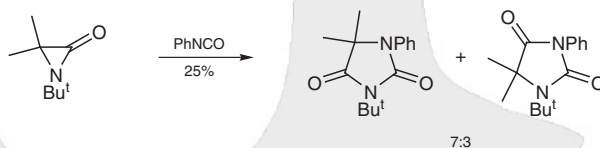
Scheme 20 The Synthesis of 1,2,4-Triazine-3,6-diones Using Hydrazine Nucleophiles^[46]**2-Benzyl-4-cyclohexyl-1,2,4-triazine-3,6-dione, (38, $R^1 = \text{Cy}$; $R^2 = \text{Bn}$); Typical Procedure:**^[46]

A soln of ethyl *N*-cyclohexyl-*N*-mesyloxymalonamide (**37**, $R^1 = \text{Cy}$; 2.5 mmol) in dry THF (15 mL) was added dropwise (15 min) to stirred suspension of NaH (2.75 mmol) in dry THF (15 mL) at 0 °C. Next a soln of BnNHNH_2 (2.5 mmol) in THF (15 mL) was added dropwise (15 min) and the mixture was stirred at 0 °C for 1 h and then at rt for 10 h. The solvent was removed under reduced pressure and the residue was taken up in EtOAc (50 mL). The soln was washed with brine (10 mL), dried (MgSO_4), and evaporated. The product **38** ($R^1 = \text{Cy}$; $R^2 = \text{Bn}$) was purified by flash chromatography to give a colorless solid; yield: 71%; mp 130–131 °C; ^1H NMR (δ): 3.6 (s, 2H), 4.7 (s, 2H); IR $\tilde{\nu}_{\text{max}}$: 1693, 1956 cm^{-1} .

21.8.2.2

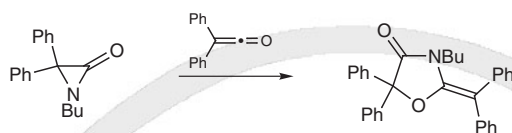
Method 2:**Cycloaddition Reactions Involving α -Lactams**

There have been several reported cases of [3+2]-cycloaddition reactions involving α -lactams, although yields are generally poor. The formation of a hydantoin ring has been reported when 1-*tert*-butyl-3,3-dimethylaziridinone is reacted with phenyl isocyanate to give a mixture of two isomers of imidazolidine-2,4-dione in 25% yield (Scheme 21).^[60] The ratio of the two isomers is 7:3. When less stable α -lactams are generated in situ in the presence of an isocyanate at -50°C , only hydantoins arising from 1–3 cleavage are formed.

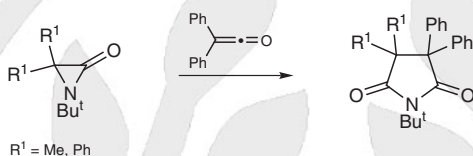
Scheme 21 Cycloaddition Reaction of 1-*tert*-Butyl-3,3-dimethylaziridinone with Phenylisocyanate To Yield a Mixture of Hydantoins^[60]

The formation of either an oxazolidinone or succinimide occurs when an α -lactam is treated with diphenylketene (Schemes 22 and 23).^[61] The product obtained is dependent on the stability of the starting α -lactam. The cycloaddition products are obtained in approximately 20% yield.

Scheme 22 Cycloaddition Reaction of 1-Butyl-3,3-diphenylaziridinone with Diphenylketene to an Oxazolidin-4-one^[61]

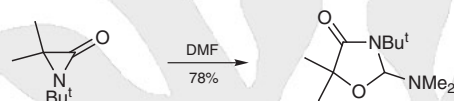


Scheme 23 Cycloaddition Reaction of More Stable α -Lactams with Diphenylketene Yielding a Succinimide^[61]



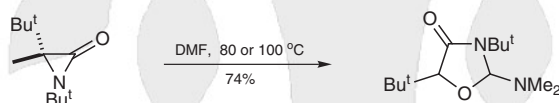
The formation of an oxazolidin-4-one from the reaction of 1-*tert*-butyl-3,3-dimethylaziridinone with dimethylformamide has also been reported (Scheme 24).^[62]

Scheme 24 Cycloaddition Reaction of 1-*tert*-Butyl-3,3-Dimethylaziridinone with Dimethylformamide To Yield an Oxazolidin-4-one^[62]



The same reaction has been reported between optically active (*R*)-1,3-di-*tert*-butylaziridinone and dimethylformamide to give the oxazolidin-4-one shown in Scheme 25.^[28] The ratio of the *cis* and *trans* diastereomers depends on the reaction time and temperature.

Scheme 25 Cycloaddition Reaction of (*R*)-1,3-Di-*tert*-butylaziridinone with Dimethylformamide To Yield an Oxazolidin-4-one^[28]



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Product Class 9: β -Lactams

C. Coates, J. Kabir, and E. Turos

General Introduction

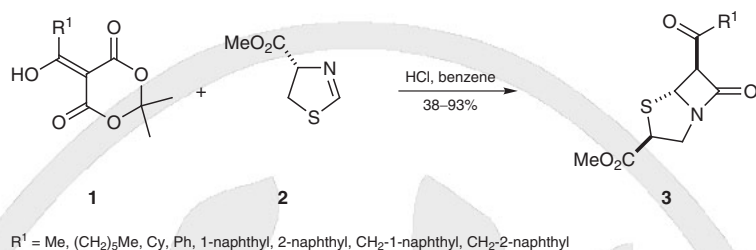
Previously published information regarding this product class can be found in *Houben-Weyl*, Vol. E 16b, pp 31–867 and Vol. 11/2, pp 518–528.

β -Lactam antibiotics have been the most important therapeutic agents in the 20th century, an era which began with the discovery of penicillin by Alexander Fleming in 1928. Numerous reviews have been written on the chemistry and biology of β -lactams. The key feature of penicillin and its analogues, such as the cephalosporins, penems, carbapenems, clavulanic acid, and monobactams, is the β -lactam nucleus. With the alarming trends in bacterial resistance to many β -lactam antibiotics it has become necessary to find more potent and chemically diverse analogues to combat drug-resistant infections. Therefore, the synthesis of the β -lactam core structure has been the subject of extensive study. While review articles on the formation of the β -lactam ring have been published, the continuing growth of the field makes it necessary to update the status of these methods. This review summarizes the different strategies that have been developed to form the β -lactam ring, with each section being categorized by the final step in which the β -lactam ring is formed.

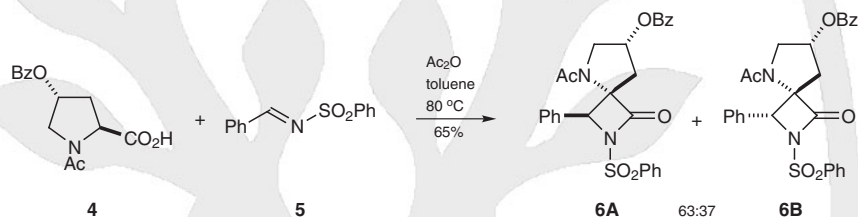
21.9.1 Synthesis of Product Class 9

21.9.1.1 Method 1: Ketene–Imine Cycloadditions

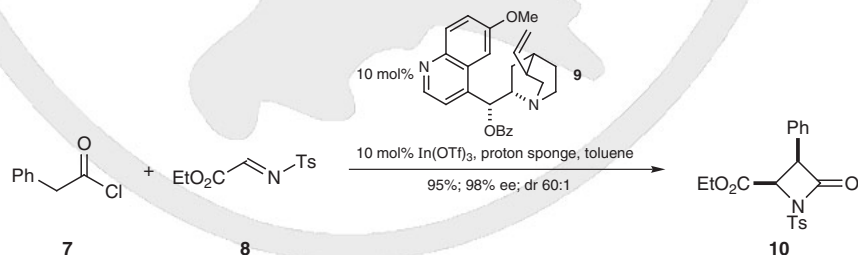
The formation of the β -lactam ring via [2+2] cycloaddition of an imine with a ketene is termed the Staudinger cycloaddition reaction.^[1] This method is generally accepted as the most versatile and efficient route for the construction of the β -lactam skeleton. These reactions proceed rapidly at low to room temperatures and generally do not require a catalyst. Imines are most commonly prepared from aldehydes or ketones, and the imine nitrogen usually has an aromatic or aliphatic substituent that can easily be removed or altered after the formation of the β -lactam ring.^[2] Ketenes can be generated in a variety of different ways; however, the most common method is by reaction of an acid chloride with a tertiary amine.^[3] The mechanism of the Staudinger cycloaddition and the rationale of the stereochemistry of the products has been investigated. It is generally accepted that the ketene is attacked by the imine to form a zwitterionic intermediate which, upon conrotatory ring closure, forms the β -lactam ring. The stereochemical outcome of reactions involving ketenes and imines has been studied using mechanistic models, and the *cis/trans* ratio of β -lactam formation is dependent on a number of factors. These factors include the order of addition of reagents, generation of the ketene, the structure of the ketene and imine, solvent, temperature, and reaction rates.^[3] Asymmetric Staudinger cycloadditions typically employ a chiral auxiliary in the ketene precursor or in the N- or C-substituent of the imine. As an example, Meldrum's acid derivatives **1**, which are acyl ketene precursors, react with optically active 4,5-dihydro-1,3-thiazole **2** under anhydrous acidic conditions to yield optically active β -lactams **3** in high yields (Scheme 1).^[4] The use of Meldrum's acids allows for the preparation of acyl ketenes, whereas acid chlorides are not suitable precursors.

Scheme 1 Stereoselective Synthesis of Optically Active β -Lactams from Meldrum's Acid Derivatives and Methyl 4,5-Dihydro-1,3-thiazole-4-carboxylate^[4]

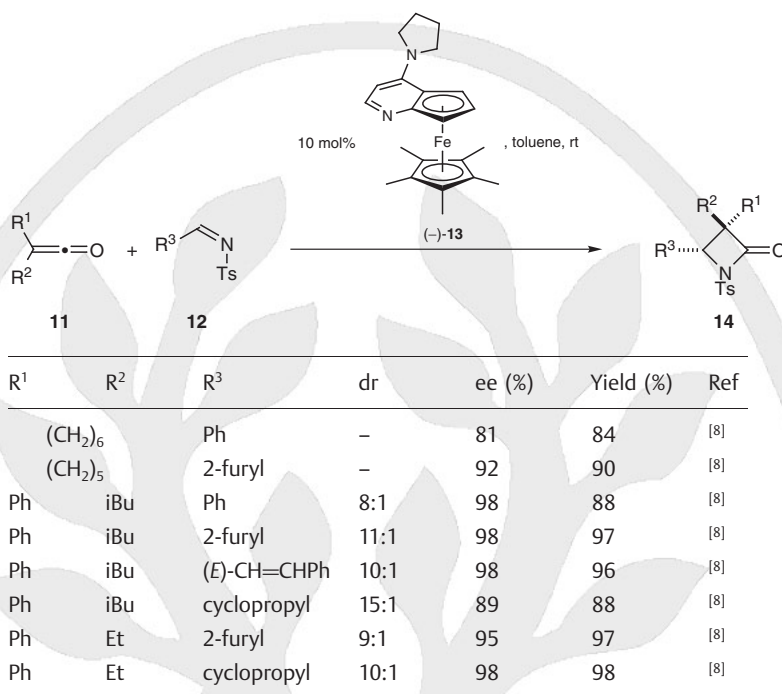
The stereoselective synthesis of *N*-(phenylsulfonyl)-substituted spiro- β -lactams can be accomplished using *N*-(benzylidene)benzenesulfonamide (**5**) and 1-acetyl-4-(benzoyloxy)-*L*-proline (**4**), as the ketene precursor, in the presence of a dehydrating agent.^[5] The above mentioned reaction gives two diastereomeric spiro β -lactams **6A** and **6B** with complete stereoselectivity at the spiro carbon (Scheme 2).

Scheme 2 Stereoselective Synthesis of Substituted Spiro β -Lactams^[5]

Asymmetric auxiliary based syntheses of β -lactams thus far rely on the reactions of imines and ketenes in the presence of stoichiometric amounts of base, a process which proceeds without a catalyst. The first catalyzed nonasymmetric Staudinger cycloaddition has been reported, in which an electron-deficient α -imino ester and diphenylketene are coupled together in the presence of 5% cobaltocenium cobaltate $[\text{Co}(\text{Cp})_2]^+[\text{Co}(\text{CO})_4]^-$ to produce the resultant β -lactam in very good yield.^[6] There are only two reports in the literature of enantioselective catalysis for the asymmetric synthesis of β -lactams. The first report shows that a catalytic asymmetric reaction between an electron-deficient imino ester **8** and the ketene derived from acid chloride **7**, in the presence of various synthetic cinchona alkaloid derivatives, e.g. **9**, as catalysts, produces optically enriched β -lactam **10** in excellent yield and enantiomeric excess (Scheme 3).^[7] The limitation to this study is that only one imine was used as substrate.

Scheme 3 Bifunctional Lewis Acid and Nucleophile-Catalyzed Synthesis of β -Lactams^[7]

The second study shows that the planar chiral ferrocene species (–)-**13** is an effective catalyst for the asymmetric coupling of symmetrical and unsymmetrical ketenes **11** to a wide range of imines **12**, giving β -lactams **14** with good stereoselectivity and yield (Scheme 4).^[8] Other examples of this type of reaction have been reported.^[9–11]

Scheme 4 Catalytic Enantioselective Staudinger Cycloaddition Reactions of Symmetrical and Unsymmetrical Disubstituted Ketenes with *N*-Tosylimines^[8]**Methyl 6-(1-Naphthoyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-3-carboxylate (3, R¹ = 1-Naphthyl); Typical Procedure:**^[4]

Meldrum's acid derivative **1** (630 mg, 2.11 mmol) and 4,5-dihydro-1,3-thiazole **2** (185 mg, 1.27 mmol) were dissolved in dry benzene (28 mL) (**CAUTION: carcinogen**) and cooled to 5 °C. HCl(g) was bubbled through the mixture for 10 min. The resulting turbid mixture was heated for 1.5 h at 79 °C and then cooled to rt. The resulting mixture was diluted with EtOAc and washed with ice-cold H₂O and brine. The aqueous phase was extracted with CH₂Cl₂ (2 ×), and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated. Flash chromatography (heptane/EtOAc 1:1 to 3:7) gave **3** as a white foam; yield: 403 mg (93%); [α]_D²⁰ +2.7 (c 1.77, CHCl₃).

Ethyl (2*R*,3*R*)-4-Oxo-3-phenyl-1-tosylazetidine-2-carboxylate (10):^[6]

To a suspension of In(OTf)₃ (3 mg, 0.013 mmol), benzoylquinine **9** (5.6 mg, 0.013 mmol), and a proton sponge (28 mg, 0.13 mmol) in toluene (7.5 mL) at –78 °C was added dropwise 1-chloro-2-phenylethanone (**7**; 20 mg, 0.13 mmol) in toluene (0.5 mL). A soln of imine **8** (32 mg, 0.13 mmol) in toluene (1 mL) was then added via syringe pump over 1 h. The reaction was allowed to warm to rt over 6 h, before it was quenched with 1 M HCl (3 mL). The aqueous layer was extracted with CH₂Cl₂ (2 ×) and the combined organic layers were dried (MgSO₄) and filtered through Celite. Absorption onto silica gel followed by column chromatography (Et₂O/hexanes 4:1) afforded **10**; yield: 46 mg (95%); 98% ee; dr 60:1.

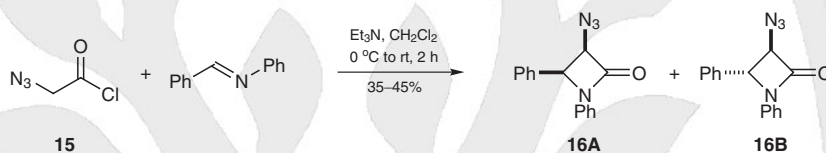
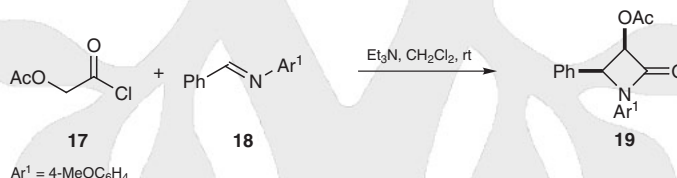
3-(2-Furyl)-2-tosyl-2-azaspiro[3.5]nonan-1-one [14, R¹, R² = (CH₂)₅; R³ = 2-Furyl]:^[8]

In a N₂-filled glove box, an equimolar soln of cyclohexylidenemethanone [**11**, R¹, R² = (CH₂)₅] and *N*-(2-furylmethylene)-4-toluenesulfonamide (**12**, R³ = 2-furyl) in toluene (0.31 mL) was heated with the catalyst (–)-**13** (10 mol%). The mixture was stirred at rt for 18 h, then purified directly by flash column chromatography to give the product; yield: 90%; 92% ee.

21.9.1.1.1

**Variation 1:
Using Acid Chlorides**

The acid chlorides most commonly used in the synthesis of β -lactams are azidoacetyl chloride (**15**) and the protected hydroxyacetyl chloride **18**. The reaction of the former reagent with an imine is known as the Bose reaction and allows for the introduction of a latent amino group at the C3 position of the β -lactam ring, e.g. formation of β -lactams **16A** and **16B** (Scheme 5).^[12] The only limitation to the Bose reaction is that it is unsuitable for large-scale preparations because of the potentially explosive decomposition of azidoacetic acid and its derivatives.^[13] Reaction of a protected hydroxyacetyl chloride, e.g. **17**, with imines such as **18**, allows for the introduction of a C3 hydroxy group, upon removal of the protecting group, onto the β -lactam, e.g. the synthesis of 3-acetoxy derivative **19** (Scheme 6). The protecting groups used include acetoxy, benzyl, and trialkylsilyl, which can be easily removed under standard conditions. The corresponding β -lactams are versatile synthons for penicillins and α -hydroxy- β -amino acids.

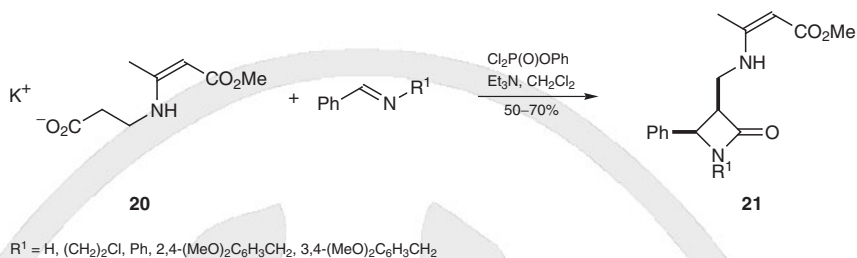
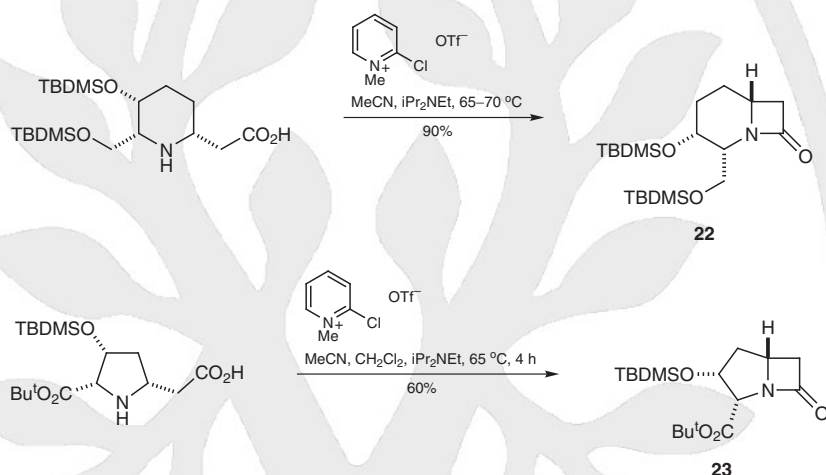
Scheme 5 Bose Reaction of Azidoacetyl Chloride with an Imine^[12]**Scheme 6** Reaction of Acetoxyacetyl Chloride with an Imine^[14]**3-Acetoxy-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (19); General Procedure:**^[14]

A soln of acetoxyacetyl chloride **17** (7.3 mol) in dry CH_2Cl_2 (50 mL) was added dropwise over 1 h to a mixture of the imine **18** (8.76 mol) and Et_3N (17.5 mol) in dry CH_2Cl_2 (100 mL) at rt. The mixture was stirred for an additional 1 h at rt and was then washed with H_2O . The organic layer was separated and dried (NaSO_4). Removal of the solvent under reduced pressure and purification by column chromatography gave the product.

21.9.1.1.2

**Variation 2:
Using Carboxylic Acids or Their Salts**

Carboxylic acids or their salts can be used in the synthesis of β -lactams; however, they require an activating reagent such as Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide),^[15] phenyl dichlorophosphate,^[16] or a mixed anhydride. The most commonly used activating agent is phenyl dichlorophosphate, where the reactive species is a ketene derived from a mixed carboxylic–phosphoric acid anhydride and a tertiary amine base, which then reacts with an imine to produce the β -lactam.^[16] This procedure has been adapted for the synthesis of β -lactams **21** from the carboxylic acid salt **20** (Scheme 7).^[16] A modified Mukaiyama reagent^[17] has been used for the synthesis of carbapenems (e.g., **22** and **23**) via ring closure of a functionalized piperidine or pyrrolidine (Scheme 8).^[18]

Scheme 7 Synthesis of a β -Lactam Using Phenyl Dichlorophosphate^[16]**Scheme 8** Intramolecular Cyclization To Give a β -Lactam Using a Modified Mukaiyama Reagent^[17,18]

(3R,4R)-1-(3,4-Dimethoxybenzyl)-3-[(4-oxo-4-methoxybut-2-en-2-yl)amino]methyl-4-phenylazetidin-2-one [21; $\text{R}^1 = 3,4-(\text{MeO})_2\text{C}_6\text{H}_3\text{CH}_2$]:^[16]

Potassium 3-[(4-methoxy-4-oxobut-2-en-2-yl)amino]propanoate (**20**; 2.12 g, 10 mmol) was suspended in anhyd CH_2Cl_2 (25 mL) to which was added Et_3N (4.2 mL, 30 mmol) and the imine (10 mmol). The mixture was cooled to 0°C and phenyl dichlorophosphate (1.5 mL, 10 mmol) was added. The mixture was stirred overnight at rt, washed sequentially with H_2O (2×20 mL), 5% aq NaHCO_3 (20 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave the crude β -lactam which was recrystallized (EtOH); yield: 70%; mp $156-157^\circ\text{C}$.

***tert*-Butyl (2S,3R)-3-(*tert*-Butyldimethylsiloxy)-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (**23**):^[18]**

To a soln of 2-chloro-1-methylpyridinium trifluoromethanesulfonate (2.17 g, 7.90 mmol) and $i\text{Pr}_2\text{NEt}$ (5.20 mL, 29.8 mmol) in MeCN (475 mL) was added a soln of the amino acid (0.835 g, 2.32 mmol) in $\text{MeCN}/\text{CH}_2\text{Cl}_2$ (16:1, 170 mL) dropwise over 4 h at 65°C . After the addition was complete, the soln was heated at 65°C for an additional 15 min, allowed to cool to rt, and stirred for 12 h. The soln was diluted with CH_2Cl_2 (150 mL) and concentrated to half of its original volume. Additional CH_2Cl_2 (200 mL) was added, and the soln was concentrated to 100 mL and then partitioned between CH_2Cl_2 (300 mL) and H_2O (300 mL). The aqueous phase was extracted with CH_2Cl_2 (3×100 mL), and the combined organic layers were dried (MgSO_4), filtered, and concentrated to afford a dark red oil. Chromatogra-

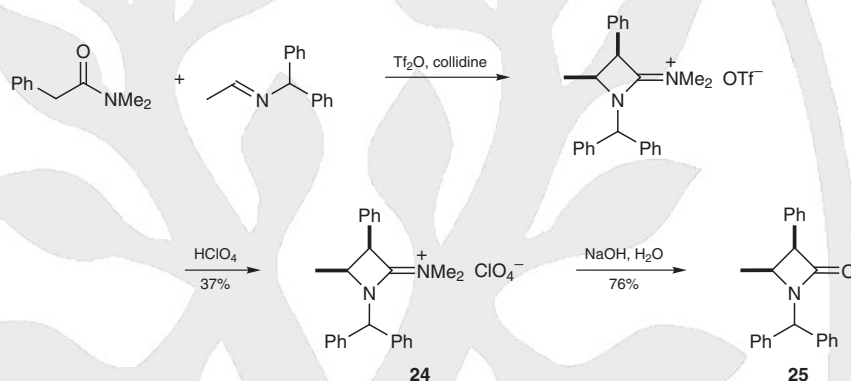
phy (silica gel, hexanes/EtOAc 4:1) gave a white solid; yield: 0.477 g (60%); mp 41–42 °C; $[\alpha]_{\text{D}}^{22} +135.0$ (c 0.01, CHCl_3).

21.9.1.1.3

Variation 3:**Using Amides via an Azetidin-2-ylideneammonium Salt**

The synthesis of β -lactams via amides usually takes place by $\text{S}_{\text{N}}2$ displacement of a leaving group at the β -position of the amide. It has been reported that reactions between amides and aryl- or alkylimines lead to the formation of azetidin-2-ylideneammonium salts, e.g. **24**.^[19] These salts can be hydrolyzed under aqueous basic conditions to give β -lactams **25** (Scheme 9). It is proposed that the course of the reaction is similar to that of the ketene–imine [2+2] cycloaddition, and the stereochemical outcome of the reaction is analogous, forming *cis*-substituted β -lactams.

Scheme 9 Synthesis of a β -Lactam via an Azetidin-2-ylideneammonium Perchlorate^[19]



(3R,4S)-4-Methyl-3-phenylazetidin-2-ylidene(dimethyl)ammonium Perchlorate (24):^[19]

An equimolar mixture of the imine and collidine in 1,2-dichloroethane was added at –20 °C to a soln of the amide and TiF_2O . The progress of the reaction was monitored by IR following the formation of the azetidin-2-ylideneammonium trifluoromethanesulfonate peak at 1695–1720 cm^{-1} . The solvent was removed under reduced pressure, and the *cis/trans* product distribution of the azetidin-2-ylideneammonium trifluoromethanesulfonates was determined by ^1H NMR. The oily residue was repeatedly extracted with Et_2O and dissolved in CH_2Cl_2 . The mixture of the *cis/trans* azetidin-2-ylideneammonium trifluoromethanesulfonates was converted into the corresponding perchlorate salts on treatment with HClO_4 . The collidine perchlorate was extracted from the mixture by washing with 6 M HCl and H_2O , and the organic layer was dried (Na_2SO_4). Removal of the solvent under reduced pressure gave **24**, which was purified by flash column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeCN}$).

(3R,4S)-1-(Diphenylmethyl)-4-methyl-3-phenylazetidin-2-one (25):^[19]

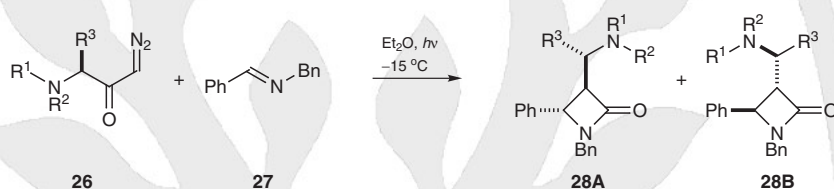
1 M aq NaOH (10 mL) was added to a soln of **24** (0.41 g, 0.9 mmol) in acetone/ H_2O (10 mL). The soln was left at 25 °C for 1 h, then concentrated under reduced pressure and extracted with CH_2Cl_2 . The organic layer was dried (Na_2SO_4). After removal of the solvent under reduced pressure, chromatography of the residue (pentane/EtOAc 13:2) afforded **25** as an oil; yield: 0.22 g (76%).

21.9.1.1.4

**Variation 4:
By Decomposition of α -Diazoketones**

When the photochemical decomposition of α -diazoketones **26** to give ketenes derived from protected α -amino acids is carried out in the presence of imines, e.g. **27**, β -lactams **28A** and **28B** are formed in which the substituents at the C3 and C4 positions are *trans* (Scheme 10).^[20] The unusual *trans*-selectivity could be attributed to the photochemically induced *syn/anti*-isomerization of the imines. This methodology can be applied to diazoketones derived from oligopeptides to form peptidomimetic compounds that incorporate a β -lactam ring.^[21] Microwave irradiation of α -diazoketones in the presence of imines can also lead to the formation of *trans*-disubstituted β -lactams.^[22] In another report it is shown that α -diazo thioesters, e.g. **29** in the presence of rhodium(II) acetate undergo a “thia-Wolff rearrangement” producing sulfanyl-substituted ketenes that react with imines to form *trans*-substituted β -lactams, e.g. **30** (Scheme 10).^[23]

Scheme 10 Decomposition of α -Diazoketones in the Presence of Imines To Form β -Lactams^[20,23]

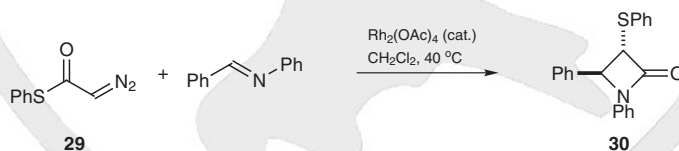


R ¹	R ²	R ³	Yield (%)	Ratio (28A / 28B) ^a	Ref
Cbz	H	Me	71	67:33	[20]
Cbz	H	iPr	89	82:18	[20]
Cbz	H	s-Bu	90	83:17	[20]
Cbz	H	t-Bu	88	93:7	[20]
Boc	(CH ₂) ₃		63	63:37	[20]
Cbz	H	(CH ₂) ₃ NHBoc	70	70:30	[20]
Cbz	H	CH(Me)OTBDMS	45	80:20	[20]
Boc	H	CH(Me)OTBDMS	37 ^b	80:20 ^c	[20]

^a Ratio of diastereomers determined by HPLC.

^b Isolated yield of **28A**.

^c Determined by ¹H NMR spectroscopy.


3-(Aminomethyl)-1-benzyl-4-phenylazetidin-2-ones **28A/**28B**; General Procedure:**^[20]

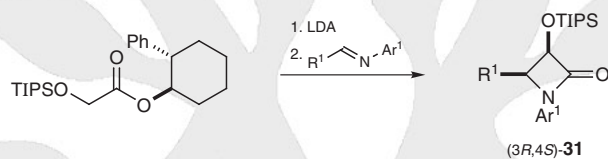
In a quartz photoreactor the diazo ketone **26** and the imine **27** (1.5 equiv) were dissolved in Et₂O (300 mL), and the mixture was cooled to –15 °C and irradiated for 90 min. The mixture was stirred for another 30 min at that temperature and warmed to rt. The soln was concentrated and the imine and other non-polar compounds (polymerized ether) were removed by filtrative column chromatography (silica gel, petroleum ether/EtOAc 7:1 to 1:1). After determination of the isomer ratio (HPLC and ¹H NMR), the diastereomers **28A** and **28B** were separated by chromatography.

21.9.1.2

**Method 2:
Ester Enolate–Imine Cyclocondensations**

The first report of a one-pot ester enolate–imine condensation for the synthesis of β -lactams was by Gilman and Speeter in 1943.^[24] Since that time a number of papers have appeared dealing with the formation of the β -lactam ring via ester enolate–imine condensation.^[25] Ojima's method for the asymmetric synthesis of β -lactams via chiral lithium ester enolate–imine condensation produces optimal results with respect to enantiomeric excess of the β -lactams formed, as shown by the formation of **31** (Scheme 11).^[26] The chiral auxiliary used is (–)-*trans*-2-phenylcyclohexanol, which can be readily obtained on a large scale,^[26] and recycled after the reaction. Ojima's method produces β -lactams with *cis*-substitution with excellent enantiomeric excess. Enantioselective reactions have also been performed by reaction of achiral lithium enolates with imines in the presence of a chiral ligand, affording β -lactams, e.g. **32**, in high yield and enantioselectivity.^[27] This study shows that the reactions of lithium enolates derived from 1-ethylpropyl 2-methylpropanoate with imines can be accelerated by the addition of a chiral bidentate ether and an excess of a lithium amide (Scheme 11). It is also shown that use of only a catalytic amount of the chiral ligand can lead to products in high yields and enantioselectivities.

Scheme 11 Asymmetric Synthesis of β -Lactams via Chiral Ester Enolate–Imine Condensation^[26,27]

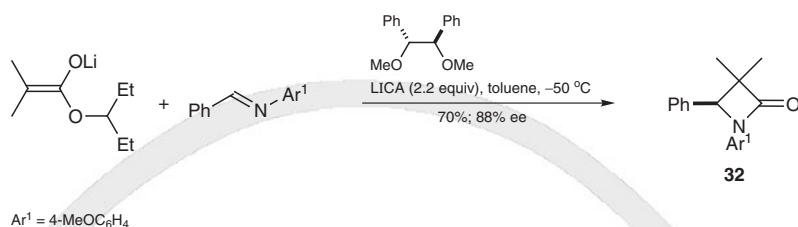


R ¹	Yield (%)	ee (%) ^a	Ref
Ph	98	89	[26]
4-FC ₆ H ₄	98	81	[26]
4-F ₃ CC ₆ H ₄	99	84	[26]
2-furyl	92 ^b	78 ^c	[26]
(<i>E</i>)-CH=CHPh	96	85	[26]
	94	72	[26]
CH ₂ iPr	92	85	[26]
CH ₂ Cy	90	85	[26]

^a Determined by chiral HPLC on chiral column (DAICEL CHIRACEL-OD) using hexane/propan-2-ol as the solvent.

^b Obtained as a mixture of *cis*- and *trans*-isomers (*cis*/*trans* 91:9).

^c Enantiomeric excess for the *cis*-isomer.

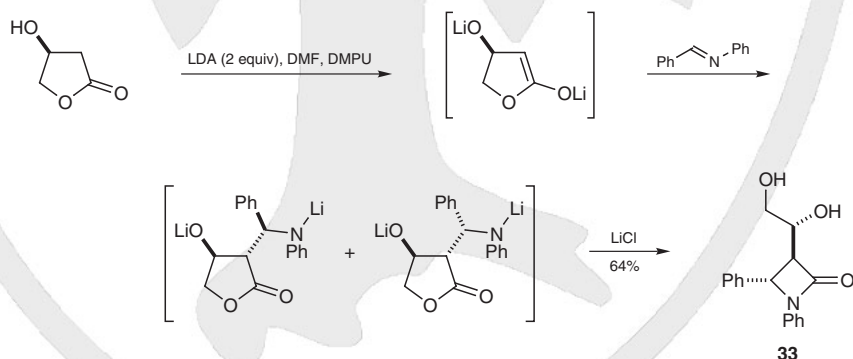
**1-(4-Methoxyphenyl)-3-(triisopropylsiloxy)azetidin-2-ones 31; General Procedure:**^[26]

To a soln of iPr_2NH (2.20 mmol) in THF (2.0 mL) was added 2.5 M BuLi (2.20 mmol) in THF (1.0 mL) at 0 °C. The soln was stirred for 30 min at 0 °C and then cooled to -78 °C. To the mixture was added a soln of the ester (2.0 mmol) in THF (2.0 mL). The soln was stirred for 2 h followed by addition of a soln of the imine (2.0 mmol) in THF (2.0 mL). The mixture was stirred at -78 °C for 4 h, and then slowly allowed to warm to rt, and was further stirred overnight. The reaction was quenched with sat. aq NH_4Cl (50 mL), and the mixture was extracted with CHCl_3 (3 \times 25 mL). The combined extracts were dried (MgSO_4) and concentrated under reduced pressure. The residue was submitted to short column chromatography (silica gel, hexane/EtOAc 6:1) to give the β -lactam **31**; yield: 72–89%.

21.9.1.2.1

**Variation 1:
From γ -Lactones**

β -Lactams **33** can be prepared stereoselectively from the condensation of (*S*)-3-hydroxy- γ -lactone with an aryl-substituted imine (Scheme 12).^[28] Initial studies reveal both electron-withdrawing and electron-donating substituents on the aromatic rings are tolerated in the reaction; however, the reaction does not work well with imines bearing alkyl groups. The reaction occurs diastereo- and enantioselectively to give the corresponding *trans*- β -lactams in good yields. These products can be further converted into the corresponding β -lactam cholesterol absorption inhibitors.^[29]

Scheme 12 Synthesis of a β -Lactam from an (*S*)-3-Hydroxy- γ -lactone^[29]**(3*S*,4*S*)-3-(1,2-Dihydroxyethyl)-1,4-diphenylazetidin-2-one (33):**^[29]

To a dry 5-L, three-necked flask equipped with a mechanical stirrer, thermometer, and addition funnel were added sequentially THF (500 mL), DMPU (400 mL), and iPr_2NH (120 mL, 0.92 mol). To the cooled mixture at -45 to -40 °C was added dropwise 2.5 M BuLi in hexane (368 mL, 0.92 mol). After 20 min, the lactone (47 g, 0.46 mol) in THF (250 mL) was introduced and the reaction was agitated at -45 to -40 °C for 2 h. To the resulting mixture was added dropwise a soln of the imine (100 g, 0.33 mol) in DMF (1 L) over a period of 30 min.

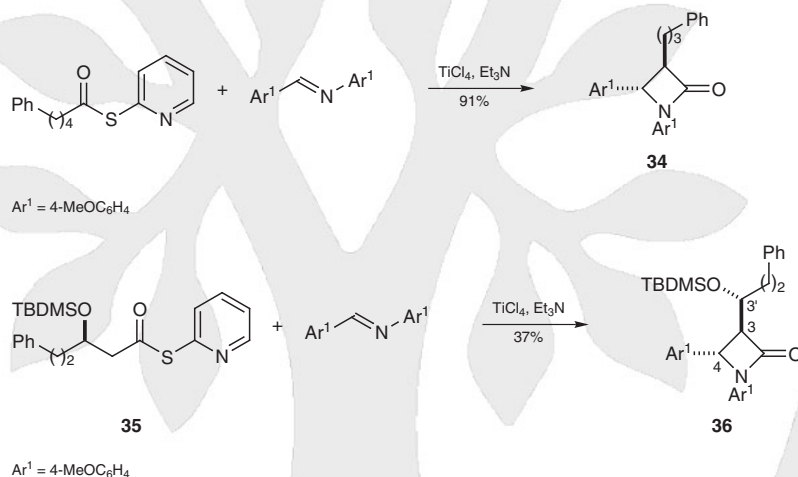
The reaction was maintained at -30 to -25°C for 14–18 h and -17 to -13°C for another 4 h. To the mixture was added LiCl (14 g) dissolved in DMF (400 mL). After another 2 h at -15°C , AcOH (200 mL) was added to the mixture. The mixture was poured slowly into a 10-L extractor containing 3 M HCl (2 L), ice (1 L), and EtOAc (2.5 L). The mixture was stirred for 15 min and separated into layers. The aqueous layer was extracted with EtOAc (2×1 L). The combined organic layers were washed with brine (4×2 L) and concentrated. Addition of toluene (250 mL) led to crystallization of *trans*-**33**. The solid was collected by filtration and dried at 50°C to give pure *trans*-**33**; yield: 85.5 g (64%).

21.9.1.2.2

Variation 2: From 2-Pyridyl Thioesters

β -Lactams can be produced by one-pot condensation of the titanium enolate of *S*-2-pyridyl thioesters with the corresponding imine. The reaction proceeds with complete stereoselectivity to afford the *trans*- β -lactam adduct.^[30] Attempts to obtain β -lactam **34** in enantiomerically enriched form led to the use of chiral thioester (*R*)-**35**, which gives a 94:6 mixture of 3,3'-*anti*-3,4-*trans* and 3,3'-*syn*-3,4-*trans* isomers in 37% yield (Scheme 13). The 3,3'-*anti* isomer **36** can be isolated in enantiomerically pure form by column chromatography.

Scheme 13 Stereoselective Condensation of *S*-2-Pyridyl Thioesters with an Arylimine^[30]



(3*S*,4*S*)-1,3-Bis(4-methoxyphenyl)-3-(3-phenylpropyl)azetidin-2-one (**34**); General Procedure:^[29]

To a 0.05 M soln of the thioester (1–10 mmol) and 1 M TiCl₄ in dry CH₂Cl₂ (1 equiv) cooled at -78°C and kept under N₂, Et₃N (1.1 equiv) was added dropwise. The dark purple soln was stirred at -78°C for 15 min, and a 1 M soln of the imine (0.5 equiv) in CH₂Cl₂ was added dropwise. After 5 h stirring at -78°C , the mixture was warmed to rt and stirred overnight. The reaction was quenched by the addition of sat. NaHCO₃ and the resulting slurry was filtered through Celite. The organic phase was separated and the aqueous phase was extracted with CH₂Cl₂ (2 \times). The combined organic phases were dried, and concentrated under vacuum. The residue was dissolved in THF and treated with 1 M aq KOH (2 equiv) to hydrolyze the excess of the thioester. This procedure does not alter the diastereomeric composition and greatly simplifies the NMR analysis of the crude product. Et₂O was added to the mixture and the organic phase was separated, washed with brine, dried, and concentrated under vacuum to give the product, which was analyzed by ¹H NMR to deter-

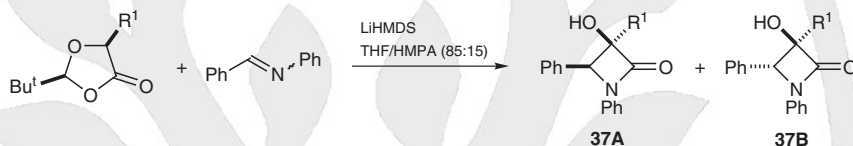
mine the diastereomeric ratio. Flash chromatography (hexanes/Et₂O 4:1 or 7:3) gave the pure product.

21.9.1.2.3

Variation 3: From 1,3-Dioxolan-4-ones

The reaction of imines with enolates of chiral 1,3-dioxolan-4-ones can be applied to the synthesis of 3-alkyl-3-hydroxy- β -lactams. The 1,3-dioxolan-4-ones are used as a diastereomeric mixtures to produce the corresponding non-racemic mixtures of lithium enolates. These enolates undergo addition to the imine followed by cyclization and removal of the auxiliary, to afford the corresponding β -lactams, e.g. **37A** and **37B**, as diastereomeric mixtures with high enantiomeric excess (Scheme 14).^[31] The best results are obtained when the enolates are generated in situ by slow addition of the lactones to a soln of lithium hexamethyldisilazane and imine at -90°C , or -50°C for the (5*S*)-phenyl-1,3-dioxolan-4-one, in a tetrahydrofuran/hexamethylphosphoric triamide (17:3) solvent system.

Scheme 14 Reaction of the Lithium Enolate of a Chiral 1,3-Dioxolan-4-one with an Imine^[31]



R ¹	Yield (%)	Ratio (37A / 37B)	ee (%)	Ref
Me	69	18:82	94	[31]
Ph	82	44:56	99	[31]
iPr	59	71:29	97	[31]
CH ₂ CO ₂ H	45	78:22	99	[31]

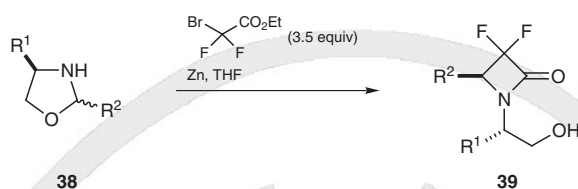
(3*S*,4*S*)-3-Hydroxy-3-isopropyl-1,4-diphenylazetidin-2-one (**37A**, R¹ = iPr) and (3*S*,4*R*)-3-Hydroxy-3-isopropyl-1,4-diphenylazetidin-2-one (**37B**, R¹ = iPr); **Typical Procedure:**^[31]

A THF soln of the 1,3-dioxolan-4-one (1.61 mmol) was added via syringe pump (8 h) to a soln of the imine (3.0 mmol) in THF/HMPA (17:3) and LiHMDS (2.9 mmol) at -90°C under stirring. Occasionally, the temperature was raised for the time required. The mixture was treated with sat. aq NH₄Cl. The organic layer was extracted with brine (2 \times) and dried (Na₂SO₄), and the solvent was removed under reduced pressure. The *Z/E*-isomer ratio was determined by ¹H NMR analysis of the residue. The diastereomeric β -lactams were separated by flash chromatography (silica gel, EtOAc/pentane 2:13) or, when possible, by recrystallization, to afford the mixture of **37A** (R¹ = iPr) and **37B** (R¹ = iPr); yield: 59%.

21.9.1.2.4

Variation 4: From Ethyl Bromodifluoroacetate

The Reformatsky reaction of ethyl bromodifluoroacetate with imines to provide β -lactams has been previously described by Kobayashi; however, only moderate diastereoselectivities were reported using (α -methylbenzyl)imines.^[32] Reaction of chiral oxazolidines **38** with ethyl bromodifluoroacetate in the presence of zinc dust gives 3,3-difluoro- β -lactams **39** with good yields and high diastereoselectivity (Scheme 15).^[33]

Scheme 15 Reformatsky Reaction of Ethyl Bromodifluoroacetate and Chiral Oxazolidines^[32,33]

R ¹	R ²	de (%)	Yield (%)	Ref
Ph	Ph	>99 ^a	65	[33]
Et	Ph	96 ^a	69 ^c	[33]
Et	(CH ₂) ₄ Me	90 ^b	35	[33]
Et	2-furyl	85 ^a	62	[33]
Et	(<i>E</i>)-CH=CHMe	96 ^b	32	[33]

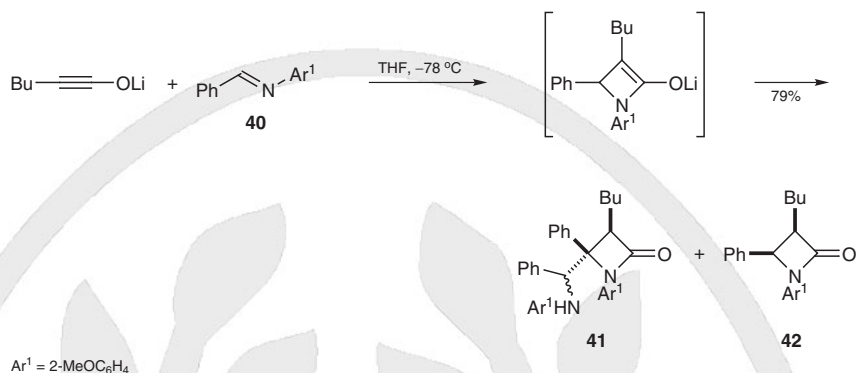
^a Diastereomeric excess was determined by HPLC–mass spectrometry.^b Diastereomeric excess was determined by ¹⁹F NMR spectroscopy.^c 5% of the noncyclized compound was observed.**(4*S*)-3,3-Difluoro-1-[(1*S*)-1-(1-hydroxymethyl)propyl]-4-phenylazetidin-2-one (39, R¹ = Et; R² = Ph); Typical Procedure:**^[32]

The oxazolidine **38** were used without purification but were dried before use by azeotropic distillation with toluene. Zn was freshly activated and dried. Moisture-sensitive reactions were carried out in predried glassware and under an argon atmosphere. To a refluxing suspension of freshly activated Zn dust (2.3 g, 35.4 mmol) in dry THF (10 mL) was added a soln of the oxazolidine **38** (R¹ = Et; R² = Ph) (1.3 g, 7.38 mmol) and ethyl bromodifluoroacetate (5.24 g, 25.83 mmol) in THF (1.5 mL) at a rate so as to maintain a vigorous reflux. After 1 h, the mixture was cooled and the reaction was quenched by addition of sat. NH₄Cl (20 mL). After filtration, the aqueous layer was extracted with CH₂Cl₂ (2 × 20 mL). The organic layers were combined, dried (MgSO₄), and concentrated under reduced pressure. The residue was then purified by flash column chromatography (EtOAc/cyclohexane 1:9) to give a colorless oil; yield: 1.45 g (69%); [α]_D²⁵ –15.4 (*c* 1, CHCl₃).

21.9.1.2.5

**Variation 5:
From Lithium Ynolates**

Lithium ynolates, prepared from ethyl 2,2-dibromohexanoate, react with *N*-sulfonylimines and with *N*-(2-methoxyphenyl)imines to form β -lactams (Scheme 16).^[34] *N*-(4-Methoxyphenyl)imines are found to be much less reactive toward lithium ynolates, and further attempts to promote the addition with a variety of Lewis acids have proved to be ineffective. The 2-methoxyphenyl substituent on the nitrogen of imine **40** (Ar¹ = 2-MeOC₆H₄) is shown to accelerate the reaction, due to coordination with the lithium ynolate. The intermediate β -lactam enolate is much more nucleophilic than the lithium ynolate; therefore the β -lactam **41** is comprised of 2 equivalents of the starting imine, and little or no formation of β -lactam **42** is observed.

Scheme 16 Cycloaddition of Ynolates with *N*-(2-Methoxyphenyl)phenylimine^[34]**3-Butyl-1-(2-methoxyphenyl)-4-[(2-methoxyphenyl)amino(phenyl)methyl]-4-phenylazetidin-2-one (41):**^[34]

The *N*-(2-methoxyphenyl)imine **40** (1.0 mmol) was added to a THF soln of the lithium ynolate (8 mL), prepared from the dibromo ester (1.2 mmol) and *t*-BuLi (4.8 mmol), at -78°C . The starting imine disappeared within 2 h at -78°C and, after workup, the β -lactam **41** was produced as a single isomer; yield: 79%.

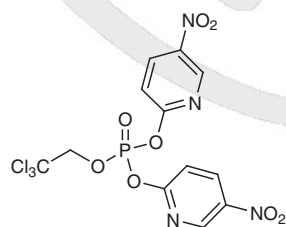
21.9.1.3

**Method 3:
Cyclocondensation of β -Amino Acid Derivatives**

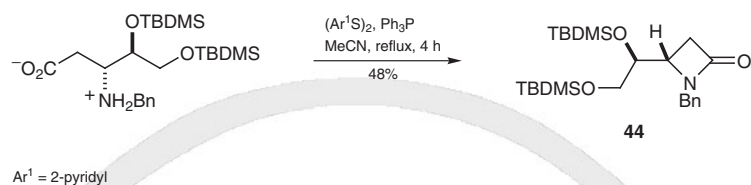
The cyclization of β -amino acids to β -lactams is a common method, requiring either activation of the carboxylate or formation of an amide anion. Examples of condensing reagents include organophosphorus compounds, e.g. phosphorus trichloride, ethyl dichlorophosphate,^[35] phenyl dichlorophosphate,^[35] phenylphosphonic dichloride,^[35] bis(5-nitro-2-pyridyl) 2,2,2-trichloroethyl phosphate,^[36] acetyl chloride, thionyl chloride, methanesulfonyl chloride, and triphenylphosphine/2,2'-dipyridyl disulfide.^[37–40] Examples are shown in Scheme 17 for the synthesis of β -lactams **43** and **44**.

Scheme 17 Dehydrative Cyclization of β -Amino Acids with Condensing Reagents^[35,36,38]

Condensing Reagent	Base/Solvent	Yield (%)	Ref
$\text{Cl}_2\text{P}(\text{O})\text{OEt}$	$\text{Et}_3\text{N}/\text{MeCN}$	99	[35]
$\text{Cl}_2\text{P}(\text{O})\text{OEt}$	$\text{Et}_3\text{N}/\text{MeCN}$	95	[35]
$\text{Cl}_2\text{P}(\text{O})\text{Ph}$	$\text{Et}_3\text{N}/\text{MeCN}$	96	[35]

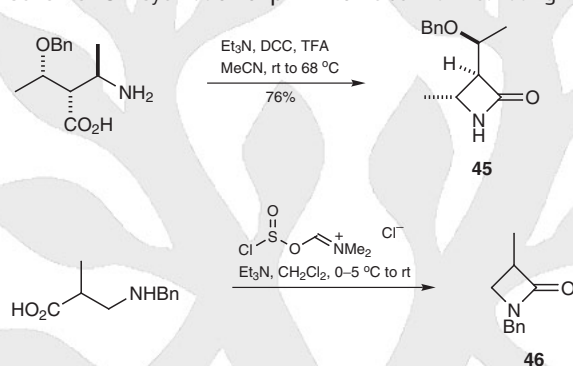


$\text{Et}_3\text{N}/\text{MeCN}$ 93 [35]

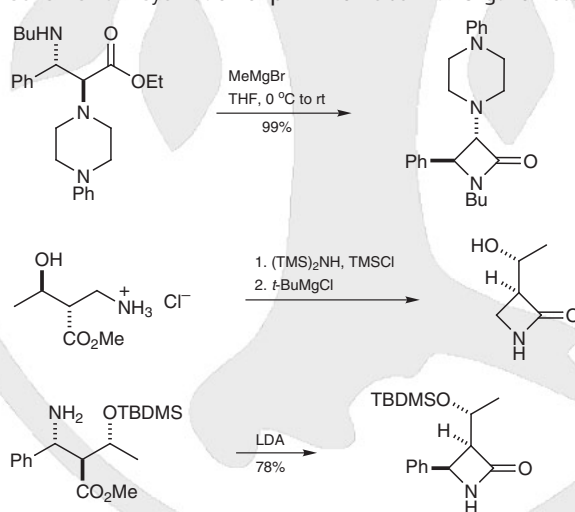


Other reagents include dicyclohexylcarbodiimide, e.g. the formation of **45**,^[41] methylenebis(chlorosulfonyl)oxy(methyl)ammonium chloride, e.g. the formation of β -lactam **46**,^[42] and Mukaiyama's reagent^[15] (Scheme 18). Cyclization of β -amino acids can be promoted with organometallic reagents such as methylmagnesium bromide,^[43,44] phenylmagnesium bromide,^[45] *tert*-butylmagnesium chloride,^[46–48] *tert*-butyllithium,^[49] lithium diisopropylamide,^[50,51] and lithium hexamethyldisilazide^[52] (Scheme 19).

Scheme 18 Cyclization of β -Amino Acids with Activating Reagents^[41,42]



Scheme 19 Cyclization of β -Amino Acids with Organometallic Reagents^[43,47,51]



(3*S*,4*R*)-3-[(1*S*)-(Benzyloxy)ethyl]-4-methylazetidin-2-one (45**):^[41]**

The β -amino acid (448 mg, 1.33 mmol) was dissolved in TFA (25 mL) and MeCN (91 mL) and treated sequentially with Et₃N (3.0 equiv) and DCC (2.2 equiv) at rt. The mixture was then stirred at 65–68 °C for 5.5 h, cooled to rt, and concentrated under reduced pressure. The residue was dissolved in a small amount of Et₂O and filtered to remove suspended material (thorough washing with Et₂O). The filtrate was then concentrated under reduced pres-

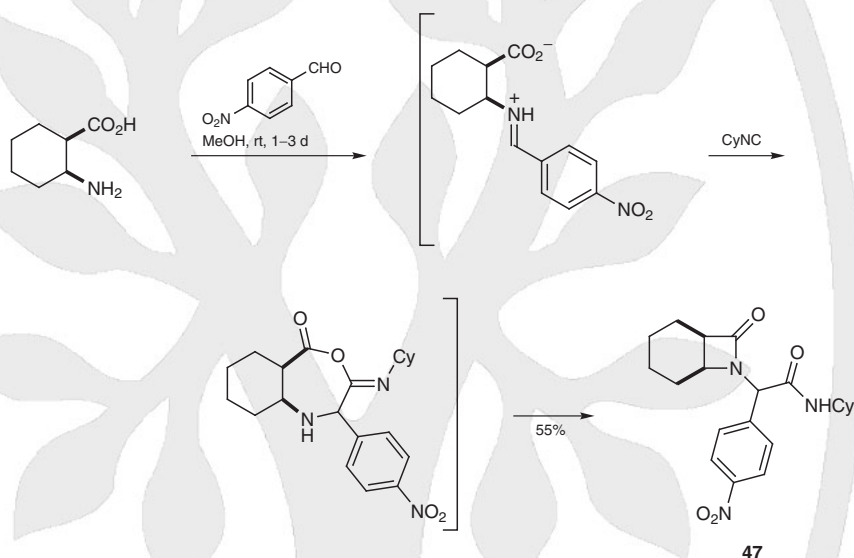
sure and chromatographed (silica gel, hexanes/EtOAc 7:3) to give a pale yellow oil; yield: 76%; $[\alpha]_{\text{D}}^{25} +35.5$ (c 19.8, CH_2Cl_2);

21.9.1.3.1

Variation 1: Via Ugi Three-Component Reaction

Cyclic β -amino acids can be utilized to form *cis*-substituted β -lactams, e.g. **47**, through a one-pot Ugi coupling reaction.^[53] The three components employed in the reaction are an alicyclic *cis*- β -amino acid, an aldehyde, and an isocyanide (Scheme 20). *trans*-Substituted β -amino acids fail to give the corresponding *trans*-substituted β -lactams. In this study only racemic alicyclic *cis*- β -amino acids were used; however in principle the reaction could be amenable to enantioselective synthesis.

Scheme 20 Formation of β -Lactams from Alicyclic β -Amino Acids^[53]



(1R,6S)-7-[(N-Cyclohexylamino)carbonyl](4-nitrophenyl)methyl-8-oxo-7-azabicyclo[4.2.0]octane (47**):**^[53]

The β -amino acid (1.2 mmol) and 4-nitrobenzaldehyde (1.0 mmol) were dissolved in MeOH (5 mL). The soln was allowed to stand at rt for 30 min. The isocyanide (1.0 mmol) was added to the soln and the resulting mixture was stirred at rt for 1–3 days. When the reaction was indicated to be complete by TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97:3), the solvent was removed and the residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97:3). The major isomer **47** was obtained as a 4:1 diastereomeric mixture by recrystallization (Et_2O); yield: 55%; mp 187–189 °C.

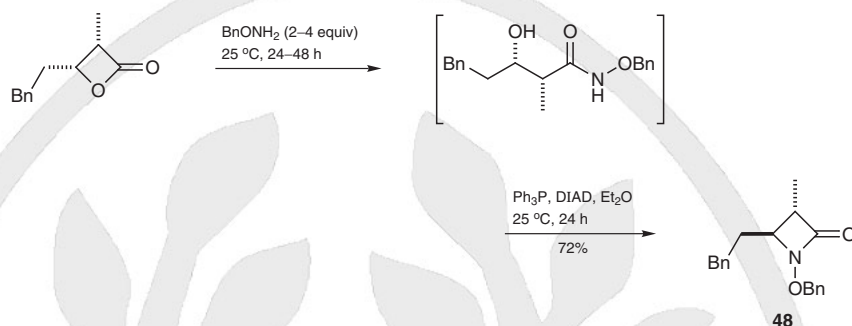
21.9.1.3.2

Variation 2: From β -Lactones

β -Lactones can be directly transformed to β -lactams in a one-pot conversion via a ring-opening/Mitsunobu reaction sequence.^[54] The β -lactone is first converted into a β -hydroxy hydroxamic acid with *O*-benzylhydroxylamine, and without isolation, treated with triphenylphosphine and diisopropyl azodicarboxylate (DIAD) to afford the β -lactams, e.g. **48**, in good overall yields. Because the Mitsunobu reaction step proceeds with inversion

of configuration at the β -carbon, *trans*- β -lactones give the corresponding *cis*- β -lactams and *cis*- β -lactones give the corresponding *trans*- β -lactams (Scheme 21).

Scheme 21 Preparation of β -Lactams from β -Lactones^[54]



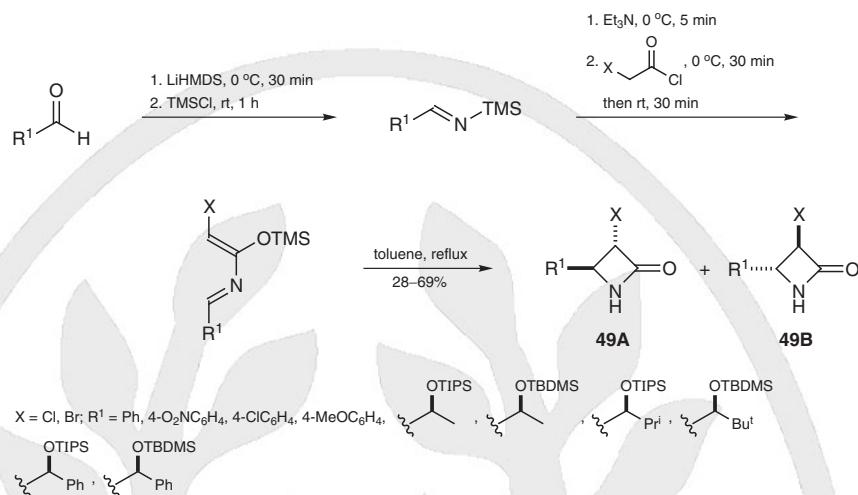
(3*S*,4*S*)-1-(Benzyloxy)-3-methyl-4-(2-phenylethyl)azetidin-2-one (48):^[54]

A mixture of BnONH_2 (2.02 mmol) and the β -lactone (1.02 mmol) was stirred for 2 h at 25 °C, at which point the mixture could not be stirred due to the formation of white precipitates. Anhyd Et_2O (0.3 mL) was added, and the resulting white slurry was stirred for an additional 20 h at 25 °C or until judged complete by TLC analysis. Additional anhyd Et_2O (2 mL) was added to the mixture, and then solid Ph_3P (2.04 mmol) and neat DIAD (95% purity, 2.07 mmol) were sequentially added at 0 °C. The resulting yellow-green soln was stirred at 25 °C for 23 h. The reaction was quenched with 1 M HCl , extracted with Et_2O /EtOAc, dried (Na_2SO_4), filtered, concentrated in vacuo, and purified twice by flash column chromatography (EtOAc/hexane 1:3 and CH_2Cl_2); yield: 72% (*cis/trans* 1:>19).

21.9.1.4

**Method 4:
Ring Closure of 2-Aza-1,3-dienes**

The preparation of β -lactams from a two-step Staudinger cycloaddition reaction of 2-aza-1,3-dienes has been explored, and this procedure generally utilizes a refluxing hydrocarbon solvent such as toluene to promote the ring closure of the azadiene, affording exclusively *trans*-substituted β -lactams.^[55] The 2-aza-1,3-dienes can be easily prepared from the corresponding imine and acid chloride. This methodology can be applied to the synthesis of 3-halo substituted β -lactams, e.g. **49A** and **49B**, which are valuable intermediates for the synthesis of biologically active compounds (Scheme 22).

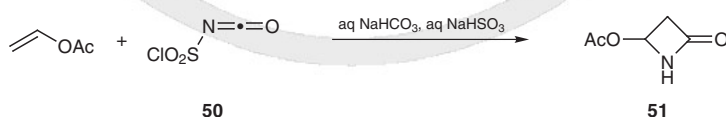
Scheme 22 Preparation of β -Lactams from 2-Aza-1,3-dienes^[55]**3-Chloro-4-phenylazetidin-2-ones 49A and 49B ($R^1 = \text{Ph}$); Typical Procedure:**^[55]

A soln of the *N*-(trimethylsilyl)imine was prepared by dropwise addition of a heptane soln (5 mL) of benzaldehyde (1.0 mmol) to a cooled (0 °C) soln of LiHMDS (1.1 mL, 1.1 mmol). The mixture was stirred for 30 min at this temperature. The formation of the imine was confirmed by an IR spectrum of the mixture ($\tilde{\nu}_{\text{max}} \text{CN} = 1685 \text{ cm}^{-1}$). The imine soln was then warmed to rt, TMSCl (0.15 mL, 1.1 mmol) was added in one portion, and this mixture was allowed to stir for 1 h. The mixture was then cooled to 0 °C and Et_3N (0.30 mL, 2.2 mmol) was added in one portion. After stirring this mixture for 5 min at 0 °C, a toluene soln of chloroacetyl chloride (1 mmol) was added very slowly (over 5 min) via syringe. Stirring was maintained for 30 min at 0 °C and 30 min at rt. This yellow-orange mixture was then filtered through Celite. The resultant crude mixture of 2-azabuta-1,3-diene was refluxed in toluene overnight to give **49A** and **49B**; yield: 37%.

21.9.1.5

**Method 5:
Alkene–Isocyanate Cycloadditions**

The [2+2] cycloaddition of an alkene and an isocyanate is a general route to mono- and bicyclic β -lactams. The most useful application of this procedure is the synthesis of 4-acetoxiazetidin-2-one, a versatile synthon in β -lactam-based methodologies.^[56] The reaction between vinyl acetate and chlorosulfonyl isocyanate (**50**) produces 4-acetoxiazetidin-2-one (**51**) in good yield (Scheme 23).^[57] The [2+2] cycloaddition of chlorosulfonyl isocyanate and allylsilanes can be applied to the synthesis of 4-(silylmethyl)-substituted β -lactams.^[58] In another report, optically enriched (allenylmethyl)silanes afforded β -lactams with enantiomeric excesses of about 50%.^[59] Sugar vinyl ethers were subjected to tosyl isocyanate to afford the corresponding β -lactams with high asymmetric induction.^[60]

Scheme 23 [2+2] Cycloaddition of Vinyl Acetate and Chlorosulfonyl Isocyanate^[56]

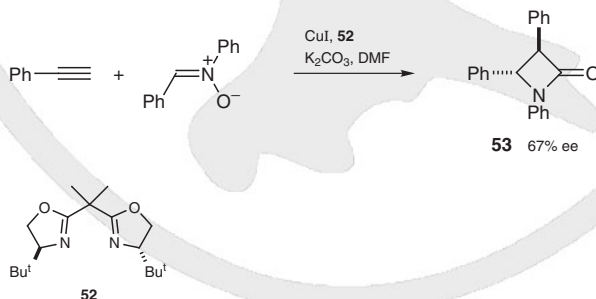
4-Acetoxyazetidin-2-one (51); Typical Procedure:^[56]

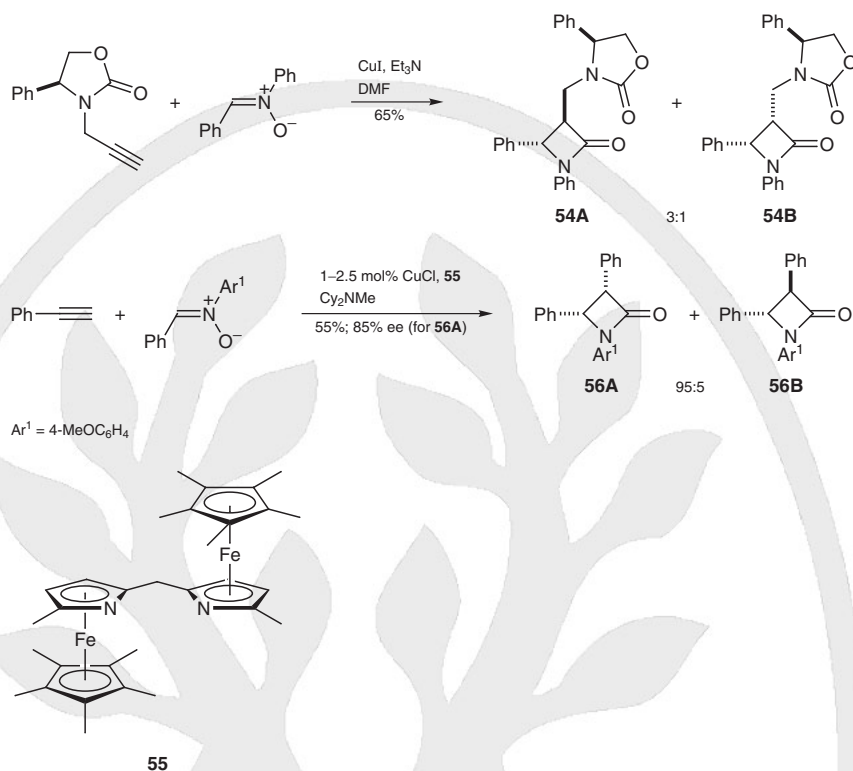
A 500-mL, four-necked, round-bottomed flask equipped with a mechanical stirrer, rubber septum with a N₂ source, thermometer, and a pressure-equalized dropping funnel was charged with vinyl acetate (150 mL, 1.63 mol). Stirring was initiated and the mixture was cooled in an ice-water bath to 3 °C. CSI (**50**; 25 mL, 0.28 mol) was added as rapidly as possible from the addition funnel while allowing the temperature to rise to 10 °C. At this point an exothermic reaction began and intermittent cooling was required to keep the temperature at 10–15 °C for 40 min. The dark red mixture was then cooled to –40 °C in a dry ice/acetone bath. A three-necked, 1.0-L flask equipped with a thermometer, mechanical stirrer, and a septum cap was charged with a mixture of NaHCO₃ (67 g, 0.80 mol), NaHSO₃ (71.5 g, 0.69 mol), and H₂O (200 mL). This mixture was cooled to –20 °C in a dry ice/acetone bath with vigorous stirring. The mixture was added dropwise via cannula at a rate such that the temperature remained at –10 °C (30–40 min). When approximately half of the reaction soln had been added, additional NaHSO₃ (35.7 g, 0.34 mol) was added. After the addition was complete, the mixture was stirred for an additional 40 min at –10 °C. The light yellow mixture (pH 7) was extracted with CHCl₃ (3 × 500 mL). The combined organic extracts were dried (MgSO₄) and concentrated on a rotary evaporator at 40 °C/70 Torr. Removal of solvent under reduced pressure gave a two-phase, oily mixture. The mixture was stirred with hexane (3 × 100 mL), and the hexane extracts were decanted and discarded. Removal of the final traces of solvent under reduced pressure gave **51** as a light orange oil, which slowly solidified upon standing at –20 °C; yield: 16.1–22.8 g (44–62%, based on CSI). The resulting solid melts at 34 °C.

21.9.1.6

**Method 6:
Nitrone Cycloadditions Employing Alkynes**

The cycloaddition of a copper(I) acetylide and a nitrone to afford a β -lactam was first described by Kinugasa in 1972.^[61] An asymmetric version of the Kinugasa reaction exists, which employs the C₂-symmetric dihydrooxazole **52** as the chiral ligand for the copper catalyst; however, the reaction achieves enantiomeric excesses of only 40–60% for the synthesis of β -lactam **53**.^[62] Investigations into the asymmetric Kinugasa reaction reveal that an Evans chiral auxiliary directly attached to the acetylene component gives high enantioselectivity but poor diastereoselectivity, giving diastereomers **54A** and **54B**.^[63] In another report, which employs a C₂-symmetric planar-chiral bis(azaferrocene) catalyst **55**, β -lactams **56A** and **56B** are obtained with good enantiomeric excesses and *cis*-diastereoselection (Scheme 24).^[64]

Scheme 24 Asymmetric Kinugasa Reactions^[62–64]



3,4-Diphenyl-1-(4-methoxyphenyl)azetidin-2-one (56A/56B):^[64]

The catalyst was prepared by adding a soln of ligand **55** (10% excess relative to CuCl) in MeCN to CuCl and stirring the resulting mixture for 1 h (catalyst loading: 2.5 mol%). This soln was then added to Cy₂NMe (39.4 mg, 0.202 mmol or a 20-fold excess relative to CuCl), and the resulting mixture was transferred to a Schlenk tube that contained the nitronium (93.4 mg, 0.411 mmol). The mixture was cooled to 0 °C, and a soln of the alkyne (62.4 mg, 0.611 mmol) in MeCN (total volume 2.0 mL) was added dropwise under an atmosphere of argon. In many cases, the mixture was initially heterogeneous, but turned homogeneous as the reaction proceeded. If the reaction was air-free, the soln was orange. If air was present, then the mixture turned brown, and the catalyst lost its activity. After TLC showed that the nitronium had been consumed, the mixture was passed through a plug of silica gel (MTBE/CH₂Cl₂) to obtain a mixture of **56A** and **56B** as a pale yellow solid; yield: 74.1 mg (55%); (**56A/56B**) 19:1.

21.9.1.7

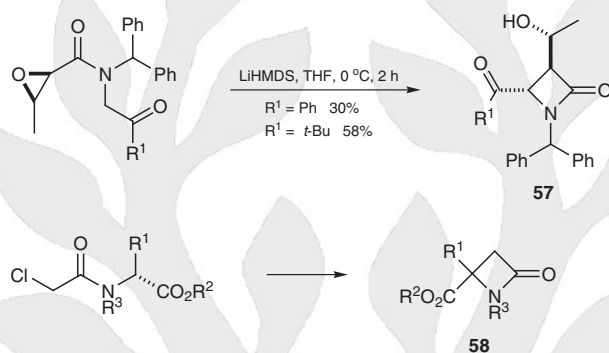
Method 7:

Ring Closures by Nucleophilic S_N2 Displacement

A common means for forming the β-lactam ring is via ring closure by S_N2 displacement. The reaction generally occurs by direct displacement of a leaving group by nucleophilic attack of an amide nitrogen to form the N1—C4 bond of the β-lactam ring, or by a carbanion, forming the C3—C4 bond of the β-lactam ring. Most recent synthetic strategies involve the C3/C4 ring closure of (2*R*,3*R*)-epoxybutanamide precursors or from *N*-benzyl-*N*-chloroacetyl-substituted-α-amino acids (Scheme 25).^[65,66] In the former case, ring closure of (2*R*,3*R*)-epoxybutanamide with lithium hexamethyldisilazanide as the base gives the corresponding β-lactams, e.g. **57**, in moderate to good yields. Other bases such as potassium carbonate or lithium carbonate lead to the formation of the β-lactam in low yields.^[65] *N*-Benzyl-*N*-chloroacetyl-substituted α-amino acids undergo base-promoted intramolecu-

lar alkylation with a variety of different bases to give the corresponding C3-unsubstituted, C4-disubstituted β -lactams **58** (Scheme 25).^[66] Sodium hydride or cesium carbonate give the best results; however, with cesium carbonate, longer reaction times are required.^[66] In a systematic survey of *N*-benzyl-*N*-chloroacetyl-substituted α -amino acids, phenylalanine, alanine, glutamic acid, and ornithine afford optimal results, whereas glycine and leucine analogues give incomplete or complex reaction mixtures.^[66] Asymmetric intramolecular alkylations using phenylalanine and alanine derivatives bearing (+)- or (–)-*N,N*-dicyclohexyl-7,7-dimethylbicyclo[2.2.1]heptane-1-sulfonamide as the chiral auxiliary yield β -lactams, e.g. **59A** and **59B**, with high diastereomeric excesses (Scheme 25).^[67]

Scheme 25 Ring Closures by Nucleophilic S_N2 Displacement^[65–67]

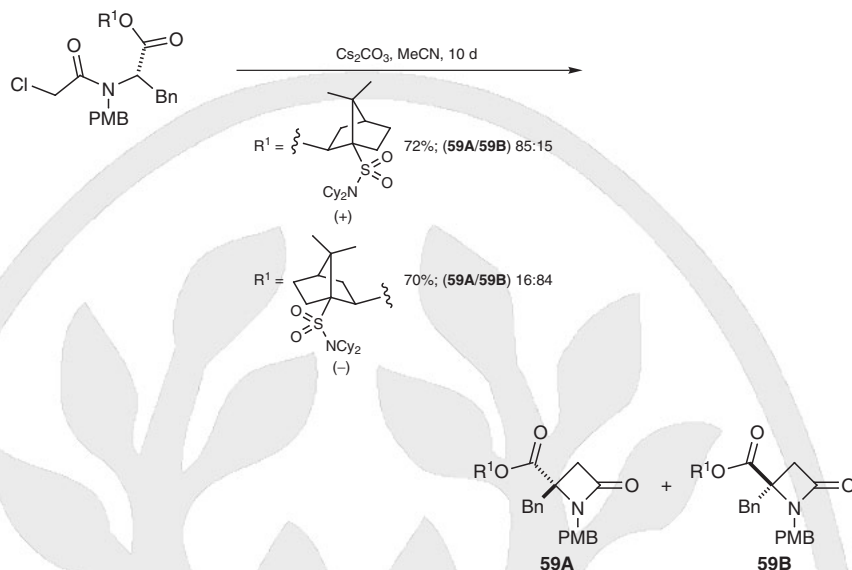


R^1	R^2	R^3	Base	Solvent	Time (d)	Yield (%)	Ref
Me	<i>t</i> -Bu	Bz	NaH	MeCN	1	60	[66]
Bn	<i>t</i> -Bu	Bz	NaH	MeCN	1	62	[66]
Bn	Me	4-MeOC ₆ H ₄	Cs ₂ CO ₃	MeCN	6	74	[66]
Bn	Me	4-MeOC ₆ H ₄	Cs ₂ CO ₃	DMF	1	68 ^a	[66]
Bn	Bz	4-MeOC ₆ H ₄	Cs ₂ CO ₃	MeCN	7	75	[66]
Bn	Bz	4-MeOC ₆ H ₄	Cs ₂ CO ₃	DMF	2	68 ^a	[66]
CH ₂ CHMe ₂	<i>t</i> -Bu	4-MeOC ₆ H ₄	Cs ₂ CO ₃	MeCN	20	19 ^b	[66]
(CH ₂) ₂ CO ₂ <i>t</i> -Bu	Me	4-MeOC ₆ H ₄	NaH	MeCN	1	11 ^c	[66]
(CH ₂) ₂ CO ₂ <i>t</i> -Bu	Me	4-MeOC ₆ H ₄	Cs ₂ CO ₃	MeCN	4	65	[66]
(CH ₂) ₃ NHCbz	Bz	4-MeOC ₆ H ₄	Cs ₂ CO ₃	MeCN	1	72	[66]

^a Product from intramolecular O-alkylation was also isolated.

^b Starting material was also recovered in 12% yield.

^c Hydrolysis of the methyl ester was observed (~24% estimated by HPLC).



Methyl 1-(4-Methoxybenzyl)-2-benzyl-4-oxoazetidine-2-carboxylate (58, $\text{R}^1 = \text{Bn}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = 4\text{-MeOC}_6\text{H}_4$); Typical Procedure:^[66]

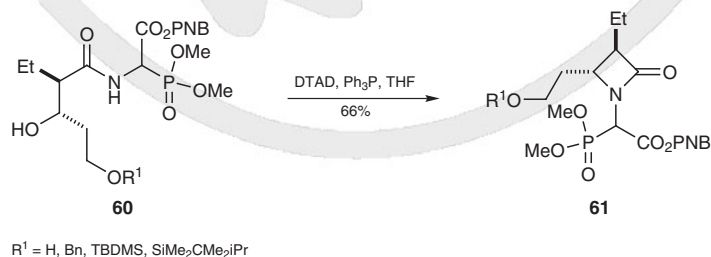
A soln of methyl *N*-(chloroacetyl)-*N*-(4-methoxybenzyl)phenylalaninate (1.6 mmol) in dry MeCN or DMF (20 mL) was treated with Cs_2CO_3 (1.04 g, 3.2 mmol) and stirred at rt until disappearance of the starting material was observed. After removal of the solvent under reduced pressure, the residue was partitioned between EtOAc and H_2O , and the phases were separated. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, leaving a residue which was purified by column chromatography (EtOAc/hexane 1:5).

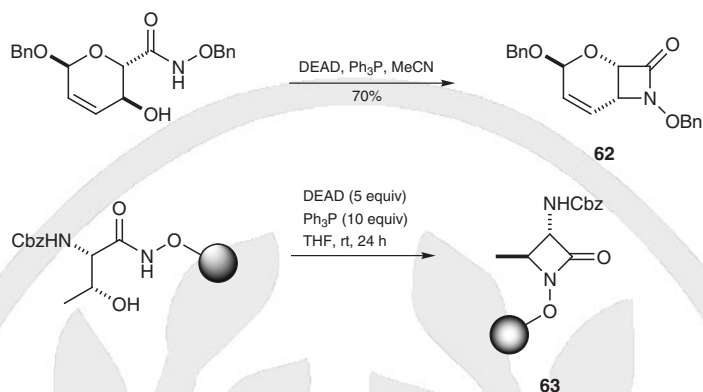
21.9.1.7.1

**Variation 1:
Mitsunobu Reactions of β -Hydroxy Hydroxamates**

The Mitsunobu reaction has proven to be very useful for the cyclization of β -hydroxy-substituted amides, e.g. **60**, to β -lactams.^[68] Activation of the hydroxy group under the usual conditions of triphenylphosphine and an azodicarboxylate, e.g. di-*tert*-butyl azodicarboxylate (DTAD), ensures that the reaction proceeds with complete inversion of stereochemistry at the β -hydroxy-bearing position, as indicated for compound **61** (Scheme 26).^[69] Novel bicyclic β -lactams, e.g. oxoazabicyclo[4.2.0]octenone **62**, are produced from glucuronic acid glycosides containing a β -hydroxy hydroxamate via N1—C4 bond closure.^[70] This methodology can also be successfully applied to the solid-phase systems of β -lactams, e.g. **63**, for use in combinatorial β -lactam synthesis (Scheme 26).^[71]

Scheme 26 Cyclization of β -Hydroxy-Substituted Amides via the Mitsunobu Reaction^[69–71]





(1*S*,3*S*,6*R*)-3,7-Bis(benzyloxy)-2-oxa-7-azabicyclo[4.2.0]oct-4-en-8-one (62); Typical Procedure:^[70]

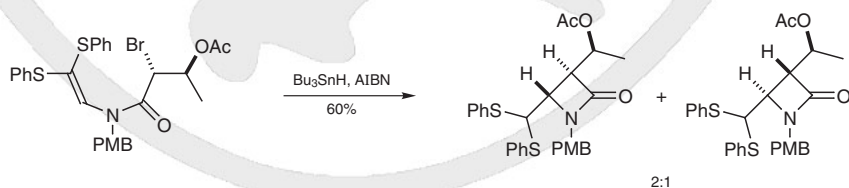
To the hydroxamate (3.70 g, 10.4 mmol) and Ph_3P (4.11 g, 15.7 mmol) in a dry round-bottomed flask under argon was added dry MeCN (100 mL). The resulting suspension was cooled with an ice bath to 0 °C. To the chilled suspension was then added DEAD (2.3 mL, 14.61 mmol) via syringe pump over 25 min. After the addition of DEAD was complete, the resulting soln was stirred at 0 °C for 20 min and then warmed to rt and stirred for 2 h and 15 min. After this time, the reaction was concentrated on the rotary evaporator and the residue was chromatographed (hexanes/EtOAc 4:1) to give a white solid (yield: 3.09 g, 88%), which was then recrystallized (Et_2O /hexanes) to give white needles; yield: 2.45 g (70%); mp 57–59 °C; $[\alpha]_{\text{D}}^{25}$ –54 (*c* 0.25, CHCl_3).

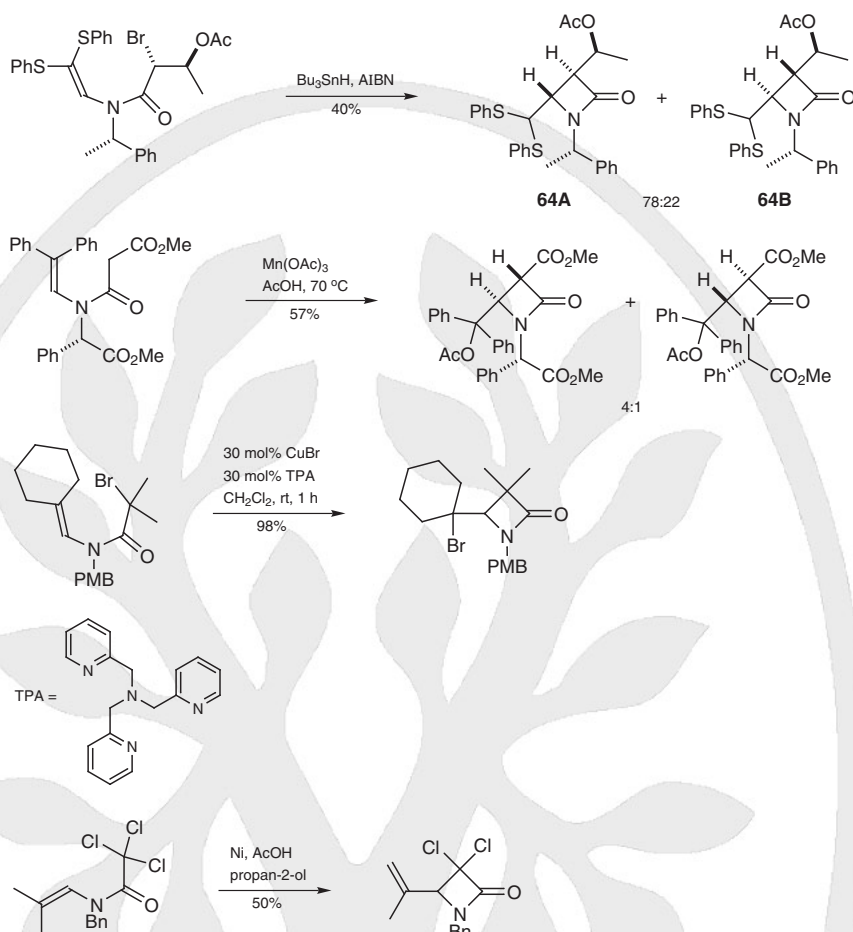
21.9.1.8

**Method 8:
Radical Ring Closures**

A unique method for forming the β -lactam ring is by 4-*exo-trig* radical ring closures of enamides to afford *trans*-substituted β -lactams. The radical intermediate from the α -bromo precursor can be generated using tributyltin hydride and 2,2'-azobisisobutyronitrile, e.g. for the synthesis of **64A** and **64B** (Scheme 27),^[72–74] a copper(I) bromide–tripyridylamine complex,^[76] or nickel powder and acetic acid (Scheme 27).^[78] Non α -bromo enamides can also be used to form the β -lactam ring via radical ring closure in the presence of manganese(III) and cerium(IV) salts.^[75] In most cases the 4-*exo-trig* cyclization is kinetically favored over the 5-*endo-trig* route. In tributyltin hydride mediated processes, the ratio of 4-*exo* versus 5-*endo* products is temperature dependent with lower temperatures favoring the 4-*exo* products.^[72]

Scheme 27 4-*Exo-Trig* Radical Cyclizations To Prepare β -Lactams^[73–77]





3-(1-Acetoxyethyl)-4-[bis(phenylsulfanyl)methyl]-1-(1-phenylethyl)azetidin-2-one (**64A**/**64B**):^[74]

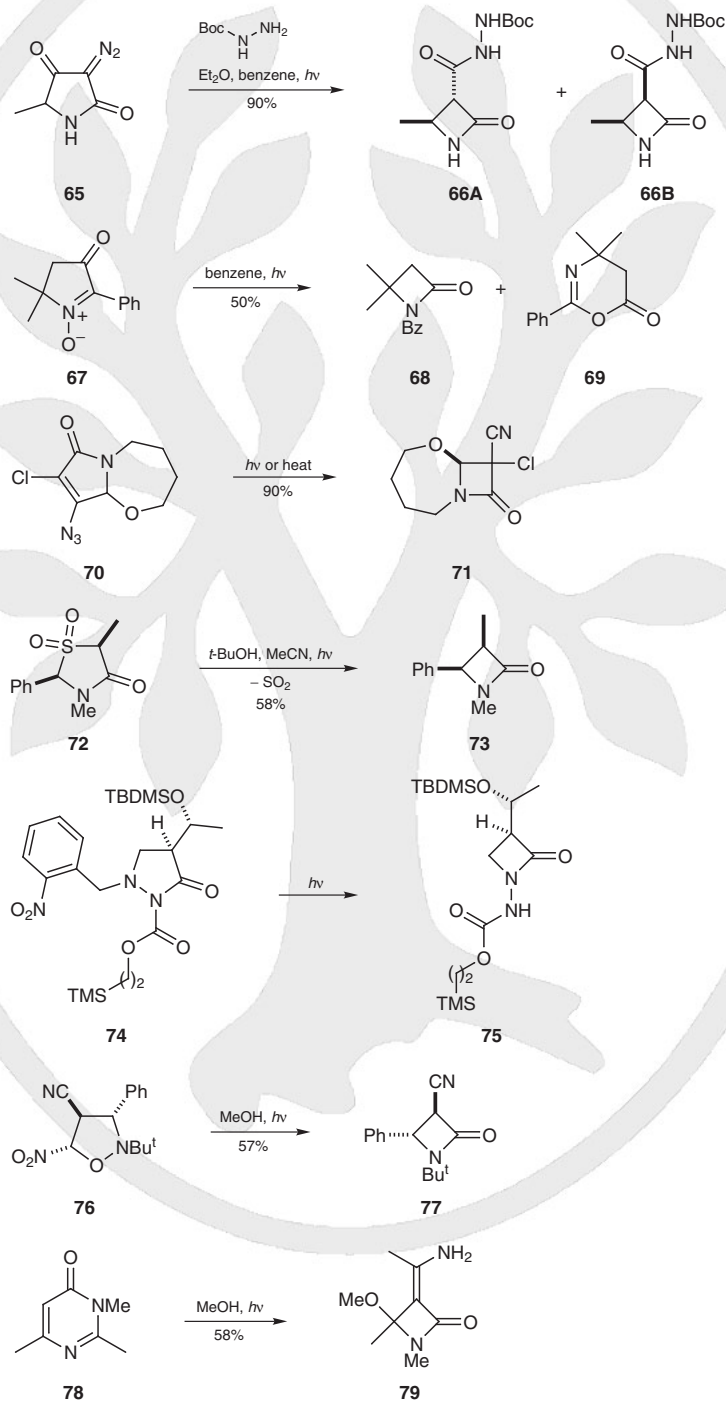
The α -bromo enamide (220 mg, 0.39 mmol) was treated with Bu_3SnH (123 mg, 0.42 mmol) and AIBN (8 mg, 0.05 mmol) in boiling benzene (**CAUTION: carcinogen**), and the crude material was chromatographed (silica gel, hexane/EtOAc 10:1) to give an oily mixture of **64A** and **64B** in a ratio of 78:22 (determined by ^1H NMR); yield: 75 mg (40%).

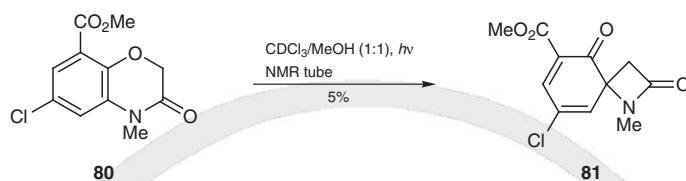
21.9.1.9 Method 9: Photochemical Ring Contractions

A variety of photochemical methods have been developed to prepare β -lactam compounds. One of the earliest methods is the photolytic Wolff rearrangement of 2-diazocyclopentane-1,3-dione **65** to afford a stereoisomeric mixture of *cis*- and *trans*-disubstituted β -lactams **66A** and **66B** (Scheme 28).^[78,79] 4,5-Dihydropyrrol-3-one 1-oxides, e.g. **67**, undergo photochemically induced ring contractions to β -lactams **68**, although the ring-expanded oxazinone **69** is also obtained as a side product (Scheme 28).^[80] 4-Azido-1,5-dihydropyrrol-2-ones, e.g. **70**, also undergo ring contraction under either photochemical or thermal conditions with complete stereoselectivity to yield 3-cyano-substituted β -lactams **71** (Scheme 28).^[81] The photochemically induced extrusion of sulfur dioxide from 1,4-thiazolidin-4-one 1,1-dioxide **72** affords β -lactam **73** in moderate yield but with low stereocontrol (Scheme 28).^[82] Photochemical ring contraction of pyrazolidin-3-one **74** gives *N*-amino

substituted β -lactams **75** (Scheme 28),^[83] which can then be further transformed by reduction to give the N-unsubstituted β -lactam. Photolysis of isoxazolidine **76** produces *trans*-substituted β -lactam **77** with retention of stereochemistry via an initial N—O bond scission, followed by internal hydrogen transfer, and subsequent cyclization (Scheme 28).^[84] Pyrimidin-4-one **78**^[85] and benzoxazinone **80**^[86] also undergo ring contractions upon photoirradiation to give β -lactams **79** and **81** (Scheme 28).

Scheme 28 Photochemical Ring Contractions^[78,80–86,87]





1-*tert*-Butyl-2-oxo-4-phenylazetidine-3-carbonitrile (77); Typical Procedure:^[84]

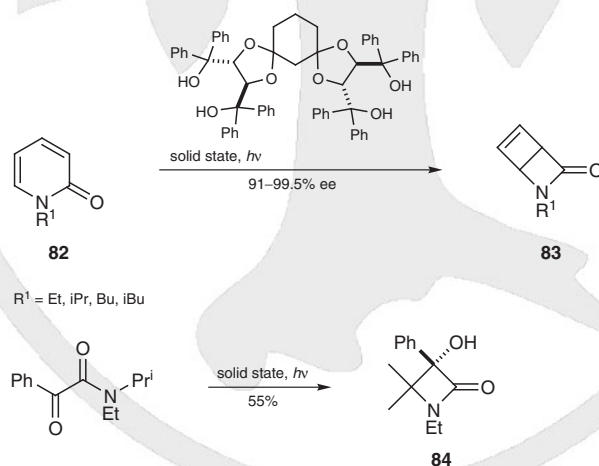
A soln containing isoxazolidine **76** (200 mg, 0.73 mol) in abs MeOH (150 mL) was photolyzed with a low-pressure Hg lamp (2537 Å) for 2.5 h. The solvent was removed under reduced pressure, leaving behind a pale oil which was fractionally recrystallized (acetone/hexane 2:23): yield: 57%; mp 180–181 °C.

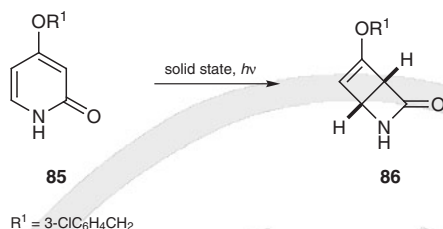
21.9.1.9.1

Variation 1: Photochemical Processes in the Solid State

Intramolecular photocyclization reactions of pyridin-2-ones, oxo amides, amides, and thioamides in the solid state can be used to synthesize β -lactams, and there are a few approaches toward enantioselective photocyclizations to afford optically active β -lactams. Photocyclization of pyridin-2-ones **82** as a 1:1 inclusion complex within an optically active host gives β -lactams **83** with high enantioselectivities and yields in the solid state (Scheme 29).^[88] Photocyclization of phenylglyoxylamides and 2-[acyl(alkyl)amino]cyclohex-2-enones as inclusion complexes with optically active hosts affords optically active β -lactams, e.g. **84**.^[89,87] In an interesting variation of this procedure 4-[(3-chlorobenzyl)oxy]pyridin-2(1*H*)-one (**85**) crystallized in chiral space groups, and subsequent irradiation of a single crystal led to the enantiomerically enriched β -lactam **86** (Scheme 29).^[90] This methodology can also be applied to photoinduced cyclizations of acyclic monothioimides and α -oxo amides as a means of synthesizing β -lactams in the solid state.^[91,92]

Scheme 29 Photoisomerizations of Pyridin-2-ones and α -Oxo Amides in the Solid State^[88,87,90]





2-Alkyl-2-azabicyclo[2.2.0]hex-5-en-3-ones **83**; General Procedure:^[88]

A suspension of a powdered 1:1 inclusion complex of the chiral dispiro compound and **82** (3.8 g, 3.6 mmol) in H_2O (200 mL) containing hexadecyltrimethylammonium bromide (0.2 g) as a surfactant was irradiated for 168 h. The product was filtered, dried, and chromatographed (silica gel, hexane/EtOAc 1:1) to give (–)-**83** as a colorless oil.

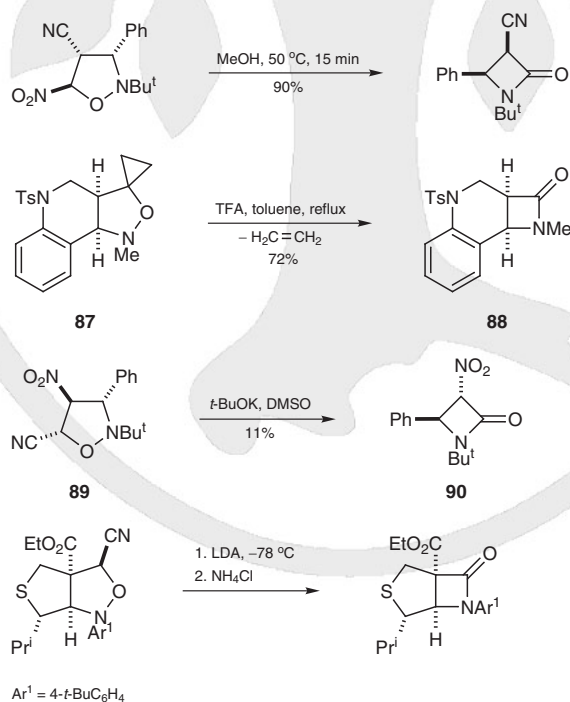
21.9.1.10

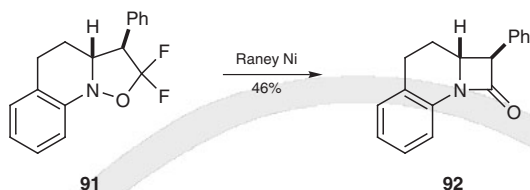
Method 10:

Ring Contractions of Isoxazolidines (Non-Photochemical Processes)

Ring contraction of isoxazolidines to give β -lactams can occur under a variety of different reaction conditions. Examples are shown in Scheme 30. Thermal extrusion of ethene from spirocyclopropane isoxazolidine **87** proceeds in the presence of a small excess of trifluoroacetic acid to produce the *cis*-substituted β -lactam **88** in good yield (Scheme 30).^[93] Isoxazolidines, e.g. **89**, also undergo conversion into β -lactams, e.g. **90**, in the presence of a base^[90] such as potassium *tert*-butoxide/dimethyl sulfoxide, 1,5-diazabicyclo[4.3.0]-non-5-ene, or lithium diisopropylamide^[94] (Scheme 30). There is one report of the use of Raney nickel to cause the ring contraction of a difluoroisoxazolidine **91** to give β -lactam **92**.^[95]

Scheme 30 Thermal Ring Contractions of Isoxazolidines^[90,93–95]



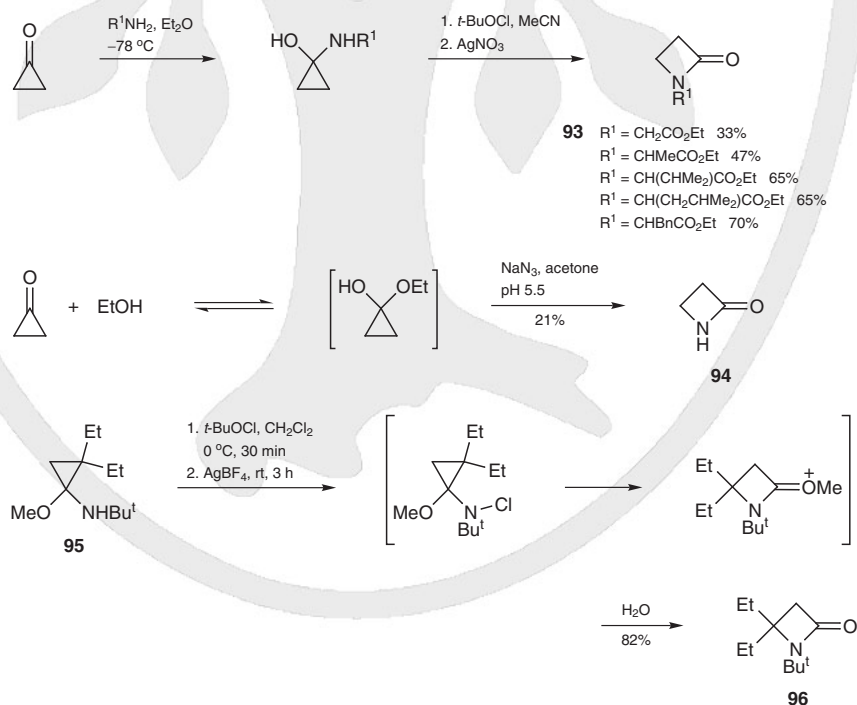


21.9.1.11

Method 11: Ring Expansion of Cyclopropanones

Ring expansion of cyclopropanones to form β -lactams is one of many methods used to prepare the β -lactam ring; however, the major drawback to this methodology is the difficulty in preparing the cyclopropanone itself. Consequently, this method has been modified to eliminate the use of cyclopropanone. In original experiments, it is demonstrated that the addition of primary amines to cyclopropanones at low temperature gives labile hydroxyamines, which when treated with *tert*-butyl hypochlorite and subsequently reacted with a silver(I) salt, produce β -lactams **93** in low to good yields (Scheme 31).^[96,97] Thus far this methodology has not been applied to substituted cyclopropanones. However, the addition of azide to cyclopropanones gives an unstable adduct that undergoes spontaneous rearrangement to the β -lactam, e.g. formation of **94** from cyclopropanone and ethanol, on treatment with sodium azide (Scheme 31).^[98–101] Until recently there were only three examples of the rearrangement of substituted cyclopropanones via the azide adduct to give β -lactams.^[99–101] A modification of the above procedure utilizes 1-methoxycyclopropanamines **95** via an α -chloro ketone to afford trisubstituted β -lactams **96** (Scheme 31)^[102] that are inaccessible using the earlier methods.^[102]

Scheme 31 Ring Expansion of Cyclopropanones To Give β -Lactams^[96–98,102]



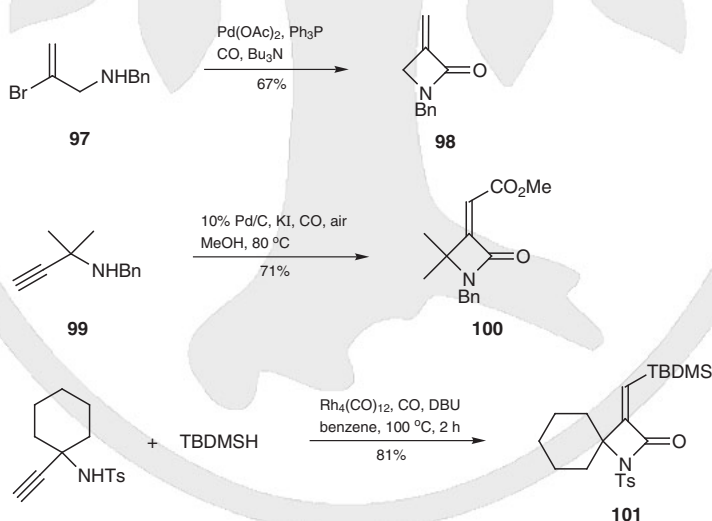
1-*tert*-Butyl-4,4-diethylazetidin-2-one (96); General Procedure:^[102]

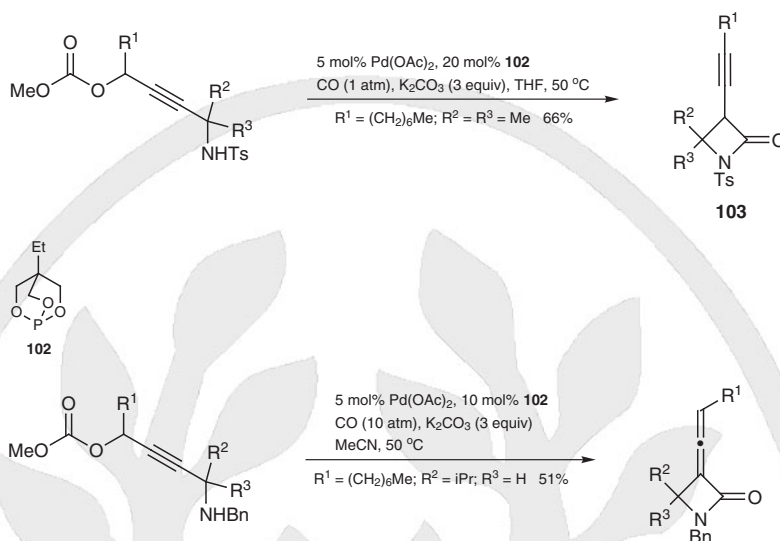
A soln of *N-tert*-butyl-2,2-diethyl-1-methoxycyclopropanamine (**95**; 5 mmol) in dry CH_2Cl_2 (5 mL) was cooled to 0°C and treated dropwise with *t*-BuOCl (0.57 g, 5.3 mmol) in CH_2Cl_2 (2 mL). The soln was stirred at 0°C for 30 min, after which AgBF_4 (0.98 g, 5.3 mmol) was added. The mixture was further stirred at rt for 3 h in the dark. After the precipitated AgCl was removed by filtration, the filtrate was treated with H_2O (10 mL) and the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (2×5 mL), and the combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure. The remaining residue consisted of **96** in a purity of 90–95%. Purification was performed by vacuum distillation because flash chromatography (silica gel) led to complete decomposition of the labile **96**.

21.9.1.12

**Method 12:
Transition-Metal-Catalyzed Processes**

Transition-metal catalysts are frequently used to prepare β -lactams. One such method is the palladium-catalyzed carbonylation of 2-bromoallylamine **97** to yield 3-methyleneazetidin-2-one **98** (Scheme 32).^[103] Various *N*-substituents in addition to aromatic and alkyl are tolerated. Oxidative carbonylation of *N*-benzyl-2-methylbut-3-yn-2-amine (**99**) in the presence of 10% palladium on carbon and potassium iodide in methanol gives β -lactam **100** in good yield (Scheme 32).^[104] Also, mono- and disubstituted propyn-2-amines undergo rhodium-catalyzed silyl carbonylation with dodecacarbonyltetraphosphonium in the presence of a trialkylsilane to afford the corresponding silyl-substituted β -lactams, e.g. **101** (Scheme 32).^[105] Palladium-catalyzed carbonylation of methyl [3-(tosylamino)alk-1-ynyl]alkyl carbonates in the presence of cyclic phosphite **102** gives alkynyl- **103** or vinylidene-substituted β -lactams depending on the reaction conditions and substituents that are employed.^[106] Electron-withdrawing and electron-donating protective groups on the amine are both tolerated under these conditions, and a wide range of alkyl groups can be introduced as R^1 , R^2 , or R^3 substituents.

Scheme 32 Palladium-Catalyzed Carbonylation of Alkenyl- and Alkynylamines^[103–106]



1-Tosyl-4,4-dimethyl-3-non-1-yn-1-ylazetid-2-one [**103**, R¹ = (CH₂)₆Me; R² = R³ = Me].^[106]

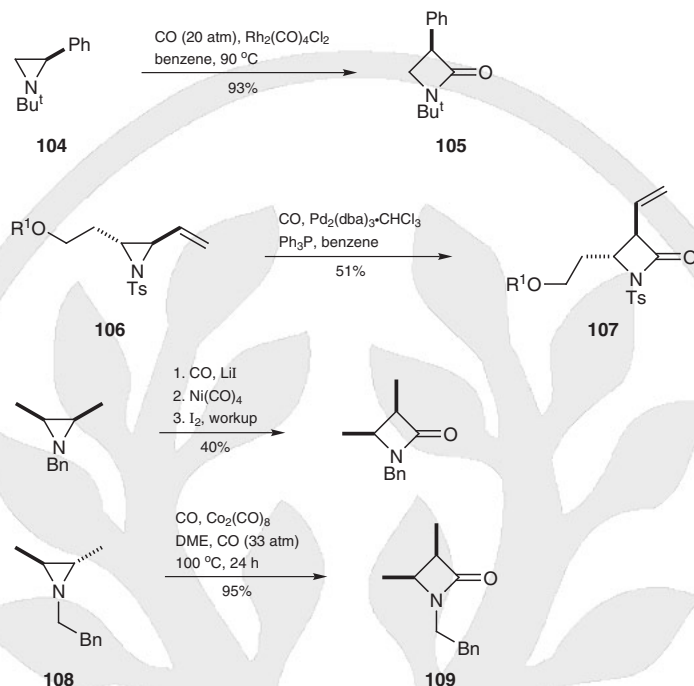
CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

In a round-bottomed flask were added 5 mol% Pd(OAc)₂ (6 mg, 0.027 mmol), 20 mol% of the cyclic phosphite **102** (17 mg, 0.105 mmol), and K₂CO₃ (1.5 mmol) in THF (1 mL). A soln of methyl 1-[3-methyl-(3-tosylamino)but-1-ynyl]octyl carbonate (0.5 mmol) in THF (2 mL) was then added. The reaction was carried out at 50 °C under an atmosphere of CO for 7.5 h. After workup, **103** was isolated; yield: 126 mg (66%).

21.9.1.12.1

Variation 1: Carbonylation of Aziridines

The ring expansion of aziridines via transition-metal-catalyzed carbonylation is a useful method for the preparation of β -lactams. One example is the reaction of 2-phenyl-1-*tert*-butylaziridine (**104**) with carbon monoxide in the presence of a catalytic amount of bis[(dicarbonyl(chloro)rhodium] to give β -lactam **105** (Scheme 33).^[107] The reaction gives regiospecific insertion of carbon monoxide into the aryl substituted N—C bond, with complete retention of stereochemistry and in quantitative yield. The same result is obtained with 2-vinylaziridines **106** using a palladium(0) complex [Pd₂(dba)₃•CHCl₃] and triphenylphosphine, giving vinyl-substituted β -lactams **107**.^[108] These methods are limited to only those aziridines bearing an aryl activating group at the 2-position. For aziridines that have alkyl groups (e.g., Me, Et), carbon monoxide insertion can be carried out using tetracarbonylnickel(IV) followed by workup with iodine. In these cases, carbon monoxide insertion is directed to the less substituted aziridino N—C bond with net retention of configuration.^[109] However, β -lactams are obtained in only moderate yields and an excess of the very toxic tetracarbonylnickel(IV) is required. A later method developed for carbon monoxide insertion into unactivated aziridines, e.g. **108**, utilizes the inexpensive octacarbonyldicobalt(0) as the catalyst.^[110] The reaction proceeds by insertion into the less substituted aziridino N—C bond, this time with inversion of configuration, affording an excellent yield of the β -lactam products, e.g. **109**. A modification to this reaction uses the cobalt complex, [bis(triphenylphosphine)iminium]tetracarbonylcobalt [Co{N(=PPh₃)₂}(CO)₄] in conjunction with the Lewis acid tris(pentafluorophenyl)borane as both the catalyst and the source of carbon monoxide.^[111]

Scheme 33 Carbonylation of Aziridines^[107–110]**(3R,4S)-Dimethyl-1-(2-phenylethyl)azetidin-2-one (109):^[110]**

CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

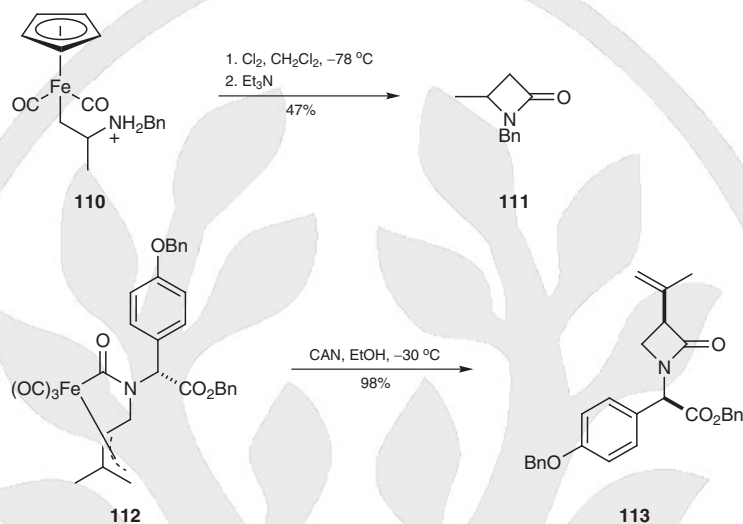
Aziridine **108** (6.0 mmol), dry and O₂-free DME (10 mL), and $\text{Co}_2(\text{CO})_8$ (17.4 mg, 0.05 mmol) were placed in a stainless steel autoclave equipped with a stirring bar. The autoclave was purged with CO (3 ×) and then was charged with CO (33 atm). The reaction vessel was placed in an oil bath at 100 °C and stirred overnight. The autoclave was opened and left in contact with air for a few hours to induce decomposition of the catalyst. Addition of a small amount of Et₂O accelerated the process. A precipitate was formed, and the mixture was filtered through a small column packed with silica gel, using Et₂O as the eluent, to give **109** in high purity.

21.9.1.12.2**Variation 2:****Use of Organoiron–Alkene Complexes**

Procedures are reported for the synthesis of β -lactams using organoiron complexes. A cationic dicarbonyl(η^5 -cyclopentadienyl)(propene)iron complex reacts with 1 equivalent of benzylamine to give the alkylation adduct **110**, which upon oxidation with a solution of chlorine followed by addition of triethylamine, affords the β -lactam **111** in moderate yield.^[112] Iron vinylidene complexes $\{[\text{Fe}(\text{C}=\text{CMe}_2)(\text{Cp})(\text{CO})\{\text{P}(\text{OMe})_3\}]\text{OTf}\}$ react with imines and dihydrothiazoles to produce [2+2] cycloadducts in good yields, and subsequent oxidation with iodosobenzene affords the monocyclic and bicyclic β -lactams, respectively.^[113] The reaction of 2-phenyl-2-azabicyclo[2.2.2]oct-5-en-3-ones with nonacarbonyldiiron in benzene at 40 °C produces β -lactams but in very low yields and accompanied by other products.^[114] (π -Allyl)tricarbonyliron complexes, e.g. **112**, cyclize to β -lac-

tams **113** in the presence of ammonium cerium(IV) nitrate. This methodology can be used toward the synthesis of (+)-thienamycin and the nocardicins (Scheme 34).^[115,116]

Scheme 34 Decomplexation of a (π -Allyl)tricarbonyliron Complex To Give a β -Lactam^[112,116]



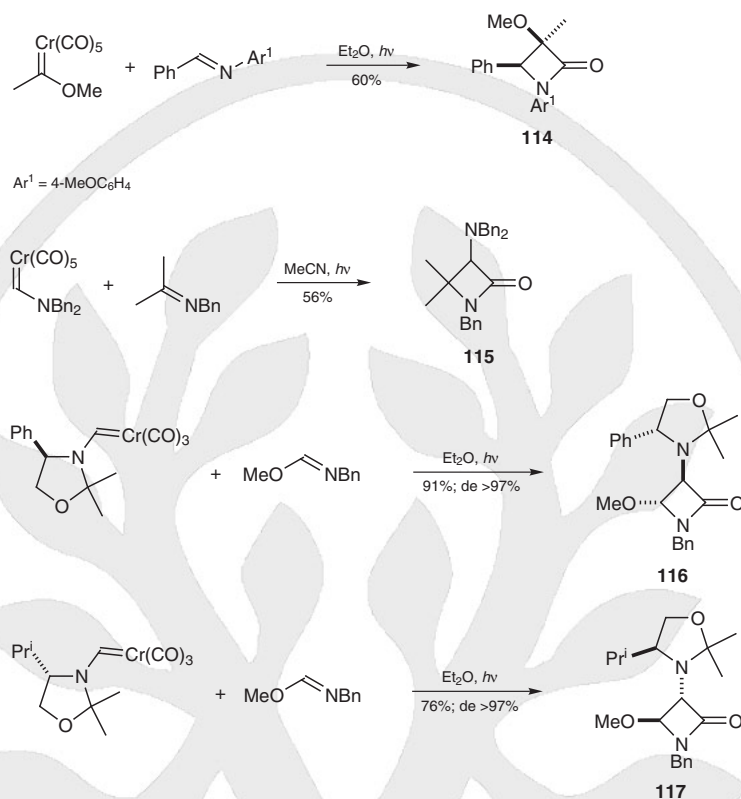
1-[(*R*)-(Benzyloxy)carbonyl][4-(benzyloxy)phenyl]methyl)-(3*R*)-3-isopropenylazetidin-2-one (113**):^[116]**

A soln of the complex **112** (1.126 g, 1.98 mmol) in EtOH (70 mL) was cooled to -30°C and a soln of CAN (5.42 g, 9.9 mmol) in EtOH (70 mL) was added with stirring over a period of 10 min. The mixture was allowed to warm to rt over 2 h, whereupon the solvent was removed and the residue was partitioned between H_2O (60 mL) and CH_2Cl_2 (220 mL). The organic layer was further washed with H_2O (60 mL) and brine (60 mL) to give, after drying and chromatography (Et_2O /petroleum ether 9:11), an oil, which slowly crystallized as white rosettes; yield: 0.865 g (98%); mp 68°C ; $[\alpha]_{\text{D}}^{22} -52.1$ (c, 2.0, CHCl_3).

21.9.1.12.3

**Variation 3:
Additions of Fischer Carbenes to Imines**

Chromium carbene complexes react with both acyclic and cyclic imines, including dihydroisoquinolines, quinolines, benzothiazines, and dihydrothiazoles, under photochemical conditions, to produce monocyclic and bicyclic β -lactams, respectively.^[117] Several mechanistic studies reveal that the reactive species is a metal-bound ketene-like intermediate, which reacts with the imine to give the β -lactam, in a similar manner to the Staudinger cycloaddition reaction.^[118] Alkoxycarbene and aminocarbene complexes are both suitable reaction partners for these photolytic reactions, e.g. the formation of β -lactams **114** and **115**, respectively (Scheme 35).^[117,119] In most cases the β -lactams are formed with high diastereoselectivity. Asymmetric syntheses of β -lactams from chiral imines derived from optically active amines are reported, but give at best only moderate asymmetric induction.^[117,119] Incorporation of a chiral auxiliary into the chromium carbene complex allows reaction with imines to occur with high diastereoselectivity, e.g. the formation of **116** and **117** (Scheme 35).^[120] Typically, unsymmetrically substituted imines give the best yields and stereoselectivities, with the configuration of the newly formed chiral center at the C3 position of the β -lactam ring being the same as that of the chiral auxiliary.

Scheme 35 Photolytic Reaction of Chromium–Carbene Complexes with Imines^[117,119–121]

(3R,4R)-1-Benzyl-3-[(4R)-2,2-dimethyl-4-phenyl-1,3-oxazolidin-3-yl]-4-methoxyazetidin-2-one (116):^[120]

CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

The chromium–carbene complex (1.00 mmol) and the corresponding imine (1.05 mmol) were added to a CO-sat. soln of Et₂O (~22 mL) in a 25-mL pressure tube equipped with a 6.8-atm pressure head and a pressure-release valve. The soln was pressurized with CO (~6 atm) and then the pressure was released (3 ×). Finally, the soln was pressurized to 4 atm and carefully transported, using a protective shield, to an irradiation box and exposed to a 450-W UV lamp for 24 h. The mixture turned from bright yellow to pale yellow with a white solid at the bottom of the tube. The progress of the reaction was monitored by use of analytical TLC (silica gel). After complete consumption of the carbene, the solvent was removed. This mixture was taken up in MeOH (~20 mL) and placed in the freezer overnight. The crude product was collected by decantation and the residual solid was rinsed with MeOH. The solvent was removed under reduced pressure to leave a yellowish green to brown oil. The product was purified by chromatography (silica gel, hexane/EtOAc 4:1) to give pure **116** as a clear colorless oil; yield: 91%.

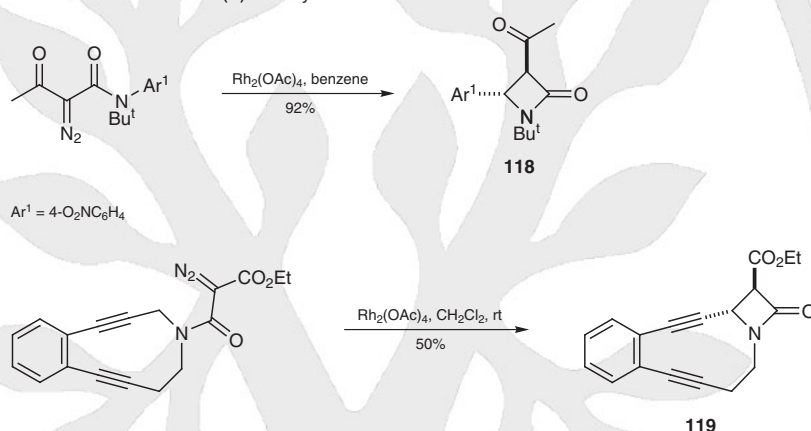
21.9.1.12.4

Variation 4: Rhodium-Catalyzed C–H Bond Insertion

Rhodium-catalyzed C–H insertion of α -diazocarboxamides is a well-established method for the formation of β -lactams. These reactions generally produce mixtures of β -lactams

and γ -lactams from α -diazocarboxamides; the regioselectivity toward formation of the β -lactams is generally high when there are strong electron-withdrawing substituents α or β to the amide nitrogen, or if the amide nitrogen bears a *tert*-butyl substituent, e.g. the formation of **118** (Scheme 36).^[121,122] Replacing the *tert*-butyl group with a 4-methoxyphenyl group leads to the formation of β -lactams but in lower yields.^[121] These results can be attributed to the influence of the amide nitrogen substituent on the transition state for C—H insertion, and to the conformationally dependent orientation of the metal carbene intermediate.^[121] Dirhodium(II) carboxylates are essential catalysts for these processes, with rhodium(II) acetate and rhodium(II) 2-phenoxybenzoate giving better selectivity for the formation of β -lactams. Dirhodium catalysts that possess chiral ligands such as pyrrolidones or oxazolidinones are proven to be effective for enantioselective C—H insertions, giving products with moderate to good enantioselectivities. This methodology can be applied to the synthesis of β -lactam-fused enediyne **119** (Scheme 36).^[123]

Scheme 36 Rhodium(II)-Catalyzed C—H Insertions^[122,123]



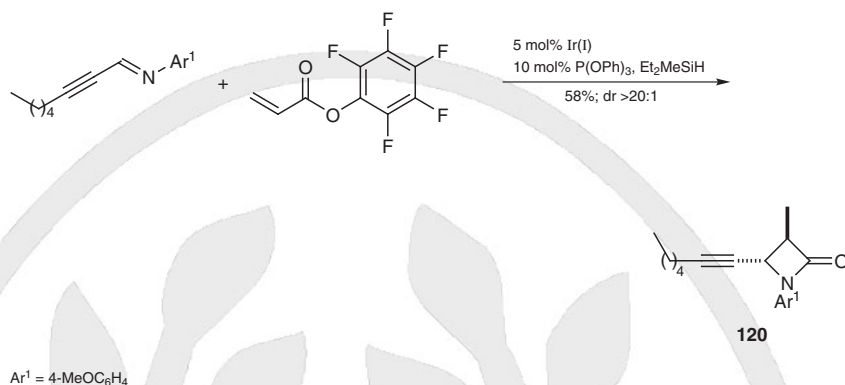
(3*S*,4*S*)-3-Acetyl-1-*tert*-butyl-4-(4-nitrophenyl)azetidin-2-one (118**):**^[122]

A soln of the α -diazooacetamide (1.0 mmol) and $\text{Rh}_2(\text{OAc})_4$ (1 mol%) in benzene (**CAUTION: carcinogen**) was refluxed. After column chromatography, the β -lactam **118** was isolated; yield: 92%.

21.9.1.12.5

**Variation 5:
Reductive Coupling of Imines with Acrylates**

Iridium-catalyzed coupling of imines with acrylates in the presence of a trialkylsilane affords *trans*-substituted β -lactams, e.g. **120**, with high diastereoselectivity (Scheme 37).^[124] The reaction is speculated to proceed via an iridium enolate that reacts with the imine to give a β -amido ester, followed by cyclization to furnish the *trans*-substituted β -lactam. Screening of metal/ligand/silane combinations reveals that bis[chloro(cyclooctadiene)]iridium(I)/triphenyl phosphite/methyldiethylsilane is the most effective catalytic system, allowing the complete conversion of acrylate and imine into the β -lactam at room temperature. Electron-deficient aryl acrylates, e.g. pentafluorophenyl acrylate, and a 2:1 ratio of ligand/metal complex result in efficient reactions and higher yields. α -Substitution in the acrylate is tolerated; however, β -substituted acrylates give low yields. Aryl-, styryl-, alkynyl-, and furylimines bearing either a phenyl or 4-methoxyphenyl group on nitrogen afford β -lactams with greater than 20:1 diastereoselectivity. However, aliphatic-substituted imines do not react under these conditions.

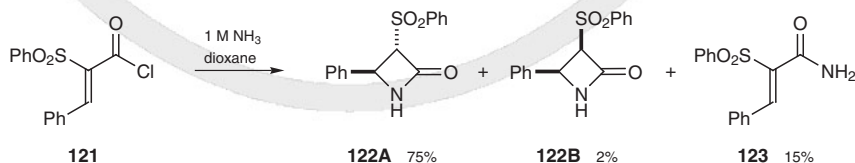
Scheme 37 Iridium-Catalyzed Coupling of Imines with Acrylates^[124]**(3R,4S)-4-Hept-1-yn-yl-1-(4-methoxyphenyl)-3-methylazetidin-2-one (120):**^[124]

A 5-mL, flame-dried sealable vessel was charged with bis[chloro(1,5-cyclooctadiene)iridium(I)] (16.7 mg, 0.025 mmol), P(OPh)_3 (31.0 mg, 0.10 mmol), and dichloroethane (500 μL). The vessel was sealed and the resulting soln was stirred for 1 h at rt. After 1 h, Et_2MeSiH (362 μL , 2.5 mmol) was added and the mixture was stirred for 15 min. Next, the stock imine (500 μL) and pentafluorophenylacrylate soln (2 M imine and 5 M in acrylate) was added to the soln. The vessel was then sealed and heated to 60 $^\circ\text{C}$ for 6 h. The resulting soln was cooled and the solvent was removed by rotary evaporation to give crude **120**, which was purified by flash column chromatography (hexanes/ EtOAc 20:1); yield: 58%

21.9.1.13

Method 13:**1,4-Addition of Amines to 3-Phenylpropenoyl Chloride**

An alternative approach to the synthesis of β -lactams is the addition of ammonia or a primary amine to an α,β -unsaturated carboxylic acid derivative. The addition of ammonia to 3-phenylpropenoyl chloride results in the formation of the corresponding acrylamide. No β -lactam formation is observed. Substituted 3-phenylpropenoyl chlorides are prepared bearing electron-withdrawing phenylsulfanyl-, phenylsulfoxo-, and phenylsulfonyl-groups to stabilize the possible zwitterionic intermediate formed by 1,4-addition of the amine to the acid chloride. Increasing the oxidation state of the phenylsulfanyl substituent increases the yields of β -lactam. The 2-(phenylsulfanyl)- and 2-(phenylsulfinyl)propenoyl chloride derivatives provide the corresponding β -lactams in very low yield with almost complete conversion into the amide, whereas 3-phenyl-2-(phenylsulfonyl)propenoyl chloride (**121**), on treatment with ammonia, gives β -lactam **122A** in addition to small quantities of the *cis*-isomer **122B** and the amide **123** (Scheme 38).^[125] In addition to ammonia, several different primary amines all produce the *trans*-substituted β -lactams in greater than 90% yield.

Scheme 38 Addition of Ammonia to 3-Phenyl-2-(phenylsulfonyl)propenoyl Chloride^[125]

(3*S*,4*S*)-4-Phenyl-3-(phenylsulfonyl)azetidin-2-one (122A):^[125]

Acid chloride **121** (0.576 g, 2.00 mmol) was prepared in situ from the carboxylic acid in CDCl_3 (3 mL) and oxalyl chloride (3 mL). The soln was refluxed for 3 h until the reaction was complete (monitored by ^1H NMR) and was then concentrated. The acyl chloride **121** was dissolved in dioxane (20 mL). To this soln was added 1.0 M NH_3 (6.0 mL) in dioxane (6.0 mmol). The resulting soln was stirred for 0.5 h at rt. The mixture was poured into H_2O (150 mL), and the products were extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with brine, dried (MgSO_4), and concentrated. The product was obtained by chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 4:1); yield: 0.43 g (75%); the *cis*-isomer **122B** was also isolated; yield: 0.011 g (2%); mp 143–144 °C (MeCN) along with 3-phenyl-2-(phenylsulfonyl)acrylamide; yield: 0.086 g (15%); mp 177–178 °C (MeCN).

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Product Class 10: γ -Lactams and Larger Ring Lactams

M. B. Smith

Product Subclass 1: Saturated Lactams

Lactams with five-membered or larger rings have found use in many areas of organic chemistry, for example, as precursors to alkaloids and pharmaceutically active non- α -amino acids, and as the monomers of important synthetic polymers. The methods for preparing these lactams read like a textbook of classical and modern organic synthetic methodology. There are many approaches to lactams,^[1] and many more synthetic manipulations of the basic lactam ring or its substituents. This contribution covers the preparation of lactams from acyclic precursors and from cyclic precursors by modification of the ring. Methods for preparing unsaturated lactams are discussed in Section 21.10.2.

Synthesis of Product Subclass 1

Synthesis by Ring-Closure Reactions

Method 1: Direct Cyclization of Amino Acids

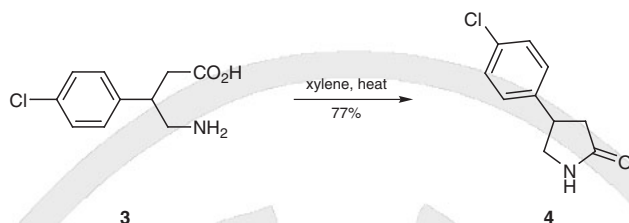
Non- α -amino acids are readily available and are common synthetic intermediates. Heating γ - or δ -amino acids **1** [4-aminobutanoic acids ($n = 1$) or 5-aminopentanoic acids ($n = 2$)] produces five- or six-membered-ring lactams **2**, respectively (Scheme 1).^[2,3]

Scheme 1 Cyclization of Amino Acids



This transformation is one of the oldest and most fundamental reactions in organic chemistry, dating to the late 19th century. In 1888, Schotten found that heating 5-aminopentanoic acid (**1**, R¹ = H; $n = 2$) to the melting point and then distilling the product gives piperidin-2-one (**2**, R¹ = H; $n = 2$).^[4] In 1889, Gabriel showed that heating 4-aminobutanoic acid (**1**, R¹ = H; $n = 1$) to 200 °C until no more water distills gives an oil, identified as pyrrolidin-2-one (**2**, R¹ = H; $n = 1$), that distills when heated to 245 °C.^[5] Both these experiments were preceded by Tafel's work in 1886, in which 4-aminopentanoic acid (**1**, R¹ = Me; $n = 1$) was heated to 250–260 °C to give 5-methylpyrrolidin-2-one (**2**, R¹ = Me; $n = 1$).^[6,7] Hexahydro-2H-azepin-2-one (**2**, R¹ = H; $n = 3$) is similarly prepared in 48% yield by heating 6-aminohexanoic acid (**1**, R¹ = H; $n = 3$) with a flame and distilling the lactam at 10–15 Torr.^[8]

A similar cyclization occurs with amino acids that contain nontrivial substituents, as illustrated by heating 4-amino-3-(4-chlorophenyl)butanoic acid (**3**, Baclofen) in refluxing xylene to give the corresponding lactam **4** (Scheme 2).^[9]

Scheme 2 Cyclization of 4-Amino-3-(4-chlorophenyl)butanoic Acid^[9]

These examples involve primary amines, but secondary amines also cyclize to give *N*-alkyl lactams. Heating 5-(methylamino)pentanoic acid to 130 °C for 15–20 minutes, allowing the temperature to rise to 160 °C, and distilling the resulting oil gives 1-methylpiperidin-2-one with a boiling point of 94–95 °C at 9 Torr.^[10]

The pyrolysis procedure for converting amino acids to lactams clearly cannot be used with tertiary amines; however, heating *N,N*-disubstituted amino acids to 200–210 °C gives lactones with a concomitant loss of a molecule of the amine.^[11] Pyrolysis of a mixture of diethyl 2,2-dibromohexanedioate and *N*-ethylaniline at 185–195 °C gives diethyl 1-phenylpyrrolidine-2,5-dicarboxylate in 63% yield, together with *N,N*-diethylaniline.^[12] The intermediate is diethyl 2,2-bis[ethyl(phenyl)amino]hexanedioate, which decomposes with evolution of *N,N*-diethylaniline.

There are many variations on the basic theme of pyrolysis of primary and secondary amino acids that are intended to improve the isolated yields of lactams and the protocols for their isolation or purification. Heating an amino acid in aqueous sodium hydroxide gives the lactam.^[13] Interestingly, heating an amino acid to 100 °C in the presence of 0.2 M aqueous hydrochloric acid also generates the corresponding lactam.^[14] Heating in toluene with triethylgallium leads to the lactam,^[15] as does heating in benzene with trimethylaluminum.^[15] In an entirely different procedure, the lactamization process is promoted by enzymes such as pancreatic porcine lipase.^[16] Of the many published procedures, three useful methods are discussed in detail in Sections 21.10.1.1.1.1–21.10.1.1.1.3.

4-(4-Chlorophenyl)pyrrolidin-2-one (4):^[9]

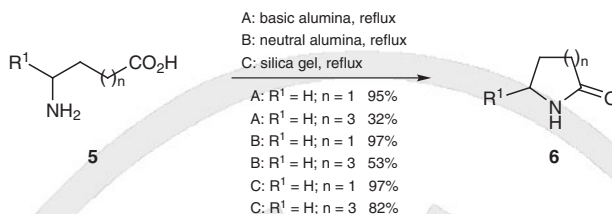
The amino acid **3** (10 g, 47 mmol) was placed in a flask containing xylene (500 mL). The powdery white amino acid did not dissolve immediately, so the mixture was stirred at reflux for 7 h until no observable undissolved material remained. The xylene was removed under reduced pressure to give a powdery product; yield: 7.0 g (77%); mp 115–116.5 °C (iPr₂O/EtOH; lit. mp 117–118 °C^[17]).

21.10.1.1.1.1

Variation 1:

By Heating an Amino Acid on Alumina or Silica Gel

Heating an amino acid with alumina or silica gel leads to cyclodehydration and the formation of γ -, δ -, or ϵ -lactams.^[2] The lactams are obtained by refluxing a mixture of the ω -amino acid (1 part by weight) and alumina or silica gel (3–4 parts by weight) in toluene (25–35 parts by volume), using a Dean–Stark trap to collect the water formed in the reaction. When small amounts of polymers are formed, the lactams can be purified by treatment with diethyl ether, in which the polymers are insoluble. The supports can be reused immediately without any special treatment or reactivation. Heating 4-aminobutanoic acid (**5**, R¹ = H; n = 1) on basic alumina for 5 hours gives a 95% yield of pyrrolidin-2-one (**6**, R¹ = H; n = 1) (Scheme 3), whereas heating on neutral alumina or silica gel gives a 97% yield.^[18] Similar heating of 6-aminohexanoic acid (**5**, R¹ = H; n = 3) for 6 hours on basic alumina gives a 32% yield of the hexahydro-2*H*-azepin-2-one (**6**, R¹ = H; n = 3), whereas heating on neutral alumina gives a 53% yield, and heating on silica gel gives an 82% yield.

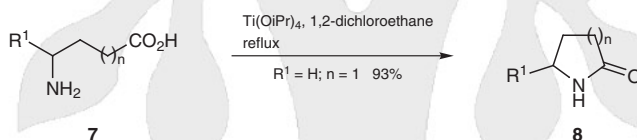
Scheme 3 Cyclization of Amino Acids Using Alumina or Silica Gel^[18]**Pyrrolidin-2-one (6, $R^1 = H; n = 1$):^[18]**

Method B: A mixture of 4-aminobutanoic acid (**5**, $R^1 = H; n = 1$; 5.2 g, 50 mmol) and neutral alumina (15 g, 150 mol) in toluene (250 mL) was refluxed in a Dean–Stark apparatus. After 10 h, the mixture was cooled and filtered. The alumina was washed several times with MeOH/CHCl₃ (1:1) and the combined organic phases were evaporated to give an oil; yield: 97%.

21.10.1.1.1.2

**Variation 2:
By Heating with Titanium(IV) Isopropoxide**

Titanium(IV) isopropoxide promotes the cyclization of ω -amino acids to the lactam in good to excellent yields (Scheme 4).^[19] The reaction of 4-aminobutanoic acid (**7**, $R^1 = H; n = 1$) for 3 hours gives a 93% yield of pyrrolidin-2-one (**8**, $R^1 = H; n = 1$). Similar reactions with other amino acids give 3-methylpyrrolidin-2-one in 81% yield from 4-amino-2-methylbutanoic acid (21 hours), *N*-methylpyrrolidin-2-one in 85% yield from 4-(*N*-methylamino)butanoic acid (5 hours), and hexahydro-2*H*-azepin-2-one in 35% yield from 6-aminohexanoic acid. Several other lactams can be similarly prepared.

Scheme 4 The Cyclization of ω -Amino Acids^[19]**Lactams 8; General Procedure:^[19]**

The ω -amino acid (3.4 mmol) was placed in a hot, oven-dried, 25-mL, round-bottomed flask equipped with a stirrer bar, reflux condenser, and N₂ inlet. The flask was alternately flushed with N₂ and evacuated three times before adding 1,2-dichloroethane (10 mL) from a syringe. This mixture was heated, and freshly distilled Ti(OiPr)₄ (9.5 mL, 1.7 mmol) was added as refluxing began. The reaction was monitored by GC. After cooling to 25 °C, the reaction was quenched with 1 M aq NaOH (76 μ L), the mixture was diluted with Et₂O, and stirred vigorously for 5 min before filtering through an Et₂O-moistened pad of Celite. The filtrate was dried (MgSO₄) and concentrated by rotary evaporation. When necessary, the products were immediately purified by Kugelrohr distillation from a pre-warmed oven.

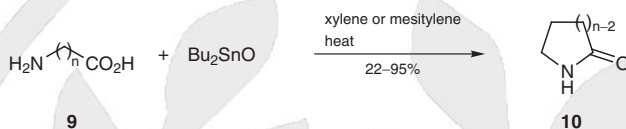
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**Variation 3:
By Dibutyltin Oxide Cyclization of Amino Acids**

A synthetically useful approach to the direct preparation of lactones and lactams, including several macrocyclic types, involves the cyclization of ω -hydroxy and ω -amino carboxylic acids, respectively, in the presence of catalytic amounts of various organotin oxides under neutral conditions. High-dilution techniques are not necessary when using this technique.^[20] For example, the cyclization of 4-aminobutanoic acid (**9**, $n = 3$) by heating

in xylene for 12 hours gives pyrrolidin-2-one (**10**, $n = 3$) in a >95% yield (Scheme 5). Similarly, heating 9-aminononanoic acid (**9**, $n = 8$) in mesitylene for 24 hours gives azacyclodecan-2-one (**10**, $n = 8$) in 22% yield, and heating 10-aminodecanoic acid (**9**, $n = 9$) in mesitylene for 24 hours gives azacycloundecan-2-one (**10**, $n = 9$) in 25% yield. Cyclization to form medium-sized rings by this method gives poor yields in accordance with the usual problems associated with forming rings of such sizes.

Scheme 5 Cyclization of Amino Acids Promoted by Dibutyltin Oxide^[20]



Lactams **10**; General Procedure:^[20]

The α -amino carboxylic acid (10 mmol) was treated with Bu_2SnO (1 mmol) in refluxing mesitylene (250 mL) for about 20 h in a Dean–Stark apparatus. The corresponding lactam was obtained in a 22–95% isolated yield.

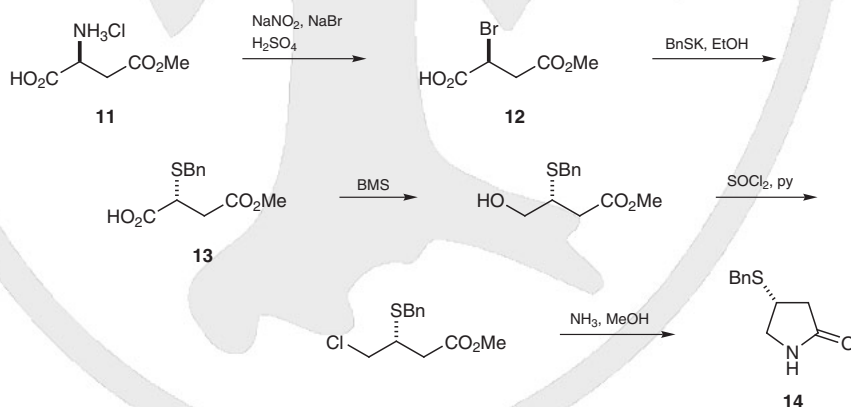
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Method 2:

Alkoxy and Alkylsulfanyl Lactams by Cyclization of Functionalized Amino Acids

It is possible to prepare an amino acid or an amino ester that contains an alkoxide or an alkylsulfanyl group. These undergo cyclization by various techniques to give the corresponding alkoxy or alkylsulfanyl amino acids. The method is illustrated by the multistep preparation of 4-(benzylsulfanyl)pyrrolidin-2-one (**14**) (Scheme 6),^[21] in which the amine unit of the aspartate ester **11** is transformed into the bromide **12** that undergoes displacement with potassium benzylsulfide to give the corresponding thioether **13**.^[21] Conversion of the free carboxylic acid group into an amino unit allows cyclization to the lactam **14**.^[21]

Scheme 6 Multistep Synthesis of 4-(Benzylsulfanyl)pyrrolidin-2-one^[21]



21.10.1.1.1.3

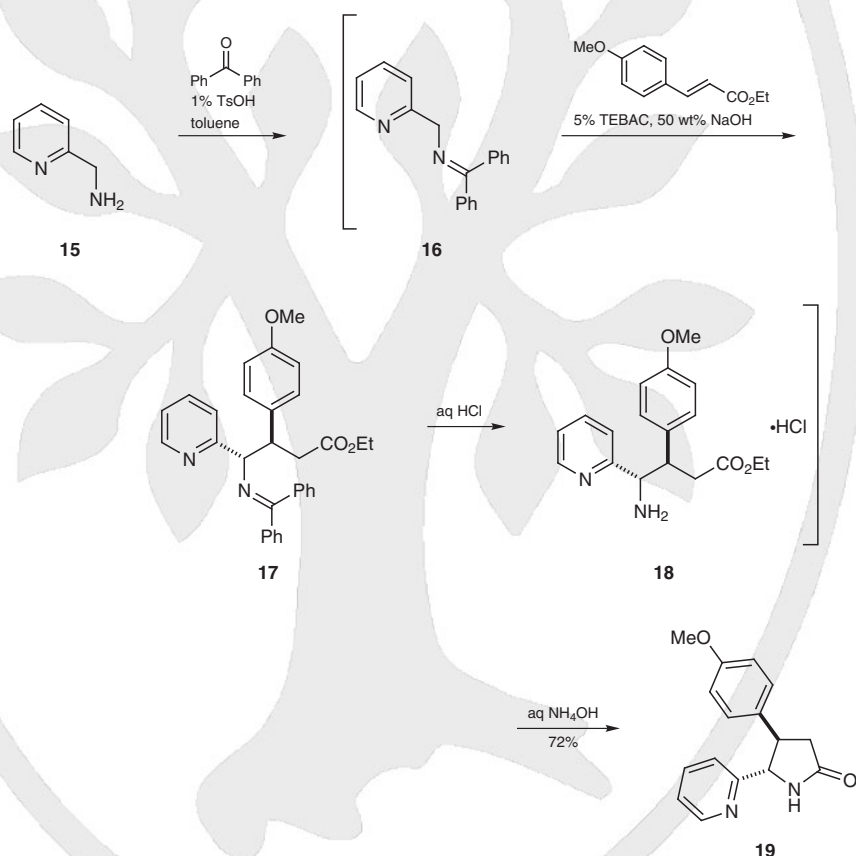
Method 3:

Direct Cyclization of Amino Esters

Although the cyclization of amino acids is a simple and well-known procedure, it suffers from poor yields, the relatively high temperatures that are required, and limitations in-

volving the isolation and handling of the amino acid. One simple method of circumventing these problems is to use amino esters instead of amino acids. The amine group usually reacts quickly with the ester through acyl substitution to give the lactam. The rapidity of the reaction often requires the amine to be generated in situ. In many cases, however, the amino ester can be isolated. One example involving this approach is the synthesis of (4*R*,5*S*)-4-(4-methoxyphenyl)-5-pyridin-2-ylpyrrolidin-2-one (**19**) (Scheme 7).^[22] The complete synthetic sequence involves protection of the amine **15** as the imine **16**, which undergoes Michael addition under phase-transfer conditions to give the Michael adduct **17**. Treatment of the Michael adduct **17** with acid removes the protecting group and liberates the hydrochloride salt of the amine **18**. This procedure allows purification by washing with organic solvents. Subsequent treatment with sodium hydroxide liberates the free amine, which undergoes rapid intramolecular reaction with the ester group to form the lactam **19**.^[22] This example illustrates the formation of an amino ester under conditions that allow its purification; it also illustrates the rapidity of the cyclization reaction.

Scheme 7 Cyclization of an Amino Ester Using an Imine Surrogate^[22]



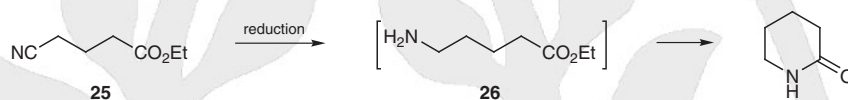
In another approach, the amino ester is generated and cyclized to the lactam in one step. For example, the reaction of ethyl 2-hydroxy-4-iodobutanoate (**20**) with allylamine generates an amino ester in situ by S_N2 displacement. The amino ester quickly cyclizes to form the lactam **21** in 90% yield (Scheme 8).^[23]

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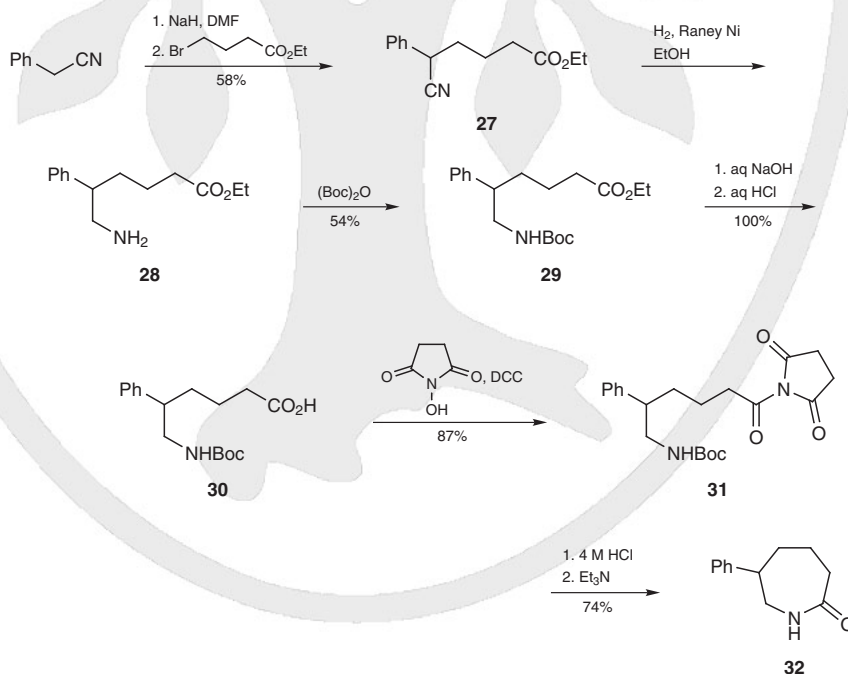
Method 5:**Cyclization of Amino Esters via Cyano Esters**

The cyano group is a surrogate for the $\text{—CH}_2\text{NH}_2$ unit by simple reduction. A variety of reducing agents can be used,^[25] but if the target is an amino ester, e.g. **26**, the precursor must be a cyano ester, for example, ethyl 4-cyanobutanoate (**25**) (Scheme 10). The reducing reagent must reduce the cyano group, but not the ester group: the most efficient and chemoselective method for this transformation is usually catalytic hydrogenation. Indeed, hydrogen with a nickel or palladium catalyst is the most common reducing agent employed in this transformation. Note that secondary amines are often produced as side products of the catalytic hydrogenation of nitriles.^[26]

Scheme 10 Cyclization of an Amino Ester Using a Nitrile Surrogate^[25]

The most common methods for preparing cyano esters involves the $\text{S}_{\text{N}}2$ displacement of primary or secondary halides or sulfonate esters with sodium or potassium cyanide,^[27,28] and the alkylation of anions derived from nitriles having an α -proton (e.g., the formation of **27**).^[29,30]

The free amino ester can be isolated, for example, in the preparation of 6-phenylhexahydro-2*H*-azepin-2-one (**32**) (Scheme 11).^[31] In this case, cyclization of the amino ester **28** to the seven-membered-ring lactam product does not occur as readily as in the case of five- and six-membered-ring lactams, so an elaborate procedure (via intermediates **29**, **30**, and **31**) is used to activate the carbonyl-to-acyl substitution.

Scheme 11 Cyclization Using a Nitrile Surrogate and Carbonyl Activation^[31]

6-Phenylhexahydro-2H-azepin-2-one (32):^[31]

A 55% dispersion of NaH in mineral oil (5 g, 110 mmol) was added portionwise to a soln of BnCN (11.7 g, 100 mmol) and Br(CH₂)₃CO₂Et (19.5 g, 100 mmol) in DMF (150 mL) in an ice/salt bath, and the mixture was stirred at rt for 4 h. EtOAc and H₂O were added and the organic phase was separated, washed with aq KHSO₄ and brine, dried (MgSO₄), and concentrated under reduced pressure. The residue was subjected to flash chromatography (EtOAc/cyclohexane 1:4) to give the cyano ester **27** as an oil; yield: 13.5 g (58%).

A soln of the cyano ester **27** (58 g, 250 mmol) in EtOH (400 mL) was hydrogenated over Raney Ni (10 mL) under H₂ at 294 Pa and 40 °C for 2.5 h. The catalyst was filtered off, and the filtrate was concentrated to give the amino ester **28** as an oil.

(Boc)₂O (55 g, 250 mmol) was added in a portionwise manner to a soln of the amino ester **28** (13.5 g, 0.25 mol) and Et₃N (40 mL, 290 mmol) in CH₂Cl₂ (300 mL) in an ice bath. The mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc and H₂O. The organic phase was separated, washed with brine, dried (MgSO₄), and concentrated under reduced pressure. The residual oil was dissolved in cyclohexane and allowed to stand. The Boc-amino ester **29** separated as crystals that were collected by filtration; yield: 25 g (30%).

The filtrate was concentrated, and the residue was subjected to flash chromatography (EtOAc/cyclohexane 1:5) to give more ester **29**; yield: 20.5 g (24%); mp 82–84 °C (hexane).

A soln of NaOH (8.8 g, 220 mmol) in H₂O (79 mL) was added to a suspension of ester **29** (37 g, 110 mmol) in EtOH (370 mL). The mixture was stirred at rt for 1 h and then the EtOH was distilled off under reduced pressure. The residual aqueous soln was washed with iPr₂O, mixed with ice and EtOAc, and adjusted to pH 2.5 with concd HCl. The organic phase was separated, washed with H₂O, dried (MgSO₄), and concentrated under reduced pressure to give the acid **30** as an oil that crystallized on standing; yield: 34 g (quant); mp 79 °C (60% aq EtOH).

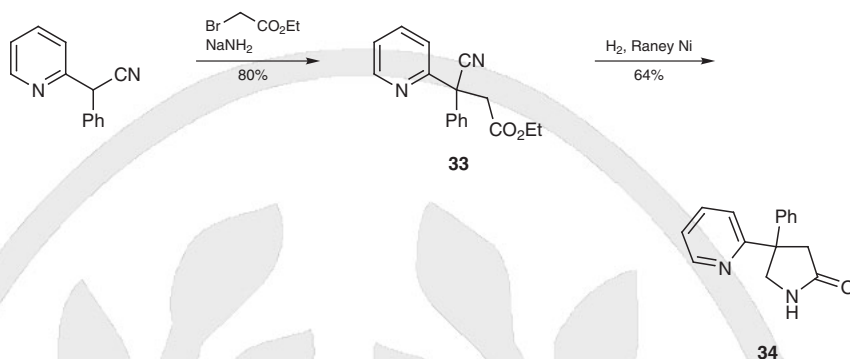
To a soln of acid **30** (23.1 g, 75 mmol) in CH₂Cl₂ (200 mL) were added *N*-hydroxysuccinimide (9.5 g, 83 mmol) and then DCC (15.5 g, 75 mmol) in an ice bath. The mixture was stirred for 2 h in an ice bath and then allowed to stand overnight at rt. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/cyclohexane 1:1) to give the imide **31**; yield: 26.5 g (87%); mp 100–102 °C (Et₂O/hexane).

A soln of imide **31** (26.5 g, 62.4 mmol) in 4 M HCl/dioxane (100 mL) was stirred at rt for 1.5 h. The slurry obtained was mixed with Et₂O (100 mL) and stirred for 1.5 h. After further addition of Et₂O (0.5 L), the imide hydrochloride **31**•HCl was collected by filtration; yield: 21.3 g (95%); mp 167 °C.

A soln of Et₃N (18 mL, 0.13 mol) in CH₂Cl₂ (50 mL) was added dropwise to a suspension of **31**•HCl (21.3 g, 62.5 mmol) in CH₂Cl₂ (213 mL) cooled in an ice bath. The mixture was stirred for 2 h in an ice bath, allowed to stand overnight at rt, and then concentrated under reduced pressure. The residue was dissolved in EtOAc and H₂O, and the organic phase was separated, washed with H₂O, dried (MgSO₄), and concentrated under reduced pressure to give the azepinone **32**; yield: 9.2 g (74%); mp 150 °C.

21.10.1.1.1.5.1**Variation 1:****Nitrile Surrogates by Nitrile–Enolate Alkylation**

Nitrile surrogates can also be prepared by alkylation of nitriles with enolates, as illustrated by the preparation of the lactam **34** (Scheme 12),^[32] which also shows that a quaternary center can be built into the lactam by using an α,α -disubstituted nitrile as the starting material. Generation of the carbanion at the α -carbon of the nitrile by reaction with sodium amide is followed by quenching with an ω -bromo ester. Subsequent reduction of the cyano group of **33** by catalytic hydrogenation in the presence of a Raney nickel catalyst leads to the amino ester, which cyclizes to the lactam.

Scheme 12 Nitrile Enolate Alkylation Route^[32]**Ethyl 3-Cyano-3-phenyl-3-(2-pyridyl)propanoate (33):**^[32]

CAUTION: Sodium amide frequently ignites or explodes on heating or grinding in air and the dust is a severe irritant.

A stirred suspension of NaNH_2 (from 13 g of Na) in toluene (200 mL) was added portion-wise to a hot stirred soln of phenyl(pyridin-2-yl)acetonitrile (97 g, 500 mmol) and redistilled $\text{BrCH}_2\text{CO}_2\text{Et}$ (90 g, 540 mmol) in dry toluene (600 mL). The mixture was refluxed and stirred for 2 h, cooled, and decomposed with H_2O . The organic layer was concentrated to a residue that was either distilled under reduced pressure or crystallized [petroleum/benzene (**CAUTION:** carcinogen) or $\text{EtOH}/\text{H}_2\text{O}$]; yield: 112.9 g (80%).

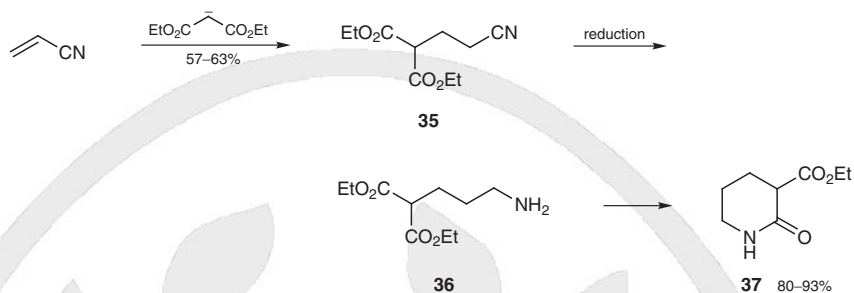
4-Phenyl-4-(2-pyridyl)pyrrolidin-2-one (34):^[32]

A soln of ethyl 3-cyano-3-phenyl-3-(2-pyridyl)propanoate (**33**; 45 g, 160 mmol) in abs EtOH (700 mL) was hydrogenated for 6 h with Raney Ni at 3.45 MPa and 75 °C. The catalyst was filtered off, the filtrate was concentrated under reduced pressure, and the solid residue was recrystallized (H_2O); yield: 24.5 g (64%); mp 165–166 °C.

21.10.1.1.5.2 Variation 2:
1,4-Addition to Conjugated Nitriles

α,β -Unsaturated nitriles readily undergo conjugate addition with enolate anions derived from esters, and particularly with malonate anions. Subsequent reduction of the cyano unit liberates the amino ester, which undergoes rapid cyclization to the lactam. This reaction offers a useful alternative for the synthesis of nitrile esters, and therefore offers a route to amino esters and lactams. The use of malonate anions is illustrated by the preparation of ethyl 2-oxopiperidine-3-carboxylate (**37**) (Scheme 13). It is easier to generate malonate anions rather than simple ester enolates, which are prone to competitive Claisen condensation reactions. Diethyl malonate adds to acrylonitrile in the presence of sodium ethoxide to give a 40–45% yield of the nitrile diester **35**^[33,34] (later improved to a 57–63% yield).^[34] Hydrogenation with Raney nickel liberates the amino diester **36**, which cyclizes to the lactam **37** in a 57% yield (later improved to an 80–93% yield).^[34] A useful advantage of using malonate derivatives, apart from the ease of forming the anion, is the option of hydrolyzing to the acid and decarboxylation to give the simple lactam.

Reaction of the lactam ester **37** with additional base to generate the enolate anion, followed by alkylation with an alkyl halide, gives 3-alkyl 3-ethoxycarbonyl derivatives, which undergo saponification of the ester and thermal decarboxylation to give the corresponding 3-alkyl lactams.^[34]

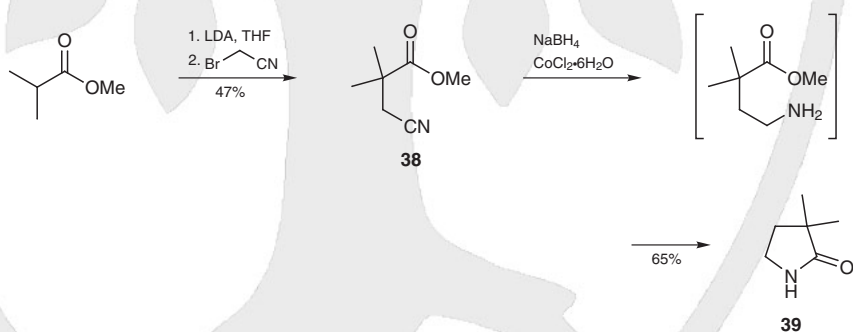
Scheme 13 Nitrile Surrogates by Conjugate Addition^[33]

The use of malonate derivatives is not essential. Esters derived from monocarboxylic acids react with bases to form enolate anions that undergo conjugate addition to acrylonitrile to give the required nitrile ester. Catalytic hydrogenation gives the amino acid, which cyclizes under the reaction conditions to give the lactam.^[35]

21.10.1.1.1.5.3

**Variation 3:
Enolate Alkylation of α -Halo Nitriles**

Alkylation of enolate esters with α -bromonitriles leads to cyano esters. For example, 3,3-dimethylpyrrolidin-2-one (39) can be prepared by this technique (Scheme 14).^[36] Alkylation of methyl 2-methylpropanoate with bromoacetonitrile at -78°C in the presence of lithium diisopropylamide as base gives methyl 3-cyano-2,2-dimethylpropanoate (38) in a 47% yield. The yield of the cyano ester decreases with increasing steric bulk of the substituent as a result of competing bromination reactions.^[36] Reduction of the nitrile by stirring with sodium borohydride and cobalt(II) chloride in aqueous tetrahydrofuran results in concomitant cyclization of the intermediate amino ester to form 3,3-dimethylpyrrolidin-2-one (39).

Scheme 14 Nitrile Esters by Reaction of Ester Enolate Anions with Halo Nitriles^[36]

This method is useful only for esters that do not have large, sterically demanding groups in the α -position. Another variation in technique is apparent in this procedure. The reduction of the nitrile by sodium borohydride/cobalt(II) chloride is selective, experimentally straightforward, and avoids the use of catalytic hydrogenation.

Methyl 3-Cyano-2,2-dimethylpropanoate (38):^[36]

A soln of iPrCO₂Me (10.2 g, 100 mmol) in THF (10 mL) was added dropwise to a soln of LDA, prepared from iPr₂NH (11.1 g, 110 mmol) and 2.5 M BuLi in hexanes (44 mL, 110 mmol), in THF (125 mL) at -78°C under N₂. The resulting mixture was stirred at -78°C for 1 h, and then a soln of BrCH₂CN (14.4 g, 120 mmol) in THF (15 mL) was introduced slowly over 30 min. The mixture became darker as the addition progressed; the resulting dark mix-

ture was allowed to warm to rt over about 3 h and then stirred overnight. The reaction was quenched by addition of 1 M aq HCl (150 mL) at 0 °C. The layers were separated and the aqueous phase was further extracted with Et₂O (3 × 75 mL). The combined organic extracts were washed sequentially with sat. aq NaHCO₃ (75 mL), H₂O (several × 75 mL), and brine (75 mL), then dried (MgSO₄). The solvent was removed under reduced pressure to give a dark-colored liquid (15.0 g). Flash chromatography (silica gel, hexanes/EtOAc 19:1) followed by short-path distillation gave a colorless liquid; yield: 6.66 g (47%); bp 95–97 °C (20 Torr).

3,3-Dimethylpyrrolidin-2-one (39):^[36]

A pink soln of CoCl₂•6H₂O (4.52 g, 19.0 mmol) and methyl 3-cyano-2,2-dimethylpropanoate (**38**; 5.36 g, 38.0 mmol) in THF (132 mL) and H₂O (66 mL) was stirred vigorously and cooled to 0 °C while NaBH₄ (7.22 g, 190 mmol) was added in portions over 30 min under N₂. The reaction was exothermic, producing a black precipitate together with copious quantities of H₂. The mixture was stirred for 48 h at rt then 28% aq NH₄OH (5 mL) was added. The mixture was centrifuged and the supernatant biphasic liquid was decanted. The sediment was washed with 2:1 aq THF (15 mL) and the combined supernatants were concentrated under reduced pressure to remove the bulk of THF. The aqueous residue was extracted with CHCl₃ (3 × 50 mL), and the combined CHCl₃ layers were washed with brine (100 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to give a colorless viscous residue (3.73 g), which was purified by flash chromatography (silica gel, 1% MeOH in CHCl₃/EtOAc 1:1) to give a colorless solid; yield: 2.80 g (65%); mp 69–70 °C (pentane).

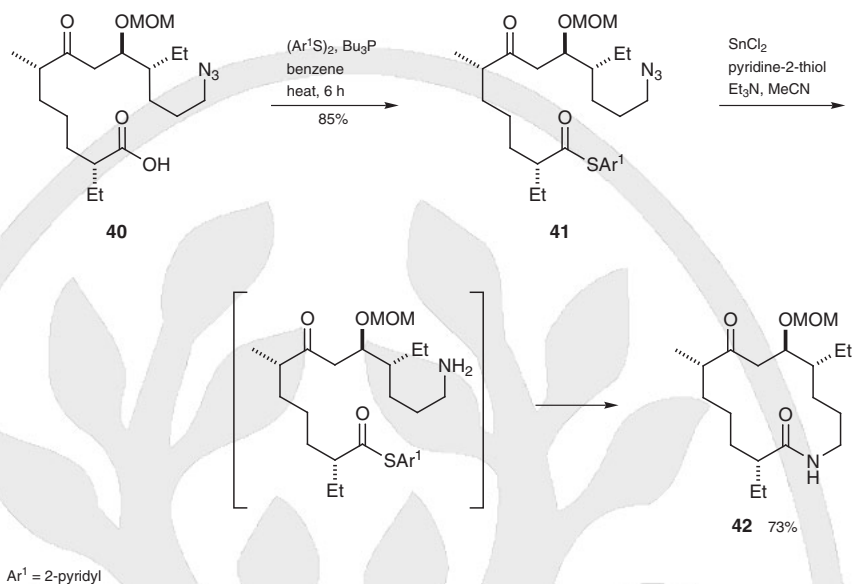
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Method 6:

Cyclization of Amino Esters via Azido Esters

The azide group is a useful amine surrogate that is readily incorporated into organic molecules. Alkyl azides are readily prepared by simple S_N2 displacement of an alkyl halide by sodium azide. There are many reducing agents that will generate the amine from an azide,^[37] but as noted with cyano groups, the reducing agent must not reduce the ester unit. Catalytic hydrogenation and reduction with tin reagents are commonly used. One significant difference between the azide and cyano group routes is that conversion via the azide incorporates only a nitrogen atom into the molecule, whereas conversion via the cyano group incorporates both a carbon atom and a nitrogen atom. This difference is often quite useful in a given synthesis. Reduction of ω-azido carboxylic acids leads to macrocyclic lactams.^[38] Similarly, reduction of azido esters leads to the corresponding lactams.

Macrocyclic lactams such as **42** (Scheme 15) can be prepared by this method.^[39] The carboxylic acid **40** is converted into a thioester **41** before reduction with tin(II) chloride and pyridine-2-thiol. The tin reagent not only reduces the azide, but facilitates coordination to the thioester unit to maximize the intramolecular acyl substitution, giving the lactam.

Scheme 15 Cyclization of Amino Esters via Azide Surrogates^[39]

(3R,7S,10R,11R)-3,11-Diethyl-10-(methoxymethoxy)-7-methylazacyclotetradecane-2,8-dione (42):^[39]

A soln of azido thioester **41** (15.0 mg, 0.036 mmol) in toluene (20 mL) was added over 3 h by means of a syringe pump to a stirred mixture of SnCl₂ (120 mg, 0.63 mmol), pyridine-2-thiol (277 mg, 2.47 mmol), and Et₃N (340 mL, 2.45 mmol) in MeCN (20 mL) at 80 °C under argon. Heating was maintained for a further 1 h and the flask was then cooled externally and the solvent was removed under reduced pressure. The residue was treated with CH₂Cl₂/MeOH (19:1, 40 mL) and washed with 2 M aq KOH (2 × 40 mL). The aqueous layers were extracted with CH₂Cl₂ (2 × 40 mL). The combined organic extracts were washed with sat. aq NaCl (100 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The resulting colorless oil was dissolved in Et₂O (20 mL) and extracted twice with 1 M HCl (20 mL). The aqueous phase was extracted with Et₂O (3 × 20 mL). The extracts were dried (MgSO₄) and purified by chromatography (silica gel, CH₂Cl₂ to CH₂Cl₂/EtOAc 3:1) to give a white foam; yield: 8.0 mg (73%).

21.10.1.1.1.7

Method 7:**Cyclization of Amino Esters via Nitro Esters**

The nitro group is a useful amine surrogate that incorporates a nitrogen atom, but not the extra carbon atom associated with the cyano group. The amine is liberated by reduction, but formation of the requisite nitro ester is usually limited to alkylation of nitro enolate anions or addition of an enolate anion to a conjugated nitro compound. There are several methods for the reduction of nitro groups to amine groups.^[40] The choice of reagent is restricted to those that do not reduce an ester group, so catalytic hydrogenation is again the method of choice in most cases.

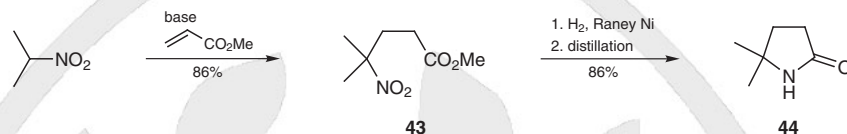
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Variation 1:**By Conjugate Addition of Nitro Enolates to Conjugated Esters**

This technique is illustrated by the preparation of 5,5-dimethylpyrrolidin-2-one (**44**) (Scheme 16). The enolate anion derived from 1-methyl-1-nitromethane adds to methyl

acrylate to give methyl 4-methyl-4-nitropentanoate (**43**) in 86% yield.^[41] Note that the conjugate addition works well with acrylate esters, but fails or gives poor yields with crotonate esters. Reduction of the nitro group by hydrogenation in the presence of Raney nickel catalyst leads to the amino ester, which cyclizes to 5,5-dimethylpyrrolidin-2-one (**44**).

Scheme 16 Conjugate Addition of Nitro Enolate Anions to Conjugated Esters^[41]



5,5-Dimethylpyrrolidin-2-one (**44**):^[41]

Methyl 4-methyl-4-nitropentanoate (**43**) was prepared essentially by the method of Brunson,^[42] except that a slightly higher temperature (85–100 °C) gave a better yield. The product was distilled through a short packed column to give a light blue liquid; yield: 86%; bp 79 °C/1 Torr.

A soln of the nitro ester **43** (148 g, 845 mmol) in abs EtOH (500 mL) was hydrogenated in the presence of Raney Ni catalyst (~25 g) at 69 °C and 6.89 MPa. The soln was filtered from the catalyst, the solvent was removed, and the residue was heated to 200 °C and then distilled under reduced pressure; yield: 82.5 g (86%); mp 37–41 °C (pentane); bp 75 °C/0.05 Torr.

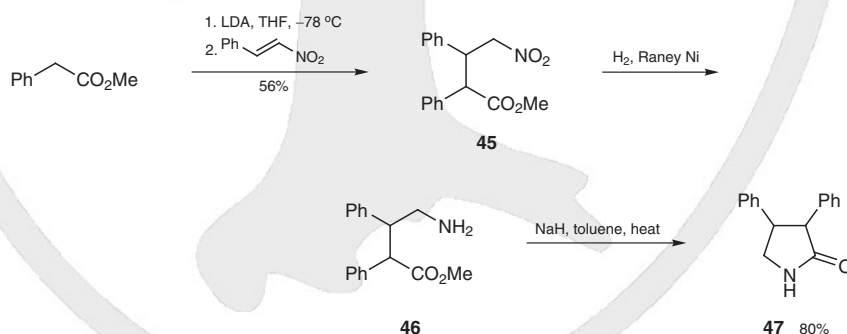
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Variation 2:

By Conjugate Addition of Enolate Anions to Nitroalkenes

This technique is illustrated by the addition of (2-nitrovinyl)benzene to the enolate anion prepared by treatment of methyl phenylacetate with lithium diisopropylamide at –78 °C, which gives a 56% yield of methyl 4-nitro-2,3-diphenylbutanoate (**45**) as a mixture of diastereomers (Scheme 17).^[43] Catalytic hydrogenation reduces the nitro unit to give the amino ester **46**. Interestingly, in this case, the amino ester **46** is treated with sodium hydride and heated in toluene for 2 days to give an 80% yield of 3,4-diphenylpyrrolidin-2-one (**47**).

Scheme 17 Conjugate Addition of Ester Enolate Anions to Conjugated Nitro Compounds^[43]



Methyl 4-Nitro-2,3-diphenylbutanoate (**45**); Typical Procedure:^[43]

BuLi (10.4 mL, 17.0 mmol) was added during 30 min to a soln of dry iPrNH₂ (2.39 mL, 17.0 mmol) in dry THF (7 mL) at –78 °C in a three-necked flask equipped with a low-temperature thermometer and a septum. The soln was stirred at 0 °C for 30 min, cooled to –78 °C, and the ester (8.21 mmol) dissolved in dry THF (50 mL) was added by means of a syringe during 30 min. The mixture was stirred at –78 °C for 30 min, and then

PhCH=CHNO_2 (9.03 mmol) dissolved in dry THF (20 mL) was added by syringe. The mixture was stirred for 3 h at -78°C , and then allowed to warm to rt overnight. Sat. aq NH_4Cl was added and the aqueous phase was extracted with EtOAc. The organic extracts were washed with H_2O and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2) as colorless crystals; yield: 56%; mp $100\text{--}136^\circ\text{C}$ (mixture of diastereomers).

3,4-Diphenylpyrrolidin-2-one (47): Typical Procedure:^[43]

A soln of the nitrobutanoate **45** (0.23 mmol) in dry Et_2O (1 mL) and dry EtOH (1 mL) was hydrogenated over Raney Ni (0.5 g) with H_2 at 1.2 MPa. After 48 h, the autoclave was flushed with N_2 , the mixture was filtered through Celite, and the Celite pad was washed with warm EtOH. The solvent was removed under reduced pressure, the residue was dissolved in toluene (5 mL), NaH (10 mg, 80% suspension in mineral oil) was added, and the mixture was refluxed for 2 d. Toluene was removed under reduced pressure and the residue was purified by column chromatography and recrystallized (Et_2O) as colorless crystals; yield: 80%; mp $170\text{--}172^\circ\text{C}$.

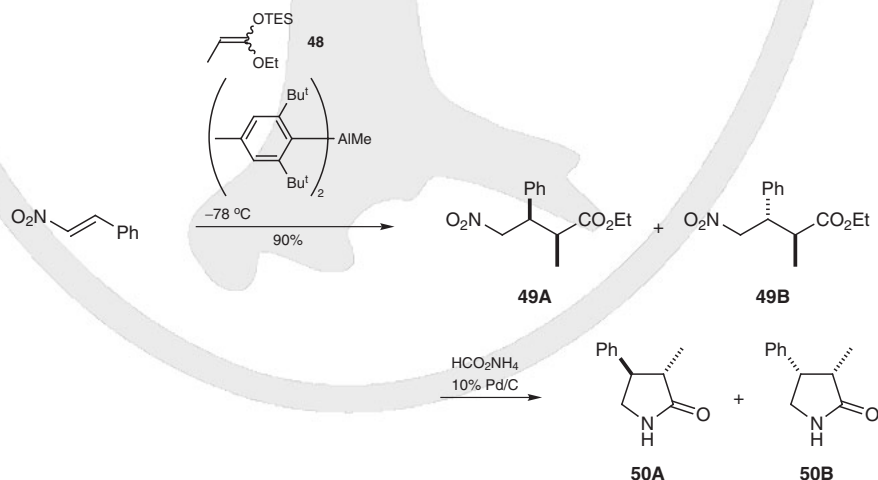
21.10.1.1.1.7.3

Variation 3:

By Lewis Acid Catalyzed Addition of Silyl Ketene Acetals to Nitroalkenes

Ester enolate anions are not the only reagents known to couple with nitroalkenes. In the presence of Lewis acids, silyl ketene acetals (obtained by trapping an ester enolate anion with a chlorotrialkylsilane)^[44] react with nitroalkenes to give γ -nitro esters after quenching the reaction. A variety of Lewis acids can be used, such as trimethylaluminum or bis(2,6-di-*tert*-butyl-4-methylphenyl)(methyl)aluminum (MAD).^[45] For example, an *E/Z* mixture of the silyl ketene acetal **48** derived from ethyl propanoate reacts with [(*E*)-2-nitrovinyl]benzene in the presence of bis(2,6-di-*tert*-butyl-4-methylphenyl)(methyl)aluminum at -78°C to give a 6.3:1 mixture of diastereomeric nitro esters **49** in 90% yield (Scheme 18). The nitro group can be reduced by ammonium formate in the presence of palladium/carbon (a mild and selective reducing agent for nitro esters), and the resulting amino ester cyclizes to the lactam **50** as a 6.3:1 mixture of diastereomers (yield not reported).

Scheme 18 Coupling Reaction of a Conjugated Nitro Compound and a Ketene Silyl Acetal^[45]



Ethyl 2-Methyl-4-nitro-3-phenylbutanoate (49A and 49B):^[45]**CAUTION:** Neat trimethylaluminum is highly pyrophoric.

2,6-Di-*tert*-butyl-4-methylphenol (6.00 mmol) was dissolved in anhyd toluene (4.5 mL) in an oven-dried, 15-mL, round-bottomed flask. The soln was deoxygenated with a stream of dry N₂ and cooled to 0 °C. Neat Me₃Al (0.288 mL, 3.00 mmol) was added dropwise from a syringe over 2–3 min. When the gas evolution became slow (5 min), the soln was warmed to 25 °C and stirred for 1 h. In a separate 50-mL, oven-dried, round-bottomed flask, a soln of the silyl ketene acetal **48** (3.0 mmol) in CH₂Cl₂ (6 mL) was cooled to –78 °C and treated with a soln of (*E*)-PhCH=CHNO₂ (2.73 mmol) in CH₂Cl₂ (6 mL). The soln was stirred for 5 min at –78 °C, then the soln of the Al reagent was added dropwise over 2 min. The resulting mixture was stirred for an additional 30 min at –78 °C and then anhyd Na₂SO₄ (0.32 g) was added, followed by Na₂SO₄•10H₂O (0.32 g). The mixture was allowed to warm to 25 °C and stirred for 30 min at this temperature. The soln was diluted with CHCl₃ (50 mL) to minimize solvent evaporation and consequent crystallization of the tri-*tert*-butylphenol within the frit during filtration, then filtered through Celite. Evaporation of the filtrate at reduced pressure gave a white solid that was purified by chromatography (silica gel, CH₂Cl₂/pentanes); yield: 90% (6.3:1 diastereomeric mixture).

cis- and trans-3-Methyl-4-phenylpyrrolidin-2-one (50A and 50B):^[45]

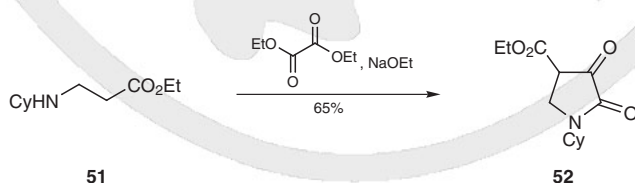
Ammonium formate (539 mg, 8.55 mmol) and 10% Pd/C (117 mg) were added to a mixture of the ethyl 2-methyl-4-nitro-3-phenylbutanoate diastereomers (**49**; 6.3:1 ratio; 429 mg, 1.71 mmol) dissolved in MeOH (2.5 mL). A mild exotherm occurred. The mixture was stirred overnight then filtered. The solvent was removed from the filtrate under reduced pressure. The residue was partitioned between CH₂Cl₂ (55 mL) and distilled H₂O (20 mL). The aqueous phase was washed with distilled H₂O (2 × 15 mL), and the combined organic extracts were dried (MgSO₄). The solvent was removed under reduced pressure; yield: not reported.

¹H NMR analysis of the product showed a 6.3:1 ratio of diastereomers. An analytical sample obtained by repeated crystallization (cyclohexane) contained a 19:1 ratio of diastereomers; mp 102–103.5 °C.

21.10.1.1.8

**Method 8:
Oxo Lactams by Cyclization with Oxalates**

Oxo lactams can be prepared by the oxidation of the alcohol unit in hydroxy lactams formed by reduction of imides (see Sections 21.10.1.1.2.2.2.1 and 21.10.1.1.2.2.2.3). Alternatively, the ketone moiety can be introduced into an acyclic precursor. For example, condensation of diethyl oxalate with ethyl *N*-cyclohexyl-β-alaninate (**51**) in the presence of sodium ethoxide gives the pyrrolidine-2,3-dione **52** (Scheme 19).^[46,47]

Scheme 19 Condensation of an Aminopropanoate and Diethyl Oxalate^[47]**Ethyl 1-Cyclohexyl-4,5-dioxopyrrolidine-3-carboxylate (52):**^[47]

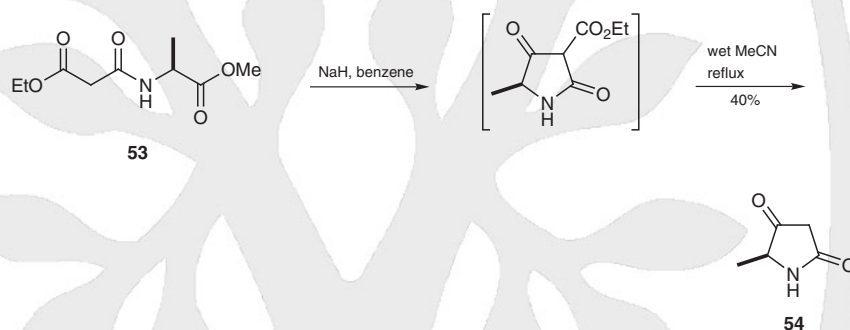
NaOEt (6.8 g; 100 mmol) was added to a soln of ethyl *N*-cyclohexyl-β-alaninate (**51**; 19.9 g, 100 mmol) and diethyl oxalate (14.6 g, 123 mmol). A vigorous reaction began at once and

the contents of the flask solidified. The mixture was refluxed on a steam bath for 1 h then the solid was removed by filtration, cooled, and washed with Et₂O. The residue was suspended in warm H₂O (500 mL). Following acidification of the mixture and several hours standing to complete the precipitation, the resulting product was collected by filtration and recrystallized (95% EtOH) as white needles; yield: 16.5 g (65%); mp 185–186 °C (188 °C on further recrystallization).

21.10.1.1.9

Method 9:**Oxo Lactams by Cyclization of Amido Diesters**

Dieckmann cyclization of α,ω -diesters is a well-established and valuable method for producing 1-alkoxycarbonyl cyclic ketones. If the linkage between the two ester units contains an amine group, cyclization gives an oxo lactam. For example, Dieckmann cyclization of the methyl ester of methyl *N*-(3-ethoxy-3-oxopropanoyl)-L-alaninate (**53**) in the presence of sodium hydride gives ethyl (5*S*)-5-methyl-2,4-dioxopyrrolidine-3-carboxylate as an intermediate (Scheme 20). Hydrolysis and decarboxylation then gives (5*S*)-5-methylpyrrolidine-2,4-dione (**54**).^[48]

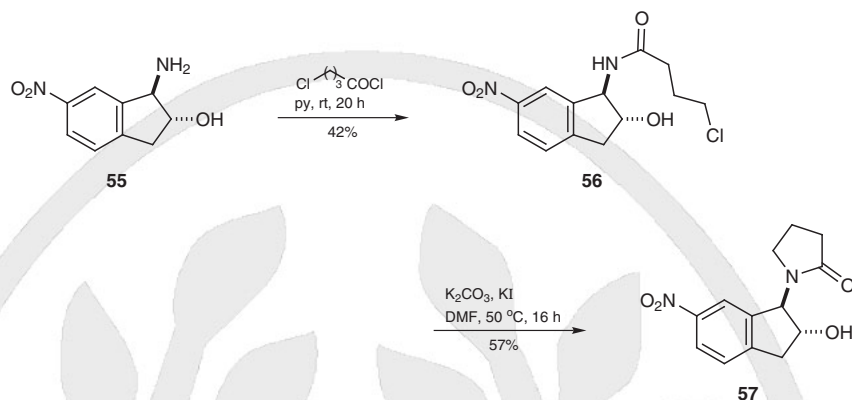
Scheme 20 Dieckmann Cyclization To Give Oxo Lactams^[48]**(5*S*)-5-Methylpyrrolidine-2,4-dione (**54**):**^[48,49]

Methyl *N*-(3-ethoxy-3-oxopropanoyl)-L-alaninate (**53**; 1.0 g, 4.6 mmol) was cyclized by refluxing in benzene (20 mL) (**CAUTION: carcinogen**) containing 60% NaH (184 mg, 4.6 mmol) for 18 h.^[49] Subsequent heating, without isolation of the intermediate, in refluxing wet MeCN (25 mL) for 6 h, followed by purification by flash chromatography (silica gel, MeOH/CHCl₃ 1:19) gave a pale yellow solid; yield: 0.2 g (40%); mp 103.5–105 °C.

21.10.1.1.10

Method 10:**Cyclization of Functionalized Acid Derivatives**

A variety of functionalized carboxylic acid derivatives can serve as precursors to lactams. There are several variations on this basic approach. One of the more common is the cyclization of ω -halo amides to give the corresponding lactam.^[50] For example, conversion of the amine **55** into the amide **56** with 4-chlorobutanoyl chloride, followed by heating with potassium carbonate and potassium iodide, gives the corresponding lactam **57** (Scheme 21).^[50]

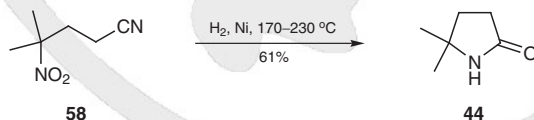
Scheme 21 Cyclization of a Chloro Amide^[50]**1-[(1R,2R)-2-Hydroxy-6-nitro-2,3-dihydro-1H-inden-1-yl]pyrrolidin-2-one (57):**^[50]

4-Chlorobutanoyl chloride (0.26 mL, 3.00 mmol) was added to a stirred soln of amino alcohol **55** (0.524 g, 2.70 mmol) in pyridine (20 mL) at 0 °C, and the mixture was stirred for 20 h at rt. 2 M aq HCl (150 mL) was then added and the product was extracted into EtOAc. Evaporation and chromatography (EtOAc) of the dried extracts gave the amide **56**; yield: 0.334 g (42%); mp 140–141 °C.

A mixture of the amide **56** (0.256 g, 0.86 mmol), KI (0.49 g, 2.95 mmol), and K₂CO₃ (5.7 g, 41.3 mmol) in DMF (15 mL) was stirred at 50 °C for 16 h, then the cooled soln was concentrated under reduced pressure. The product was isolated by partition of the residue between EtOAc and H₂O followed by chromatography (EtOAc/EtOH 19:1); yield: 0.128 g (57%); mp 204–205 °C (dec).

**21.10.1.1.10.1 Variation 1:
Reduction of Nitro Nitriles**

Just as amino esters cyclize to lactams, amino nitriles also cyclize when vigorously heated; however, this is not a straightforward reaction, and the overall procedure is rather elaborate. For example, initial reduction of the nitro nitrile **58** by iron and hydrochloric acid gives 2,2-dimethyl-3,4-dihydro-2H-pyrrol-5-amine 1-oxide.^[51] After isolation of this product, further reduction with the same iron/hydrochloric acid system gives 5-imino-2,2-dimethyl-3,4-dihydro-2H-pyrrole. Heating this imine with Raney nickel in water leads to 5,5-dimethylpyrrolidin-2-one (**44**). A more straightforward procedure that gives the lactam directly involves hydrogenation of 4-methyl-4-nitropentanenitrile (**58**) at elevated temperatures to give 5,5-dimethylpyrrolidin-2-one (**44**) in 61% yield (Scheme 22).^[52]

Scheme 22 Cyclization of an Amino Nitrile via a Nitro Precursor^[52]**5,5-Dimethylpyrrolidin-2-one (44):**^[52]

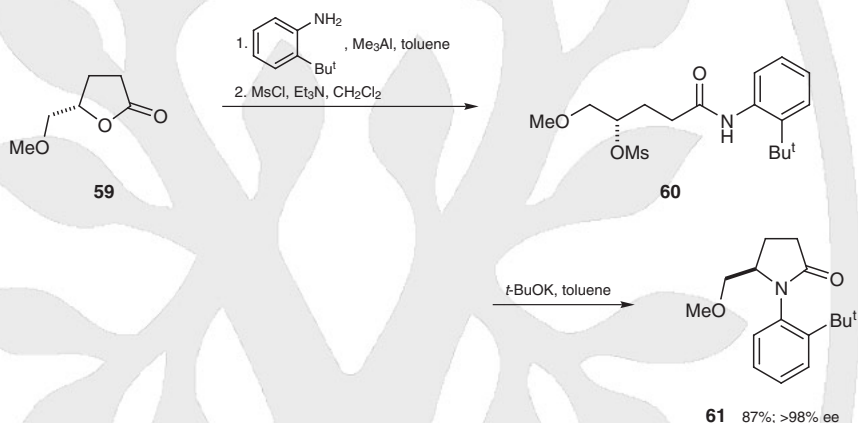
A soln of 4-methyl-4-nitropentanenitrile (**58**; 141 g, 1.0 mol) in abs MeOH (250 mL) was heated in a bomb to 170 °C without shaking in the presence of Raney Ni (12 g) under H₂ at 15.17 MPa. Initiation of shaking caused a rapid rise in temperature to 230 °C. Shaking was stopped after 1 min and resumed when the temperature fell to 200 °C. Absorption of

H₂ stopped after 10 min, and further shaking at 240 °C and 19.31 MPa resulted in no additional uptake of H₂. After removal of the catalyst and the MeOH, distillation of the residue gave a colorless liquid that solidified to a hygroscopic white crystalline solid; yield: 69 g (61%); bp 147–148 °C/32 Torr and 140–142 °C/26 Torr.

21.10.1.1.1.10.2

Variation 2:**1-Aryl Lactams by Cyclization of Aromatic Amides**

1-Aryl lactams can be prepared by cyclizing aryl amides prepared from aromatic amines and functionalized acid derivatives. Subsequent cyclization generates the 1-aryl lactam. For example, treatment of 2-*tert*-butylaniline with the functionalized lactone **59** in the presence of trimethylaluminum, followed by mesylation, gives the requisite lactam precursor **60** (Scheme 23).^[53] Cyclization with potassium *tert*-butoxide in toluene then leads to an 87% yield of the *N*-arylpyrrolidin-2-one **61**;^[53] no experimental details are reported.

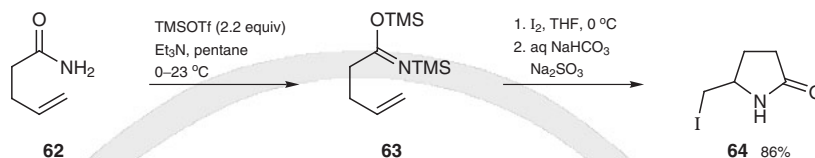
Scheme 23 Cyclization of an *N*-Aryl Amide^[53]

21.10.1.1.1.11

Method 11:**Iodolactamization**

The reaction of unsaturated carboxylic acids with iodine and a base is a useful method for the preparation of iodomethyl lactones through an intramolecular cyclization of the carboxyl anion to an iodonium unit generated in situ,^[54,55] but the formation of an iodomethyl lactam by a similar route is quite difficult. Knapp, however, successfully solved this problem, making iodolactamization a useful synthetic method.^[56] For example, the conversion of the amide unit in pent-4-enamide (**62**) into the *O*-trimethylsilyl imino ether **63**, followed by reaction with iodine and treatment with aqueous sodium bicarbonate gives an 86% yield of 5-(iodomethyl)pyrrolidin-2-one (**64**) (Scheme 24).^[56] For successful cyclization, it is necessary to separate the *N,O*-bis(silyl) derivative **63** from the oily triethylammonium trifluoromethanesulfonate that accompanies its formation.

A related cyclization of *N*-sulfonyl amino alkenes with *N*-bromosuccinimide gives the corresponding bromo lactam;^[57] similarly, *N,N*-diallyl-2,2-dichloroacetamide is converted into a dichlorolactam with iron(II) chloride.^[58]

Scheme 24 Iodolactamization of an Alkenamide^[56]**5-(Iodomethyl)pyrrolidin-2-one (**64**); Typical Procedure:**^[56]

For a 1- to 5-mmol scale preparation, a soln of pent-4-enamide (**62**; 1 equiv) and Et₃N (2.2 equiv) in dry pentane was treated at 0 °C with TMSOTf (2.2 equiv) and stirred under argon for 30 min at 23 °C. The supernatant, which contained the N,O-bis-silylated amide **63**, was transferred to a second dry flask under argon. The residue was rinsed with additional pentane, and the pentane was carefully removed from the combined organic phases (in total, about 5 mL·mmol^{−1} of substrate) by using an aspirator equipped with a CaSO₄ drying tube. THF was added, the soln was cooled to 0 °C, and a soln of I₂ (2.2 equiv) in THF was added in one portion. After 10 min, the soln was quenched with aq Na₂CO₃ and then aq Na₂SO₄, and extracted with EtOAc (3 ×). The combined organic soln was dried (Na₂SO₄) and concentrated, and the product was immediately purified by chromatography (silica gel, Et₂O/petroleum ether) to give **64** as a stable white solid that was recrystallized (Et₂O/hexane); yield: 86%; mp 68–70 °C.

21.10.1.1.12

**Method 12:
Radical Cyclization**

Radical cyclization of functionalized alkenes is a well-established method for the generation of five- and six-membered rings. ω-Haloalkenes lose a halogen atom to form a carbon radical upon treatment with reagents such as 2,2'-azobisisobutyronitrile or under photolysis conditions.^[59,60] The radical carbon adds intramolecularly to the alkene to form a cyclic compound.^[61] A hydrogen-transfer agent,^[62] such as tributyltin hydride, is usually required to quench the radical reaction, and the reduction of the halogen can be faster than the cyclization process. Given a choice between a larger and a smaller ring, radical cyclization generally gives the smaller ring,^[63] but this is not always the case.^[64,65]

Radical cyclization is compatible with the presence of other functional groups. Treatment of XCH₂CON(R¹)—C(R²)=CH₂ derivatives (X = Cl, Br, I) with triphenyltin hydride and 2,2'-azobisisobutyronitrile leads to the formation of a lactam through radical cyclization.^[66–68] This procedure gives good results when bicyclic lactams are the target.^[69,70] Cyclization of 1-(1-iodoethyl)-5-vinylpyrrolidin-2-one, for example, leads to the corresponding bicyclic lactam,^[71,72] and there are other examples of radical cyclization with molecules containing a lactam unit.

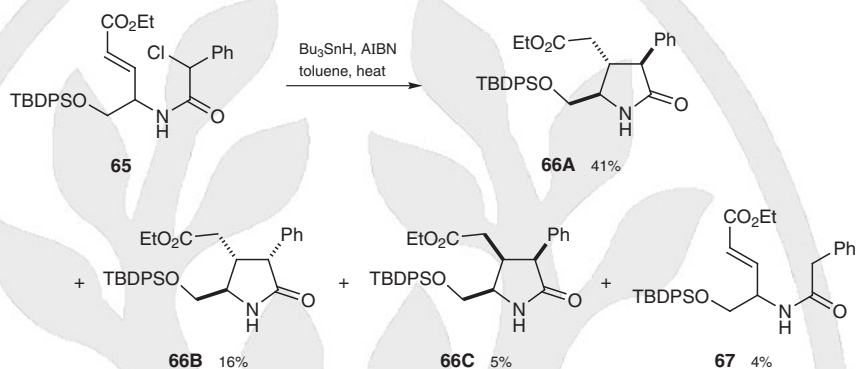
21.10.1.1.12.1

**Variation 1:
Tin Hydride Mediated Radical Cyclization of N-Monosubstituted Amides**

When an alkyl halide is treated with a radical initiator such as 2,2'-azobisisobutyronitrile, a new carbon radical is formed, and if an alkene unit is present in the molecule, radical addition leads to a new ring. Tributyltin hydride is usually added as a hydrogen-transfer agent to quench the newly formed radical and give the product. Cyclization does not always occur readily, particularly when functional groups are present on the units connecting the halide and the alkene groups. Cyclization can be assisted by incorporating a functional group on the alkene, such as a ketone or ester, to help to stabilize the newly formed radical. This is illustrated by the reaction of the α-chloro amide **65** with 2,2'-azobisisobutyronitrile/tributyltin hydride in refluxing toluene (Scheme 25).^[73] Cyclization is facilitat-

ed by the presence of the conjugated ester group, and leads to the lactam **66** in 62% yield. If the phenyl group is not present and if a conjugated alkene is not employed, the yield of lactams is often quite low.^[74] The example (Scheme 25) clearly illustrates one problem with this approach, since several stereoisomers **66A–66C** are produced, along with a reduced acyclic product **67**. Although the cyclization is stereoselective, a mixture of isomers is obtained that must be separated.

Scheme 25 Radical Cyclization of a Haloalkenyl Amide^[73]



Ethyl {2-(*tert*-Butyldiphenylsiloxy)methyl}-5-oxo-4-phenylpyrrolidin-3-yl}acetate (66A–66C**):^[73]**

Bu₃SnH (67 mg, 0.23 mmol) and AIBN (7 mg, 0.04 mmol) in toluene (17 mL) were added over 1 h to the amidoalkenyl ester **65** (155 mg, 0.28 mmol) in degassed toluene (9 mL), and the mixture was stirred and refluxed for a further 18 h. Column chromatography (CH₂Cl₂/EtOAc 4:1) gave the pyrrolidinones **66A–66C** as colorless oils in a ratio of 8.2:3.2:1; total yield: 90 mg (62%).

The dechlorinated product **67** was also isolated as a colorless oil; yield: 4 mg (4%).

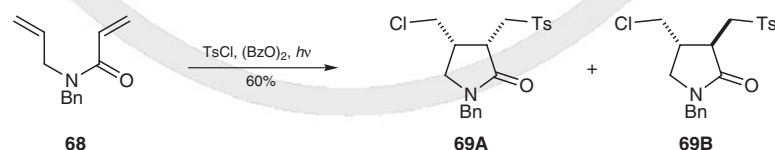
21.10.1.1.1.12.2

Variation 2:

Radical Cyclization of Unsymmetrical Dienes Containing an Amide Unit

Photolysis of alkenes in the presence of 4-toluenesulfonyl halides leads to radical addition. With a suitable substrate, this variation can generate rings. The sulfonyl radical promoted cyclizations of 1,6-unsymmetrical dienes involves the addition of 4-toluenesulfonyl halides to various 1,6-dienes bearing both a nucleophilic and an electrophilic double bond.^[75] For example, radical cyclization of *N*-allyl-*N*-benzylacrylamide (**68**) (Scheme 26) generates two isomeric pyrrolidinones **69A** and **69B**, with selectivity toward the *anti*-diastereomer **69B**.^[75] A similar addition and cyclization reaction occurs with 4-toluenesulfonyl bromide and *N*-allylacrylamide.^[76]

Scheme 26 Photoinduced Radical Cyclization of an Azadiene with 4-Toluenesulfonyl Chloride^[75]



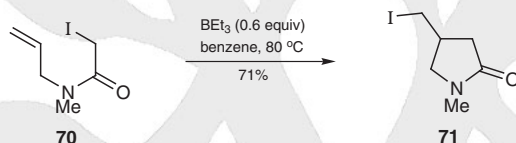
1-Benzyl-4-(chloromethyl)-3-(tosylmethyl)pyrrolidin-2-one (69A and 69B):^[75]

A soln of *N*-allyl-*N*-benzylacrylamide (**68**; 1.5 g, 7.46 mmol) and TsCl (9.03 g, 48 mmol) in toluene (75 mL) at rt was irradiated in the presence of (BzO)₂. Liquid chromatography (EtOAc/petroleum ether 1:9 to 2:3) gave a 2:7 mixture of **69A** and **69B** (1.74 g) and a 1:9 mixture of **69A** and **69B** (1.29 g); total yield: 60%.

**21.10.1.1.12.3 Variation 3:
Borane-Mediated Radical Cyclization**

Problems associated with the 2,2'-azobisisobutyronitrile/tributyltin hydride cyclization of α -halo amides to alkenes can be overcome by using an alternative radical-initiation process. 2-Iodo-*N*-(prop-2-enyl)acetamides, on treatment with triethylborane (0.2–0.6 equiv) in boiling benzene, undergo iodine atom transfer cyclization to give the corresponding 4-(iodomethyl)pyrrolidin-2-ones in high yields.^[77] The method can also be applied to the synthesis of lactones.^[77] Triethylborane in the presence of oxygen produces ethyl radicals that can abstract an iodine atom from iodoalkanes; this property has been used for the inter- and intramolecular atom-transfer radical additions of iodoalkanes to alkynes or alkenes.^[78,79] For example, the iodine atom-transfer radical cyclization of *N*-allyl-2-iodo-*N*-methylacetamide (**70**) (Scheme 27) in the presence of triethylborane provides a new route to 4-(iodomethyl)-1-methylpyrrolidin-2-one (**71**) and related compounds.^[80]

Scheme 27 Borane-Mediated Radical Cyclization^[80]

**4-(Iodomethyl)-1-methylpyrrolidin-2-one (71); Typical Procedure:**^[80]

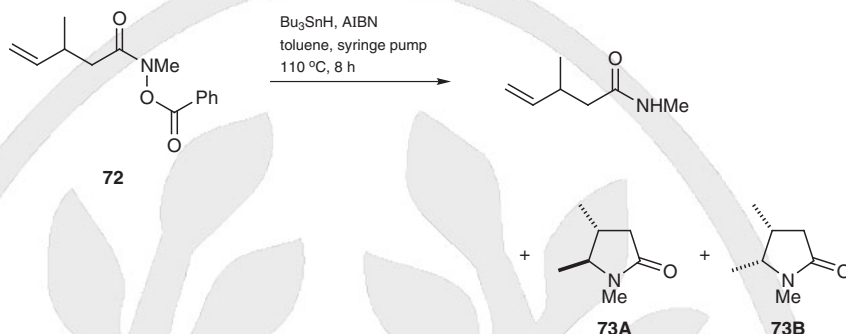
A 1.01 M soln of BEt₃ in hexane (0.14 mL, 0.146 mmol) was added all at once to a boiling soln of the *N*-allyl-2-iodo-*N*-methylacetamide (**70**; 0.243 mmol) in benzene (15 mL) (**CAUTION: carcinogen**), and the mixture was refluxed for 10 min. The mixture was washed with H₂O, dried (MgSO₄), and concentrated. The residue was chromatographed (silica gel, hexane/EtOAc 8:1 to 1:1) to give an oil; yield: 71%; IR (CCl₄) $\tilde{\nu}_{\text{max}}$: 1695 cm⁻¹.

**21.10.1.1.12.4 Variation 4:
Cyclization of Amidyl Radicals**

Previous methods (Sections 21.10.1.1.12 and 21.10.1.1.12.1–21.10.1.1.12.3) focus on generating a carbon radical that adds to an alkene unit. Radicals can also be generated at nitrogen, such as amide nitrogen radicals (amidyl radicals). Amidyl radicals are generated by the tributyltin hydride mediated homolysis of *O*-benzoyl hydroxamic acid derivatives. When the hydroxamic acid derivatives contain an alkene, 5-*exo*-cyclization gives mixtures of *cis*- and *trans*-pyrrolidinones.^[81] Alternatively, treatment of an unsaturated hydroxamic acid with *tert*-butylsulfinyl chloride and diisopropylethylamine from –50 °C to room temperature in the presence of a radical trap such as diphenyl diselenide, diphenyl disulfide, or 2,2,6,6-tetramethylpiperidin-1-yloxy gives the lactam product via an amidyl radical cyclization.^[82] For example, the reaction of the *N*-methyl hydroxamic acid derivative **72** and 2,2'-azobisisobutyronitrile generates an amidyl radical that cyclizes at the distal alkene unit, with quenching by hydrogen-atom transfer from tributyltin hydride (Scheme 28).^[81] The reaction produces a mixture of cyclized and reduced products in a ratio of 17:1, with a 47% yield of the isomeric lactams **73**. A similar cyclization with the *N*-butyl-

3-phenyl derivative gives a 12:1 mixture of cyclized to reduced products and an 82% yield of the corresponding lactams.

Scheme 28 Radical Cyclization via Amidyl Radicals^[81]



anti- and syn-1,4,5-Trimethylpyrrolidin-2-ones (73A and 73B); Typical Procedure:^[81]

A 0.15 M soln of the hydroxamic acid **72** in refluxing toluene was treated with Bu_3SnH (1.1 equiv) and 10 mol% of AIBN added from a syringe pump over 8 h. The final concentration of hydroxamic acid was 0.075 M. Workup and chromatography gave a mixture of *anti*- and *syn*-products; yield: 47%. The ratio of cyclized to reduced products was 17:1.

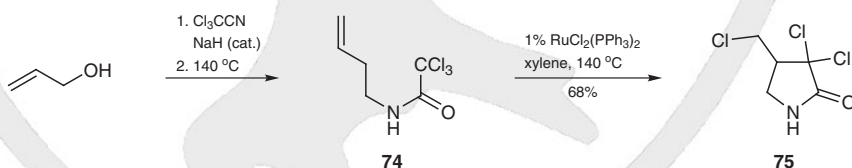
21.10.1.1.1.12.5

Variation 5:

Metal-Mediated Radical Cyclization Reactions

Metal-mediated radical reactions can lead to the formation of lactams. The key to such cyclization reactions is often the method required to prepare the precursors. The Overman rearrangement^[83] proceeds with complete 1,3-transposition of a hydroxy group and an amide group, and the subsequent ruthenium-catalyzed cyclization of the *N*-allyltrichloroacetamides that are formed provides γ -lactams selectively, despite the potential for the formation of δ -lactams.^[84] Other halogenated amides can be converted into lactams by copper-catalyzed reactions.^[85] For example, reaction of prop-2-en-1-ol with trichloroacetamide, followed by Overman rearrangement, gives the trichloroacetamide derivative **74** (Scheme 29); ruthenium-catalyzed ring closure then gives 3,3-dichloro-4-(chloromethyl)-pyrrolidin-2-one (**75**).^[84]

Scheme 29 Ruthenium-Catalyzed Cyclization of an α -Halo Alkenyl Amide^[84]



Certain metal carbene complexes containing carbonyl ligands coordinate with alkynes with insertion of a carbonyl unit and formation of a ring. If the metal-carbene complex contains an amine group, the reaction can generate lactams. For example, aminocarbene complexes of chromium [e.g., $\text{Me}_2\text{NCMe}=\text{Cr}(\text{CO})_5$] react successively with diphenylacetylene, an acid R^1H ($\text{R}^1 = \text{SPh}$, SePh , OAc), and pyridine to give functionalized pyrrolidinones (e.g., 1,5-dimethyl-3,4-diphenylpyrrolidin-2-one) via *N*-ylide complexes.^[86,87]

3,3-Dichloro-4-(chloromethyl)pyrrolidin-2-one (75): Typical Procedure:^[84]

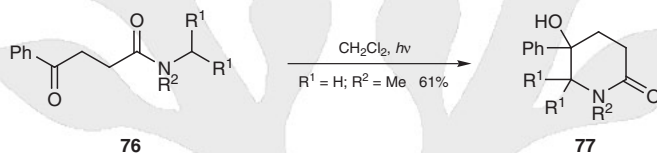
A mixture of *N*-but-3-en-1-yl-2,2,2-trichloroacetamide (**74**; 4.9 mmol), $\text{RuCl}_2(\text{PPh}_3)_3$ (47 mg, 0.05 mmol), and xylene (40 mL) was refluxed for 1 h. After removal of the solvent under reduced pressure, the mixture was purified by chromatography (silica gel, hexane/ Et_2O) to give **75** as a white solid; yield: 68%; mp 100–101 °C.

Alternatively, the reaction can be carried out in a pressure bottle with benzene (**CAUTION: carcinogen**) as the solvent.

**21.10.1.1.12.6 Variation 6:
Photocyclization**

Irradiation with light is required to induce the radical cyclization of alkenes (see Section 21.10.1.1.12.2). Other photochemical methods can also be used to prepare lactams. For example, the irradiation of 4-oxo-4-phenylbutanamides **76** leads to δ -lactams **77** by hydrogen abstraction from the ϵ -position (Scheme 30).^[88] Subsequent cyclization proceeds with excellent diastereoselectivity via a biradical intermediate. The photocyclization is compatible with several different substituents on the amide nitrogen.

Scheme 30 Ruthenium-Catalyzed Cyclization of α -Halo Alkenyl-Amides^[88]


5-Hydroxy-1-methyl-5-phenylpiperidin-2-one (77, $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{Me}$): Typical Procedure:^[88]

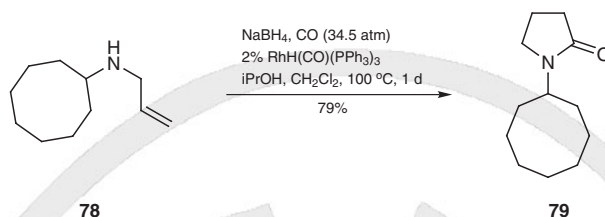
A 1 M soln of amide **76** ($\text{R}^1 = \text{H}$; $\text{R}^2 = \text{Me}$) in CH_2Cl_2 was treated with dry, O_2 -free argon for 30 min and then irradiated with a 150-W, high-pressure, Hg-arc lamp (Hanau) until no reactant was detectable by TLC. An analytically pure product was isolated by liquid chromatography; yield: 61%; mp 149–150 °C.

**21.10.1.1.13 Method 13:
Metal-Catalyzed Cyclization**

Transition metals play an extremely important role in modern organic chemistry, and the formation of lactams is no exception. Perhaps the most important reaction involving transition metals is ring-closing metathesis. The product of this reaction is a lactam having a double bond in the ring; for this reason, this important class of reactions will be discussed in Section 21.10.2. Apart from ring-closing metathesis, there are several noteworthy transition metal related lactam-forming reactions, including the variation discussed in Section 21.10.1.1.13.1.

**21.10.1.1.13.1 Variation 1:
Amine-Directed Hydrocarbonylation**

Rhodium complexes can be used to convert *N*-allyl alkyl amines into lactams. The amine reacts with carbon monoxide in the presence of sodium borohydride, propan-2-ol, and catalytic amounts of a rhodium complex.^[89] For example, the reductive carbonylation of allyl(cyclooctyl)amine (**78**) (Scheme 31) gives a 79% yield of 1-cyclooctylpyrrolidin-2-one (**79**).^[89] An alternate route to the lactams from *N*-allyl alkyl amines involves synthesis gas instead of carbon monoxide/sodium borohydride, and uses a borane catalyst in the presence of bis[tricarbonyl(dichloro)ruthenium].^[89]

Scheme 31 Rhodium-Catalyzed Cyclization of an Allyl(alkyl)amine^[89]

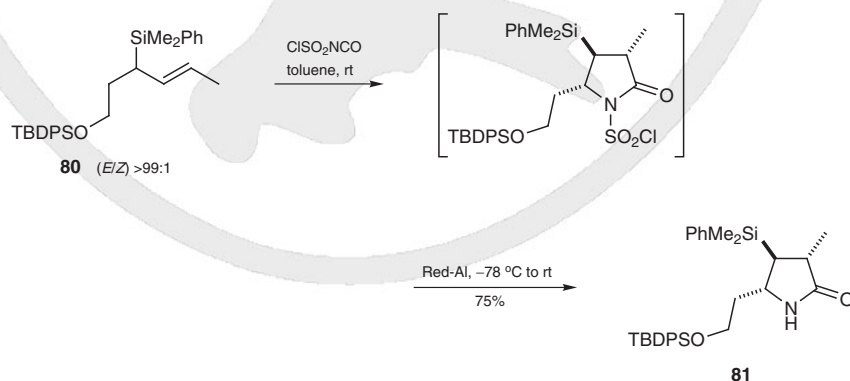
Lactams are also formed diastereoselectively by the reaction of *N*-alkenyl *N*-alkyl amines with ruthenium complexes.^[90] Homoallylic amine–ruthenium complexes react cleanly to give substituted pyrrolidin-2-one derivatives by a two-step process involving hydrometalation to form an η^2 -ruthenium complex, followed by carbonylation with retention of configuration at the migrating center to give *trans*-pyrrolidin-2-ones in a good yields and *trans/cis* ratios of 8:1 to 1:0.^[90]

1-Cyclooctylpyrrolidin-2-one (79); Typical Procedure:^[89]

A mixture of allyl(cyclooctyl)amine (**78**; 2.0 mmol), NaBH_4 (2.25 mmol), $\text{RhH}(\text{CO})(\text{PPh}_3)_3$ (0.02 mmol), iPrOH (0.5 mL), and CH_2Cl_2 (5.0 mL) was placed in a 45-mL autoclave with a glass liner. The autoclave was pressurized to 34.5 atm with CO, and the mixture was heated with stirring for 30 h at 100 °C. After cooling to rt, the reactor was opened under a fume hood and H_2O was added to destroy unreacted NaBH_4 . The organic phase was concentrated by rotary evaporation to give an oil. The product **79** was isolated by column chromatography (silica gel, hexane/EtOAc 19:1); yield: 79%.

**21.10.1.1.1.14 Method 14:
[3 + 2] Annulation**

[3 + 2]-Cycloaddition reactions are well-studied reactions for producing five-membered rings. Lactams, particularly pyrrolidin-2-one derivatives, can be formed by this approach. Annulation with chlorosulfonyl isocyanate, unlike the reactions of allylsilanes with most electrophiles, requires no Lewis acid activation. Although the unstable *N*-chlorosulfonyl amide intermediate is isolable, reduction to the stable lactam is more efficient.^[91] Of the methods known to perform this reduction, an in situ reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) is the most reliable and high yielding. For example, a two-step, one-pot protocol provides the pyrrolidin-2-one **81** from allylsilane **80** (Scheme 32), in a 75% overall yield and with a high stereoselectivity.^[91]

Scheme 32 Cyclization of Alkenes with Chlorosulfonyl Isocyanate^[91]

(3R,4S,5R)-5-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-4-[dimethyl(phenyl)silyl]-3-methylpyrrolidin-2-one (81); Typical Procedure:^[91]

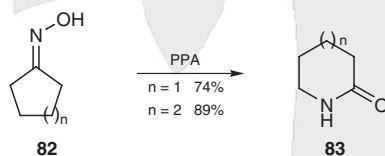
ClSO_2NCO (0.056 mL, 0.647 mmol) was added to a soln of allylic silane **80** (0.204 g, 0.431 mmol) in toluene (9 mL). After 2 h at 25 °C, the mixture was cooled to –45 °C, and a 65 wt% soln of Red-Al (0.6 mL, 2.0 mmol) in toluene was added. The mixture was kept at –45 °C for 2 h. The reaction was quenched by dropwise addition of H_2O until H_2 evolution ceased, and the mixture was warmed to 25 °C. The heterogeneous soln was filtered, and the filtrate was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (hexanes/EtOAc 3:1) gave an oil that solidified on standing; yield: 0.166 g (75%).

21.10.1.1.2 Synthesis by Ring Transformation**21.10.1.1.2.1 Ring Enlargement**

There are several procedures for transforming a cyclic ketone to a lactam with a ring one atom larger. Procedures are also available for converting smaller functionalized rings into larger lactam rings. Some of the key transformations are discussed in this section.

21.10.1.1.2.1.1 Method 1: Beckmann Rearrangement

Treatment of an oxime with phosphorus pentachloride or a similar reagent induces a rearrangement to give the corresponding substituted amide: this reaction is known as the Beckmann rearrangement.^[92–94] Cyclic ketones are readily converted into the corresponding oximes by treatment with hydroxylamine; Beckmann rearrangement of the resulting oximes causes ring enlargement to give the corresponding lactam with a ring that is one atom larger (Scheme 33).^[95] A simple example is the Beckmann rearrangement of cyclohexanone oxime (**82**, $n = 2$) with polyphosphoric acid to give hexahydro-2H-azepin-2-one (**83**, $n = 2$); similarly, cyclopentanone oxime (**82**, $n = 1$) gives piperidin-2-one (**83**, $n = 1$).

Scheme 33 Beckmann Rearrangement of Cyclic Oximes^[92–94,96]

Among the reagents that can be used for the Beckmann rearrangement are concentrated sulfuric acid, formic acid, liquid sulfur dioxide, thionyl chloride,^[97] silica gel,^[98] hydrochloric acid/acetic acid/acetic anhydride, phosphoryl chloride,^[99] and polyphosphoric acid.^[100] Alternatively, an oxime of a cyclic ketone can be heated neat with aluminum trichloride to give the lactam.^[101] Many examples of this transformation are available.

When the oxime is derived from an alkyl aryl ketone, it is generally the aryl group that migrates preferentially.

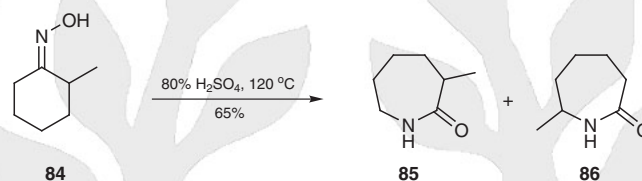
It is not necessary to isolate the oxime; treatment of a cyclic ketone with hydroxylamine-*O*-sulfonic acid on silica gel followed by microwave irradiation gives the corresponding lactam.^[13] Cyclic ketones can also be converted directly into lactams in one step by treatment with hydroxylamine-*O*-sulfonic acid and formic acid.^[102,103] Beckmann rearrangements have also been carried out photochemically.^[104–106]

Esters of oximes also undergo Beckmann rearrangement in the presence of many organic and inorganic acids; however, with many substrates, nitriles are formed in a side reaction. Under the correct conditions, cycloalkanecarboxylic acids also rearrange to

form lactams. Azacyclododecan-2-one, for example, can be prepared from cycloundecane-2-carboxylic acid by treatment with nitrosylsulfuric acid in chlorosulfonic acid.^[107,108] There are several variations on this basic transformation.

When the cyclic ketone has a substituent, regioisomeric lactams can be formed. If an *E/Z* mixture of oximes is used, the reaction commonly generates an approximately 1:1 mixture of the corresponding regioisomers. If pure *E*- or *Z*-oxime is subjected to the Beckmann rearrangement under nonisomerizing conditions, the migrating group is the one *anti* to the hydroxy group;^[109] a typical example is the Beckmann rearrangement of 2-methylcyclohexanone oxime (**84**) to azepin-2-ones **85** and **86** (Scheme 34).^[110]

Scheme 34 Beckmann Rearrangement of an Unsymmetrical Oxime^[110]



Piperidin-2-one (**83**, *n* = 1); Typical Procedure:^[96]

Cyclopentanone oxime (**82**, *n* = 1; 2.0 g, 17.7 mmol) was stirred with PPA (60 g) at 130 °C for 10 min. The mixture was poured into H₂O (300 mL) and the mixture was extracted with Et₂O/EtOAc (1:1). The combined extracts were washed with H₂O and sat. brine, then dried (MgSO₄). The product was isolated by filtration, evaporation of the solvents, and crystallization; yield: 74%.

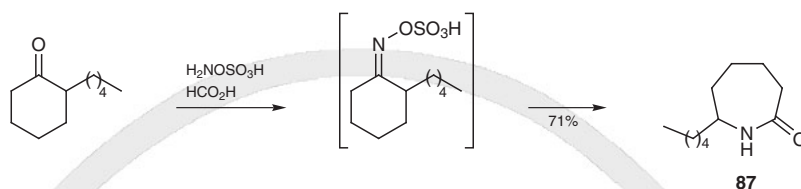
Similarly, heating cyclohexanone oxime (**82**, *n* = 2) at 115 °C with PPA gave hexahydro-2H-azepin-2-one (**83**, *n* = 2); yield: 89%.

3-Methylhexahydro-2H-azepin-2-one (**85**) and 7-Methylhexahydro-2H-azepin-2-one (**86**):^[110]

A soln of 2-methylcyclohexanone oxime (**84**; 51.0 g, 401 mmol) in 80% H₂SO₄ (70 mL) was added dropwise to 80% H₂SO₄ (30 mL) at 120 °C. When the exothermic reaction ceased, the mixture was cooled to 0 °C and neutralized with concd aq NH₄OH (230 mL) with intense external cooling. The aqueous soln was extracted with CHCl₃ (3 × 100 mL). The combined extracts were dried (Na₂SO₄) and evaporated to dryness under reduced pressure. The crystalline residue (44 g) was purified by vacuum distillation to give a mixture of azepinones; yield: 33.3 g (65%); bp 126–128 °C (0.6 Torr). Isomer ratio not reported.

21.10.1.1.2.1.1.1 Variation 1: From Ketoxime O-Sulfonic Acids

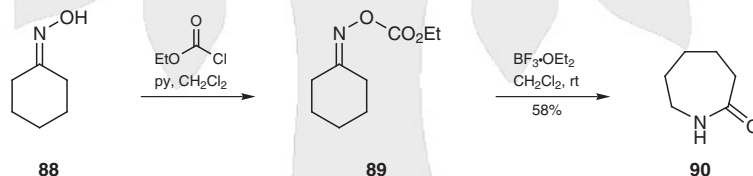
The Beckmann rearrangement can be accomplished without isolating the oxime of the cyclic ketone. Treatment of the ketone with hydroxylamine *O*-sulfonic acid in the presence of an acid such as formic acid or sulfuric acid in a second step leads to the Beckmann rearrangement. An oxime *O*-sulfonic acid is initially formed and then, upon treatment with an acid, is converted in situ into an oxime that undergoes rearrangement to the lactam.^[111,112] This reaction is illustrated by the preparation of 7-pentylhexahydro-2H-azepin-2-one (**87**) (Scheme 35).

Scheme 35 Beckmann Rearrangement of a Cyclic Oxime O-Sulfonic Acid^[113]**7-Pentylhexahydro-2H-azepin-2-one (87):**^[113]

A soln of 2-pentylcyclohexanone (16.83 g, 100 mmol) was added over 25 min to a soln of $\text{H}_2\text{NOSO}_3\text{H}$ (12.46 g, 110 mmol) in HCO_2H (50 mL) at rt, and the mixture was refluxed for 1 h. After cooling, the mixture was poured into sat. aq NH_4Cl (100 mL) and H_2O (100 mL) and extracted with CHCl_3 (4×50 mL). The extracts were washed with sat. aq NaHCO_3 (2×100 mL), dried (Na_2CO_3), and concentrated to give a solid that was recrystallized (pentane); yield: 13 g (71%); mp 57–59 °C.

21.10.1.1.2.1.2 Variation 2:
Reaction with Ketoxime O-Carbonates

If they are properly activated, oximes can undergo rearrangement upon treatment with milder acids. A variety of ketoximes, e.g. **88**, can be converted into the corresponding ethyl carbonates in high yields (generally 90–99%) through treatment with ethyl chloroformate in dichloromethane in the presence of 1 equivalent of pyridine at room temperature. The oxime ethyl carbonate, e.g. **89**, then undergoes Beckmann rearrangement on treatment with 1 equivalent of boron trifluoride–diethyl ether complex in dichloromethane at room temperature.^[114] Reaction times for a variety of oxime carbonates range from 4 to 18 hours, and the yields of the lactam products are 58–87%.^[114] The reaction is illustrated by the preparation of hexahydro-2H-azepin-2-one (**90**) (Scheme 36).

Scheme 36 Beckmann Rearrangement of a Cyclic Oxime O-Carbonate^[114]

In a related variation on this reaction, ketoxime carbamates are converted into lactams through diazotization followed by rearrangement with sulfuric acid or isoamyl nitrite.^[115,116]

Hexahydro-2H-azepin-2-one (90) by the Beckmann Rearrangement:^[114]

Cyclohexanone oxime (**88**; 1 mmol) was mixed with dry pyridine (1 mmol) in dry CH_2Cl_2 (3 mL) and the mixture was then treated with EtO_2CCl (1 mmol) at 25 °C for 3 h. Workup by washing with H_2O , drying, and evaporation of the solvent gave the oxime carbonate **89**.

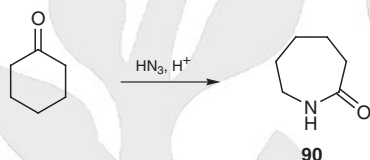
The oxime carbonate **89** (1 mmol) was dissolved in CH_2Cl_2 (2 mL) and treated with $\text{BF}_3 \cdot \text{OEt}_2$ (1 mmol) at 25 °C with stirring for 10 h. The product **90** was isolated by washing with H_2O , drying, and removal of the solvent under reduced pressure; yield: 58%.

21.10.1.1.2.1.2 Method 2: Schmidt Reaction

There are three reactions that are known by the name “the Schmidt Reaction”; these involve, respectively, the addition of hydrazoic acid to alcohols, the addition of hydrazoic acid to alkenes, and the addition of hydrazoic acid to carboxylic acids, aldehydes, or ketones.^[117] The most frequently encountered is the reaction with carboxylic acids.^[118]

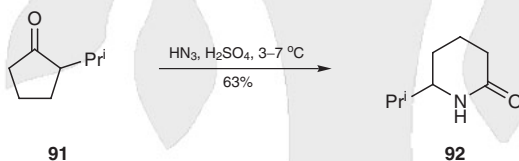
The reaction between a ketone and hydrazoic acid is a method for insertion of an NH group into a ketone to convert it into an amide.^[119,120] This reaction is illustrated by the conversion of cyclohexanone into hexahydro-2H-azepin-2-one (**90**) (Scheme 37) upon treatment with hydrazoic acid.

Scheme 37 Example of the Schmidt Reaction^[119,120]



Although, aryl substituents can migrate during this reaction, dialkyl and cyclic ketones react so much faster than diaryl or aryl alkyl ketones or carboxylic acids or alcohols that these functions can be present in the same molecule without interfering in the reaction. With alkyl aryl ketones, it is the aryl group that generally migrates to the nitrogen, except when the alkyl group is bulky.^[121,122] Exceptions to this have been noted in the case of cyclic aromatic ketones bearing electron-donating groups in *ortho*- and *para*-positions.^[122] For example, treatment of 2-isopropylcyclopentanone (**91**) with hydrazoic acid causes ring expansion to the lactam **92** in 63% yield (Scheme 38).^[123]

Scheme 38 Schmidt Reaction of Cyclohexanone with Hydrazoic Acid^[123]



6-Isopropylpiperidin-2-one (**92**):^[123]

CAUTION: Hydrazoic acid is violently explosive and of variable sensitivity in concentrated or pure states. It is a severe irritant with effects on the central nervous system.

HN_3 (0.495 g, 11 mmol) in CHCl_3 (12 mL) was added dropwise during 2 h to a stirred mixture of 2-isopropylcyclopentanone (**91**; 1.26 g, 10 mmol), concd H_2SO_4 (4 mL), and CHCl_3 (10 mL) at 3–7 °C. After addition was completed, the mixture was stirred for 1 h then poured onto ice. The phases were separated and the aqueous layer was extracted with CHCl_3 (10 \times 30 mL). The CHCl_3 extract was washed with 10% aq K_2CO_3 soln, washed with H_2O , and dried (Na_2SO_4). After removal of the CHCl_3 at reduced pressure, the crude lactam (1.01 g, 71.5%) crystallized. Recrystallization [petroleum ether (bp 30–60 °C)] of the crude product gave white needles; yield: 0.79 g; mp 85.2–86 °C.

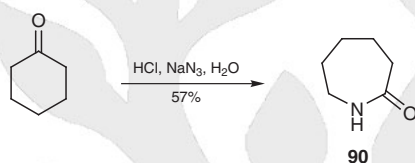
Most of the petroleum ether was distilled from the mother liquor of recrystallization and the residue was diluted to a volume of 25 mL. One-half of this soln was subjected to chromatography [silica gel/Celite, abs EtOH/benzene (**CAUTION: carcinogen**) 1:49, 500 mL]. The adsorbate was located in a narrow zone near the middle of the column. Elu-

tion of this zone with 15% abs EtOH (200 mL) in petroleum ether (bp 30–60 °C) gave additional 6-isopropylpiperidin-2-one (**92**); yield: 0.10 g; mp 85–86 °C; total yield: 0.89 g (63%).

21.10.1.1.2.1 Variation 1:
By Reaction of Cyclic Ketones with Metal Azides and Acids

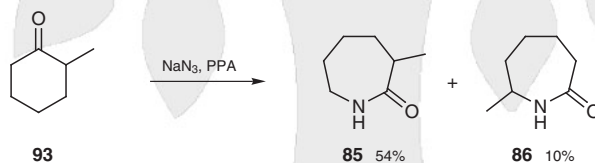
It is not necessary to add hydrazoic acid directly to the ketone. Cyclic ketones can be converted directly into a lactam by using a mixture of sodium azide and an acid, which generates hydrazoic acid in situ. This variation of the Schmidt reaction gives good yields of lactams.^[119,120,124,125] For example, treatment of cyclohexanone with hydrochloric acid and sodium azide in aqueous sodium nitrite gives a 57% yield of hexahydro-2H-azepin-2-one (**90**) (Scheme 39); a 66% yield is obtained when the reaction is performed in acetic acid.^[126]

Scheme 39 Schmidt Reaction of Cyclohexanone with Nitrous Acid^[126]



Regioisomeric mixtures of lactams are usually produced by Schmidt rearrangement, as noted with the Beckmann rearrangement (Section 21.10.1.1.2.1.1), because there are two carbon atoms adjacent to the carbonyl group in the starting material. An example of a selective rearrangement that generates two regioisomers is the reaction of 2-methylcyclohexanone (**93**) and sodium azide, in the presence of polyphosphoric acid (Scheme 40)^[127] to give two lactam products, 3-methylhexahydro-2H-azepin-2-one (**85**) and 7-methylhexahydro-2H-azepin-2-one (**86**), in 54 and 10% yields, respectively.^[128]

Scheme 40 Schmidt Reaction with an Unsymmetrical Ketone^[128]



Hexahydro-2H-azepin-2-one (90) by the Schmidt Rearrangement:^[126]

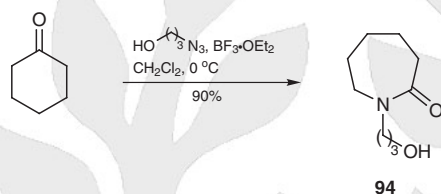
CAUTION: Sodium azide can explode on heating and is highly toxic. Contact of metal azides with acids liberates the highly toxic and explosive hydrazoic acid.

NaN₃ (2.0 g, 31 mmol) was added portionwise as quickly as the vigor of the reaction permitted to a soln of cyclohexanone (2.0 g, 20 mmol) in concd aq HCl (10 mL) at rt. The mixture was allowed to stand for several hours and then distilled to dryness under reduced pressure. The residue was taken up in a little H₂O and the soln was made alkaline with excess 50% aq NaOH. The yellow oil that separated was extracted with CHCl₃ (3 ×) and the combined extracts were washed with H₂O and the solvents removed under reduced pressure to give a mass of crystals; yield: 1.3 g (57%); mp 63–64 °C [benzene (**CAUTION: carcinogen**)/petroleum ether].

21.10.1.1.2.1.2.2 **Variation 2:**
By Reaction with Alkyl Azides and Acids

Alkyl azides can replace metal azides in the Schmidt reaction. This useful variation involves the treatment of a cyclic ketone with an alkyl azide in the presence of titanium(IV) chloride to generate a lactam.^[129–131] Other Lewis acids can be used,^[132] including boron trifluoride–diethyl ether complex, as illustrated by the reaction of cyclohexanone with 3-azidopropan-1-ol to give the lactam **94** in 90% yield (Scheme 41).^[133] There is also a variation that uses trimethylsilyl trifluoromethanesulfonate.^[134]

Scheme 41 Schmidt Reaction with an Alkyl Azide^[133]



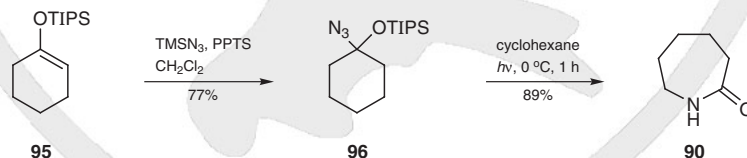
1-(3-Hydroxypropyl)hexahydro-2H-azepin-2-one (94):^[133]

A soln of cyclohexanone (200 mg, 2.04 mmol) and 3-azidopropan-1-ol (247 mg, 2.44 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C. $\text{BF}_3 \cdot \text{OEt}_2$ (0.51 mL, 4.08 mmol) was added dropwise over 5 min. Immediate gas evolution was noted upon addition. The mixture was allowed to warm to rt over 30 min and then stirred for an additional 3 h. The soln was concentrated, sat aq NaHCO_3 (5 mL) was added to the residual oil, and the mixture was stirred for 30 min. After further concentration, additional CH_2Cl_2 (100 mL) was added and the organic layer was separated, dried (Na_2SO_4), and concentrated to give a colorless oil that was purified by flash chromatography (EtOAc); yield: 320 mg (90%).

21.10.1.1.2.1.2.3 **Variation 3:**
By Photocyclization of Siloxy Azides

Alkyl azides can be generated in several ways. A useful method involves the treatment of a silyl enol ether (e.g., **95**) of a cyclic ketone with trimethylsilyl azide to give an azide (e.g., **96**) that, on irradiation with UV light, is converted into the corresponding lactam (e.g., **90**).^[135] This method constitutes a new approach to lactams through a photo-induced Schmidt rearrangement of α -azido triisopropylsilyl ethers (Scheme 42).^[135]

Scheme 42 Photochemical Schmidt Reaction of an O-Silyl Azide^[135]



1-Azidocyclohexyl Triisopropylsilyl Ether (96); Typical Procedure:^[135]

1-(Triisopropylsiloxy)cyclohex-1-ene (**95**; 127 mg, 0.50 mmol) was dissolved in anhyd CH_2Cl_2 (5 mL) and the soln was stirred at rt under N_2 . TMSN_3 (0.66 mL, 5.0 mmol) was added, followed by PPTS (256 mg, 1.02 mmol) and the resulting homogeneous mixture was stirred at rt for about 48 h. The mixture was then poured into sat. aq NaHCO_3 (25 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford a crude oil that

was purified by flash chromatography (silica gel, hexane) to give a colorless oil; yield: 114 mg (77%); IR (neat) $\tilde{\nu}_{\text{max}}$: 2948, 2892, 2865, 2104 cm^{-1} .

Hexahydro-2H-azepin-2-one (90) by the Photochemical Schmidt Reaction; Typical Procedure:^[135]

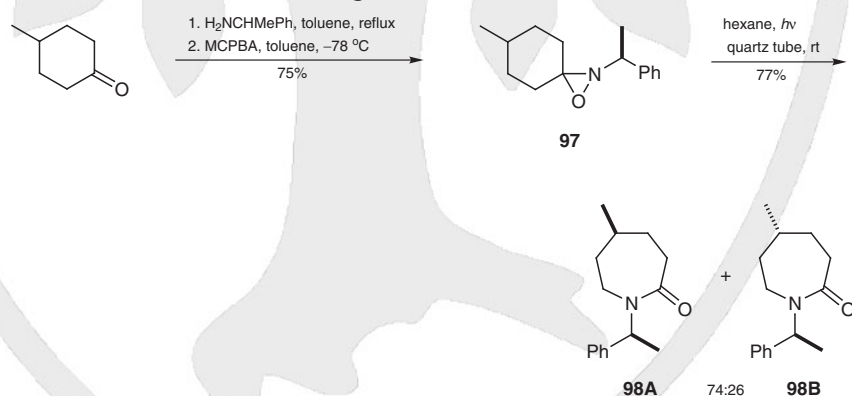
1-Azidocyclohexyl triisopropylsilyl ether (**96**; 157 mg, 0.528 mmol) was dissolved in cyclohexane (20 mL) and the soln was transferred to a quartz test tube and degassed with N_2 for about 20 min. The quartz tube was then attached to a UV lamp and cooled to 0 °C. The mixture was irradiated for about 1 h during which time it warmed up appreciably. The solvent was then removed under reduced pressure to afford a crude oil that was purified by flash chromatography (silica gel, EtOAc/hexane 1:1 then MeOH/EtOAc 1:9) to give the product as a white crystalline solid; yield: 53 mg (89%); mp 68–69 °C.

21.10.1.1.2.1.3 Method 3: Photochemical Ring Expansion of Oxaziridines

Although the Beckmann and Schmidt rearrangements are the most common ring-expansion reactions that produce lactams, others are available. Most of these are relatively specific but they can generate a variety of lactams, including chiral, nonracemic lactams and highly substituted or functionalized derivatives.

Prochiral ketones are precursors of the corresponding ring-expanded lactam. The cyclic ketone is first converted into an oxaziridine and subsequent photo-irradiation leads to the ring-expanded lactam.^[136] The key step in formation of lactams bearing a chiral substituent involves the stereoelectronically controlled photochemical rearrangement reaction of an axially dissymmetric oxaziridine, e.g. **97**, derived from the ketone, as illustrated for the preparation of the chiral lactams **98A** and **98B** (Scheme 43).^[136] The direction of stereoselectivity for the rearrangement reaction, in all cases examined, depends only on the axial chirality of the substrate oxaziridine and not on stereochemical or conformational factors.

Scheme 43 Photochemical Rearrangement of an Oxaziridine^[136]



6-Methyl-2-[(1S)-1-phenylethyl]-1-oxa-2-azaspiro[2.5]octane (97); Typical Procedure:^[136]

A soln of 4-methylcyclohexanone (252 mg, 2.25 mmol) and $\text{H}_2\text{NCHMePh}$ (411 mg, 3.39 mmol) in toluene was refluxed for 5–7 h in a round-bottomed flask equipped with a condenser connected via a Dean–Stark trap. The crude toluene soln of the imine was then cooled to rt and added through an addition funnel dropwise under N_2 to a round-bottomed flask containing a ~80% suspension of MCPBA in toluene (0.575 g, 2.7 mmol) at –78 °C (dry ice/acetone bath). The oxidation reaction was usually completed within

20 min (TLC). The reaction was quenched with sat. aq $\text{Na}_2\text{S}_2\text{O}_4$ at -78°C and the soln was poured into a separating funnel and partitioned between sat. aq $\text{Na}_2\text{S}_2\text{O}_4$ and Et_2O . The organic layer was washed with sat. aq NaHCO_3 and brine, then dried (Na_2SO_4). The product was isolated by concentration of the soln followed by column chromatography (EtOAc /hexane 1:9) as an oil consisting of a mixture of four isomers; yield: 0.391 g (75%).

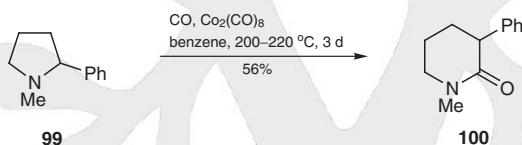
5-Methyl-1-[(1S)-1-phenylethyl]hexahydro-2H-azepin-2-one (98A and 98B); Typical Procedure:^[136]

A 0.05–0.10 M soln of the oxaziridine **97** in hexane in a quartz tube was degassed with N_2 for 20 min and then photolyzed at rt in a chamber reactor (Rayonet RPR-100; 2537 Å). The soln was concentrated and products were purified by column chromatography (EtOAc /hexane 1:4) as a 74:26 mixture of isomers; yield: 77%.

**21.10.1.1.2.1.4 Method 4:
Carbonylation of Cyclic Amines**

Octacarbonyldicobalt-catalyzed carbonylation of pyrrolidines results in ring expansion to form piperidinones.^[137] The reaction is regiospecific in most cases, and the yield of product is increased when a dodecacarbonyltriruthenium is present as a second catalyst. For example, the treatment of 1-methyl-2-phenylpyrrolidine (**99**) with carbon monoxide and octacarbonyldicobalt in dry benzene for 72 hours at 220°C and 54 atmospheres gives 1-methyl-3-phenylpiperidin-2-one (**100**) in a 56% yield (Scheme 44).^[137]

Scheme 44 Cobalt-Catalyzed Carbonylation of Pyrrolidine Derivatives^[137]



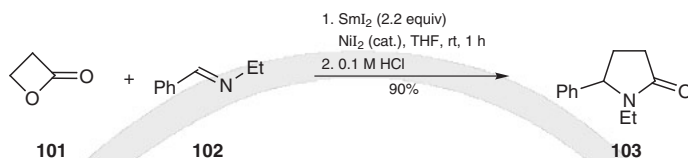
1-Methyl-3-phenylpiperid-2-one (100); Typical Procedure:^[137]

CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

A mixture of 1-methyl-2-phenylpyrrolidine (**99**; 1.32 mmol), $\text{Co}_2(\text{CO})_8$ (0.103 g, 0.30 mmol), and benzene (10 mL) (**CAUTION:** carcinogen) was placed in an autoclave containing a glass liner and a stirring bar. The autoclave was purged several times with CO then pressurized to 54 atm and the mixture was stirred at $200\text{--}220^\circ\text{C}$ for 3 d. The cooled autoclave was opened and the mixture, after standing in air, was filtered through Celite. The filtrate was concentrated by rotary evaporation to give a crude product that was purified by TLC (alumina, hexane/acetone); yield: 56%; IR (benzene) $\tilde{\nu}_{\text{max}}$: 1640 cm^{-1} (CO).

**21.10.1.1.2.1.5 Method 5:
Condensation of β -Lactones and Imines**

Treatment of β -lactones (e.g., **101**) with imines (e.g., **102**) in the presence of samarium(II) iodide results in ring expansion: hydrolysis then gives the corresponding lactam. The reaction is illustrated by the preparation of 1-ethyl-5-phenylpyrrolidin-2-one (**103**) (Scheme 45).^[138]

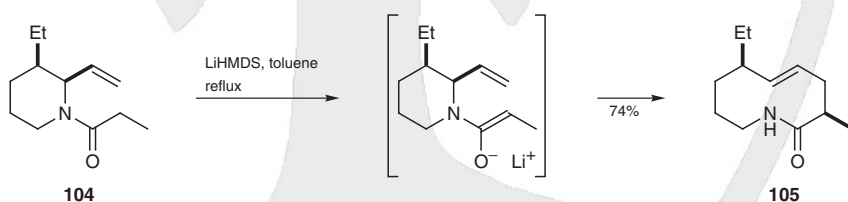
Scheme 45 Reaction of Propanolactones and Imines^[138]**1-Ethyl-5-phenylpyrrolidin-2-one (103):**^[138]

A soln of NiI_2 (0.022 mmol) in THF (2.2 mL) was added to a soln of SmI_2 (2.2 mmol) in THF (22 mL). Oxetan-2-one (**101**; 1 mmol) and the imine **102** (1 mmol) mixed in THF (4 mL) were added to the SmI_2 soln and the initially deep blue-green soln turned brown within 10 min. The mixture was stirred for a further 50 min. The mixture was quenched with 0.1 M HCl and stirred for 30 min to obtain a clear soln and then extracted with Et_2O . The combined extracts were washed with $\text{Na}_2\text{S}_2\text{O}_3$ and brine. The organic layer was dried (MgSO_4) and the solvents were removed under reduced pressure. The crude material was purified by flash chromatography (silica gel, pentane/ Et_2O 4:1) to give a yellow oil; yield: 90%.

21.10.1.1.2.1.6

**Method 6:
Aza-Claisen Ring Expansion**

Lactams can be expanded to larger-ring lactams by the aza-Claisen rearrangement. ω -Alkenyl *N*-acyl amides are converted into the enolate anion, allowing an aza-Claisen rearrangement to occur. For example, 3-ethyl-1-propanoyl-2-vinylpiperidine (**104**) is converted into the enolate anion by treatment with lithium hexamethyldisilazide in refluxing toluene (Scheme 46).^[139] The reflux conditions facilitate an aza-Claisen rearrangement to give the corresponding unsaturated lactam **105** in 74% yield. Although this reaction could be discussed in Section 21.10.2, it is placed here because it is a good example of a ring-expansion process. Catalytic hydrogenation of the $\text{C}=\text{C}$ bond provides the saturated lactam. No experimental details are available.

Scheme 46 Aza-Claisen Rearrangement^[139]

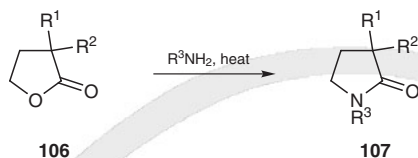
21.10.1.1.2.2

Formal Exchange of Ring Members with Retention of the Ring Size

21.10.1.1.2.2.1

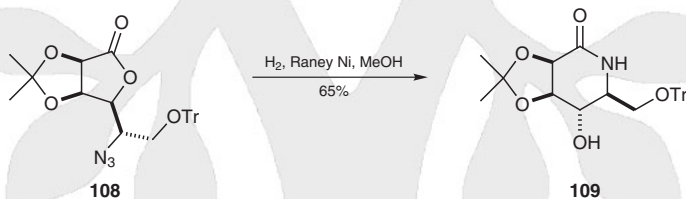
**Method 1:
Conversion of Lactones into Lactams by Reaction with Amines**

Just as esters are converted into amides by reaction with amines, so lactones are converted into lactams (Scheme 47).^[140] For example, treatment of dihydrofuran-2(3*H*)-one (γ -butyrolactone; **106**, $\text{R}^1 = \text{R}^2 = \text{H}$) with amines gives the corresponding *N*-substituted pyrrolidin-2-one derivatives **107**.^[141,142]

Scheme 47 Reaction of Amines and Lactones^[141,142]

Long-chain amines, benzylamine, and N^1,N^1 -diethylpentane-1,4-diamine react satisfactorily giving 35–45% yields of the corresponding pyrrolidin-2-ones. 5-Methyldihydrofuran-2(3*H*)-one (γ -valerolactone), and 5-ethyl-5-methyldihydrofuran-2(3*H*)-one (γ -ethyl- γ -valerolactone) react without difficulty with several amines, although under similar conditions, 5-methyldihydrofuran-2(3*H*)-one gives lower yields than does dihydrofuran-2(3*H*)-one. The pyrrolidinones obtained are high-boiling liquids or waxy solids. For example, the reaction of dihydrofuran-2(3*H*)-one (**106**, $R^1 = R^2 = \text{H}$) with dodecylamine gives an 83% yield of 1-dodecylpyrrolidin-2-one [**107**, $R^1 = R^2 = \text{H}$; $R^3 = (\text{CH}_2)_9\text{Me}$], whereas with benzylamine it gives a 33% yield of 1-benzylpyrrolidin-2-one (**107**, $R^1 = R^2 = \text{H}$; $R^3 = \text{Bn}$). Similarly, 3-methyldihydrofuran-2(3*H*)-one (**106**, $R^1 = \text{H}$; $R^2 = \text{Me}$) reacts with tetradecylamine to give a 45% yield of 3-methyl-1-tetradecylpyrrolidin-2-one [**107**, $R^1 = \text{H}$; $R^2 = \text{Me}$; $R^3 = (\text{CH}_2)_{13}\text{Me}$], and 3,3-dimethyldihydrofuran-2(3*H*)-one (**106**, $R^1 = R^2 = \text{Me}$) reacts with dodecylamine to give a 48% yield of 1-dodecyl-3,3-dimethylpyrrolidin-2-one [**107**, $R^1 = R^2 = \text{Me}$; $R^3 = (\text{CH}_2)_{11}\text{Me}$].

This procedure is not limited to simple lactones. An interesting example involves the hydrogenation of azido lactone **108** to liberate an amine unit that reacts with the lactone unit to give the lactam **109** by intramolecular acyl substitution (Scheme 48).^[143]

Scheme 48 Intramolecular Reaction of an Amino Lactone (Azide Surrogate)^[143]

N-Substituted Pyrrolidin-2-ones 107: General Procedure:^[142]

Equimolar quantities of an amine and a lactone **106** were heated with agitation at 110–130 °C for about 3 h and then at 250–270 °C for 3–6 h while distilling off H_2O . The excess reactants were distilled off under reduced pressure and the N-substituted pyrrolidin-2-one was recovered by distillation.

(3a*S*,6*R*,7*R*,7a*S*)-7-Hydroxy-2,2-dimethyl-6-(trityloxymethyl)tetrahydro[1,3]dioxolo[4,5-*c*]pyridin-4(3a*H*)-one (109):^[143]

A soln of the azidolactone **108** (51.6 mg, 0.109 mmol) in MeOH (2.0 mL) was stirred with Raney Ni under H_2 at rt for 4 h. After filtration, evaporation of the filtrate gave an oil that was subjected to preparative TLC (silica gel, toluene/acetone 2:1) to give a colorless foam; yield: 31.8 mg (65%); $[\alpha]_{\text{D}}^{23} +13.7$ (*c* 0.67, MeOH).

21.10.1.1.2.2.2

Method 2:

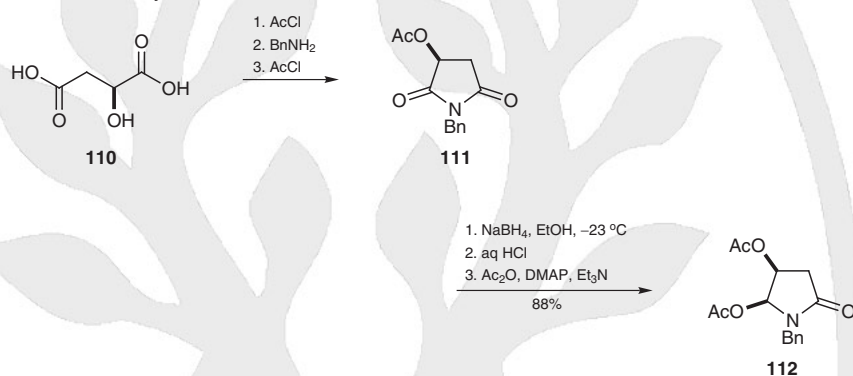
Reduction or Selective Alkylation of Imides

Cyclic imides are relatively easily prepared from dicarboxylic acids. Selective reduction of one carbonyl of the imide leads to a lactam. Alternatively, one carbonyl can react selectively with a nucleophilic reagent, such as a Grignard reagent, to give a functionalized lactam.

**21.10.1.1.2.2.2.1 Variation 1:
Reduction of Cyclic Imides**

Succinimide derivatives are obtained by reaction of succinic esters, succinoyl chlorides, or similar compounds with amines or ammonia. For example, formation of the anhydride from the hydroxy diacid **110** and subsequent reaction with benzylamine leads to the imide **111**; the hydroxy unit at the α -position of the dicarboxylic acid is protected as the acetate (Scheme 49). Reduction of the carbonyl unit between the nitrogen and protected alcohol moieties with sodium borohydride leads to a diastereomeric mixture of 5-hydroxy-pyrrolidin-2-ones, which are trapped as the acetate; the major isomer is (2*S*,3*S*)-1-benzyl-5-oxopyrrolidine-2,3-diyl diacetate (**112**), isolated in 88% yield.^[144]

Scheme 49 Hydride Reduction of a Succinimide Derivative^[144]

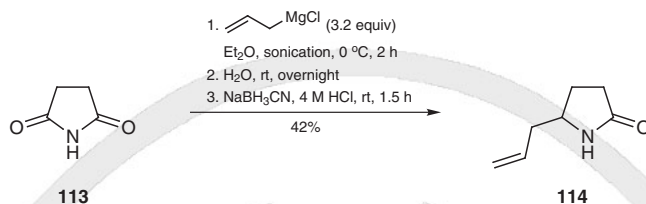


(2*S*,3*S*)-1-Benzyl-5-oxopyrrolidine-2,3-diyl Diacetate (112**):^[144]**

NaBH₄ (2.04 g, 53.7 mmol) was added portionwise over 5 min to a stirred soln of (3*S*)-1-benzyl-2,5-dioxopyrrolidin-3-yl acetate (**111**; 6.63 g, 26.8 mmol) in EtOH (100 mL) at -23 °C. After the addition was completed, the mixture was kept at -23 °C for 20 min, acidified with 1% HCl to pH 2–3, neutralized with sat. aq NaHCO₃, and extracted with CH₂Cl₂. The organic phase was dried (MgSO₄) and filtered, and the solvent was removed under reduced pressure. The residue (5.87 g) was dissolved in CH₂Cl₂ and cooled to 0 °C. Et₃N (3.51 mL, 25.0 mmol), Ac₂O (4.44 mL, 35.3 mmol), and DMAP (0.20 g, 1.64 mmol) were added. The mixture was allowed to warm up to rt and after 1 h it was diluted with CH₂Cl₂ (20 mL) and washed with 10% HCl (20 mL), sat. aq NaHCO₃ (20 mL), and H₂O (2 × 30 mL). The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was chromatographed (230–400 mesh silica gel, EtOAc/hexanes 7:13); yield: 6.87 g (88%); mp 136.5–138 °C; [α]₅₄₆²⁵ -76 (c 1.0, EtOH).

**21.10.1.1.2.2.2.2 Variation 2:
Reaction of Imides with Grignard Reagents**

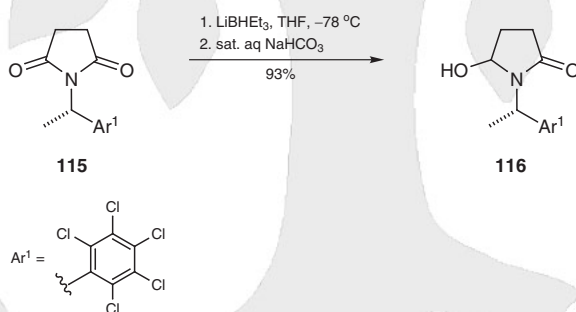
Imides react with Grignard reagents to give the corresponding alcohols. Under the proper conditions, the alcohols readily eliminate water to form imines that can be reduced to the corresponding lactams.^[145,146] The reduction is often performed in situ, without attempting to isolate the alcohol or imine intermediates. For example, the Grignard reaction of allylmagnesium chloride with succinimide (**113**), followed by treatment with sodium cyanoborohydride under acidic conditions, gives a 42% yield of 5-allylpyrrolidin-2-one (**114**) (Scheme 50).^[147]

Scheme 50 Reductive Alkylation of a Succinimide Derivative^[147]**5-Allylpyrrolidin-2-one (114):**^[147]

A 2.25 M soln of $\text{H}_2\text{C}=\text{CHCH}_2\text{MgCl}$ in Et_2O (35.0 mL, 78.8 mmol) was slowly added through a cannula to a soln of succinimide (**113**; 2.00 g, 20.2 mmol) in freshly distilled THF (40 mL) at 0 °C under a positive pressure of N_2 . The milky soln was stirred at 0 °C for 2 h with sonication, treated with distilled H_2O (15 mL), and stirred for 3 h at rt. To the soln were added, sequentially, NaBH_3CN (1.27 g, 20.2 mmol), methyl orange (~100 mg), and 4 M HCl until the mixture remained pink. The mixture was stirred for a further 2 h at rt then 6 M NaOH was added. The mixture was extracted with CH_2Cl_2 and the extracts were washed with brine and dried (MgSO_4). The product was isolated chromatographically (silica gel, EtOAc /hexane 1:1) to give a light yellow oil; yield: 1.06 g (42%).

21.10.1.1.2.2.2.3 Variation 3:
5-Hydroxy Lactams by Reduction of Imides

α -Hydroxy lactams can be conveniently prepared by the partial reduction of a substituted imide.^[148,149] For example, the treatment of the benzylsuccinimide **115** with lithium tri-ethylborohydride gives the corresponding α -hydroxy lactam **116** in 93% yield (Scheme 51).^[146] This reaction is obviously specific for generating ω -hydroxy lactams, but it is efficient and the products are useful for several synthetic transformations.

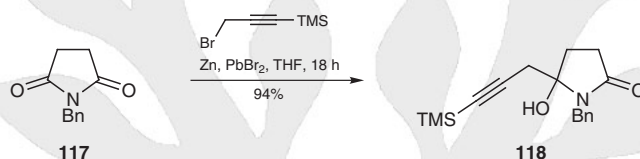
Scheme 51 Reduction of a Succinimide Derivative^[146]**5-Hydroxy-1-[(1S)-1-(pentachlorophenyl)ethyl]pyrrolidin-2-one (116):**^[146]

A 1.0 M soln of LiBHEt_3 in THF (0.47 mL, 0.47 mmol) was added to a soln of the imide **115** (111 mg, 0.30 mmol) in THF (9 mL) with stirring at -78 °C. After 40 min, the reaction was quenched with sat. NaHCO_3 (4 mL) and warmed to 0 °C. After 20 min, the THF was removed on a rotary evaporator, and the aqueous residue was extracted with CH_2Cl_2 . The combined organic extracts were dried (MgSO_4), filtered, and concentrated, and the residue was purified by flash chromatography (EtOAc) as a white solid; yield: 104 mg (93%); mp 180–181 °C.

21.10.1.1.2.2.2.4 Variation 4:
5-Alkyl-5-hydroxy Lactams

Grignard reagents, organolithium reagents, and other organometallic compounds react with carbonyl compounds to give alcohols after hydrolysis. When an imide reacts with an organometallic reagent, it is possible to trap the resulting hydroxy lactam. The success of this transformation depends on the nature of the organometallic reagent used and the reaction conditions. Grignard reagents react with lactams, but the product is usually a dihydropyrrole. The reaction of *N*-methylpyrrolidin-2-one and butylmagnesium bromide, for example, gives *N*-methyl-2-butylidihydropyrrole.^[150] Lactams can be produced by modifying the procedure, starting from imides rather than from lactams. The reaction of succinimide with a Grignard reagent followed by reduction leads to the 5-alkylpyrrolidin-2-one (see Section 21.10.1.1.2.2.2.2). The use of an organozinc reagent allows the alcohol intermediate in this process to be trapped. For example, the Barbier-type alkylation of 1-benzylsuccinimide (**117**) with 1-trimethylsilyl-3-bromoprop-1-yne gives the corresponding 5-hydroxy-5-propargylpyrrolidin-2-one **118** in 94% yield (Scheme 52).^[151]

Scheme 52 Acyl Addition Reaction of a Succinimide Derivative^[151]



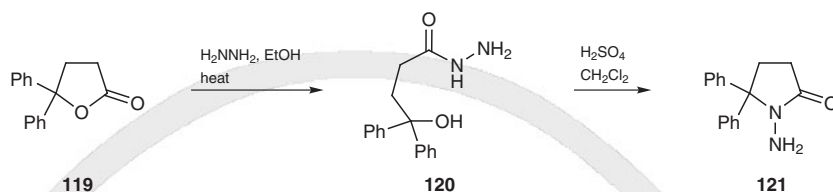
1-Benzyl-5-hydroxy-5-(3-trimethylsilylprop-2-yn-1-yl)pyrrolidin-2-one (118**):**^[151]

TMSC≡CCH₂Br (7 mmol) was added slowly during 30 min to a mixture of 1-benzylsuccinimide (**117**; 5 mmol), Zn granules (10 mmol), and PbBr₂ (0.5 mmol) in THF (3 mL). The mixture was stirred at rt until it became a sticky, greenish-gray slurry. Another portion of THF (7 mL) and TMSC≡CCH₂Br (3 mmol) were added to the mixture, and the reaction was checked by ¹H NMR. The reaction was quenched with sat. aq. NH₄Cl (30 mL) and the mixture was extracted with EtOAc (2 × 50 mL). The EtOAc extracts were washed with brine (10 mL), dried (Na₂SO₄), filtered, and concentrated to a crude product that was recrystallized (EtOAc/hexane); yield: 1.321 g.

Flash column chromatography of the mother liquor provided another crop of lactam crystals; yield: 0.097 g; total yield: 94%.

21.10.1.1.2.2.3 Method 3:
***N*-Amino-Substituted Lactams**

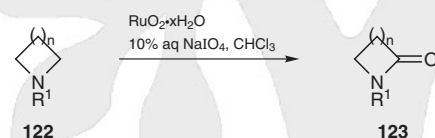
Lactams containing an *N*-amino unit are useful in preparing lactam-substituted heterocycles and related compounds. The treatment of substituted γ -butyrolactones with 100% hydrazine hydrate in refluxing ethanol results in the expected hydroxy hydrazides.^[152] Subsequent treatment with strong acid generates the lactam by trapping of the intermediate carbocation. Cyclization occurs at the amide nitrogen to produce five-membered aminopyrrolidinones, rather than the alternative hexahydropyridazin-3-ones. This reaction is, on the whole, limited to 5,5-disubstituted lactones that have carbocation-stabilizing substituents such as phenyl.^[152] For example, hydrazine reacts with the lactone **119** to give the hydroxy hydrazide **120**, and treatment with sulfuric acid gives 1-amino-5,5-diphenylpyrrolidin-2-one (**121**) (Scheme 53). The specific yield was not reported in this case, but yields of 50–65% were reported for several derivatives.^[152] Lactam **121** can also be synthesized by the direct amination of 5,5-diphenylpyrrolidin-2-one with (2,4-dinitrophenyl)hydroxylamine^[153] in tetrahydrofuran; no yields were reported.^[152]

Scheme 53 Cyclization of Hydroxy Hydrazides^[152]**21.10.1.1.2.3 Oxidation of Cyclic Amines**

Lactams can be prepared directly by the oxidation of the corresponding cyclic amines. Several metal-mediated reactions can be used. This approach permits the conversion, for example, of pyrrolidine to pyrrolidin-2-one and of piperidine to piperidin-2-one.

21.10.1.1.2.3.1 Method 1:
Direct Oxidation of Cyclic Amines by Ruthenium(IV) Oxide

Ruthenium(IV) oxide is an important reagent that oxidizes cyclic amines to lactams (Scheme 54), but the yield of the lactam depends on the substituent attached to the ring nitrogen and the size of the ring. For example, the oxidation of 1-(methylsulfonyl)piperidine (**122**, $R^1 = \text{SO}_2\text{Me}$; $n = 3$) with ruthenium(IV) oxide gives a 90% yield of the corresponding lactam **123** ($R^1 = \text{SO}_2\text{Me}$; $n = 3$).^[154] The oxidation is successful for *N*-sulfonyl, *N*-formyl, *N*-acetyl, and *N*-trifluoroacetyl derivatives of pyrrolidine, piperidine, and azacycloheptane.^[154]

Scheme 54 Ruthenium(IV) Oxide Oxidation of Cyclic Amines^[154]**Lactams 123; General Procedure:**^[154]

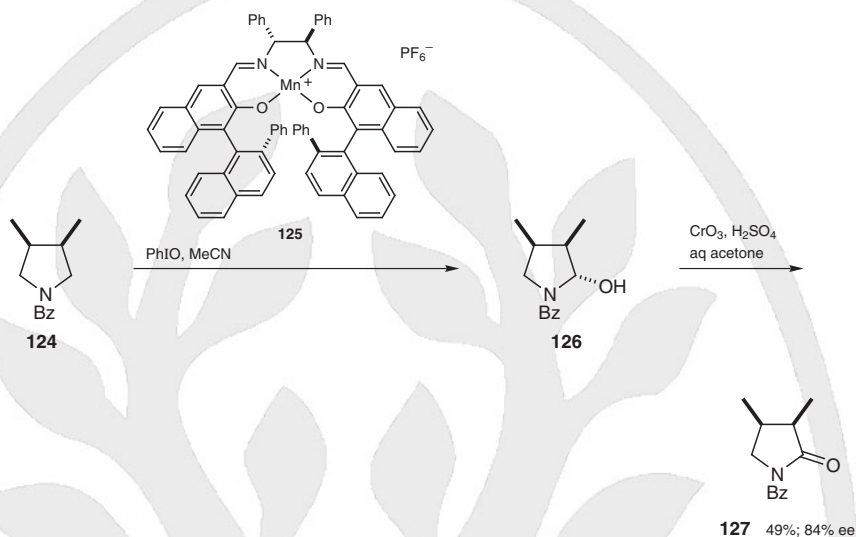
A mixture of a cyclic amine **122** (4–8 mmol) and $\text{RuO}_2 \cdot x\text{H}_2\text{O}$ (0.10–0.30 g, 0.75–2.25 mmol) in an appropriate chlorinated solvent (usually CHCl_3) was stirred at rt in a stoppered flask with 10% aq NaIO_4 (10 equiv). (If CHCl_3 is used as a solvent, it must be free of alcohol.) When the oxidation was complete (2–6 d), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 ($3 \times 75 \text{ mL}$) and CHCl_3 ($3 \times 75 \text{ mL}$). The extracts were combined with the original organic soln and a minimum amount of MeOH or *i*PrOH was added to destroy excess oxidant. The mixture was filtered and the filtrate was washed with 10% aq $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL). After drying, the filtrate was stripped of solvent and the product was isolated and purified in the appropriate manner.

21.10.1.1.2.3.2 Method 2:
Sequential Hydroxylation and Oxidation of Cyclic Amines

Manganese–salen catalysts (e.g., **125**) are very useful for the asymmetric oxidation of alkenes^[155–157] and other molecules. Such catalysts also oxidize cyclic *N*-acyl amines to the corresponding α -hydroxy amines, which can then be oxidized by conventional oxidizing agents to form lactams.^[158] For example, the oxidation of (3*R*,4*S*)-1-benzoyl-3,4-dimethylpyrrolidine (**124**) by iodosylbenzene in the presence of the manganese–salen catalyst **125** gives (2*S*,3*R*,4*S*)-1-benzoyl-3,4-dimethylpyrrolidin-2-ol (**126**) (Scheme 55).^[158] Subsequent

Jones oxidation (CrO_3 , aq H_2SO_4 , acetone) gives (3*R*,4*S*)-1-benzoyl-3,4-dimethylpyrrolidin-2-one (**127**) in 49% yield and 84% ee.^[158]

Scheme 55 Manganese–Salen Catalyzed Iodosylbenzene Oxidation of an *N*-Acyl Pyrrolidine^[158]



(3*R*,4*S*)-1-Benzoyl-3,4-dimethylpyrrolidin-2-one (127**):**^[158]

PhIO (22 mg, 0.1 mmol) was added at once to a soln of (3*R*,4*S*)-1-benzoyl-3,4-dimethylpyrrolidine (**124**; 0.1 mmol) and manganese–salen catalyst **125** (2.2 mg, 2 μmol) in MeCN (1 mL) under N_2 at -25°C . The mixture was stirred for 32 h, then the reaction was quenched by adding Me_2S and the mixture was concentrated in vacuo. The residue was passed through a short column of silica gel (EtOAc/hexane) to give the hydroxypyrrolidine derivative **126**. This crude product was dissolved in acetone (5 mL) and cooled to 10°C under N_2 . Jones reagent (25 μL , 1.7 M) was rapidly added to the acetone soln with stirring. After 20 min, a few drops of *i*PrOH were added and the soln was concentrated under reduced pressure. The residue was dissolved in EtOAc (15 mL) and the soln was washed with sat. aq NaHCO_3 and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified by column chromatography (silica gel, EtOAc/hexane) to give a colorless liquid; yield: 49% (84% ee, HPLC); $[\alpha] +8.4$ (*c* 0.4, CHCl_3).

21.10.1.1.3 Synthesis by Substituent Modification

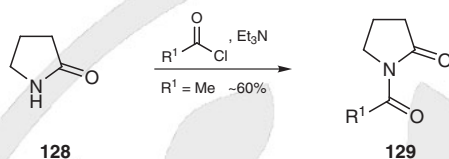
21.10.1.1.3.1 Substitution of Existing Substituents

21.10.1.1.3.1.1 Method 1: Direct *N*-Acylation

Acylation of amides and lactams does not occur as readily as acylation of amines, but the reaction of lactams with acyl chlorides and anhydrides is straightforward and gives the corresponding *N*-acyl derivative. As early as 1888, Schotten treated pyrrolidin-2-one (**128**) with acetic anhydride to give 1-acetylpyrrolidin-2-one (**129**) ($\text{R}^1 = \text{Me}$).^[4] With minor variations, this basic procedure is still the most straightforward method for preparing such compounds. Anhydrides derived from longer-chain acids can also be used.^[159]

Several 1-acylpyrrolidin-2-one derivatives **129** can be prepared by treatment of the pyrrolidin-2-one (**128**) with an acid chloride under mild conditions (Scheme 56).^[160] In some cases, an anhydride can also be used as the acylating reagent.^[160]

Scheme 56 N-Acylation of Pyrrolidin-2-one^[160]



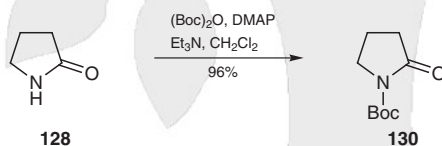
1-Acetylpyrrolidin-2-one (129, R¹ = Me); Typical Procedure:^[160]

AcCl (0.4 mol) was added gradually to a mixture of Et₃N (0.6 mol) and pyrrolidin-2-one (**128**; 0.6 mol) in THF (500 mL) at 0 °C, and the mixture was stirred for 30 min at rt. The white solid Et₃N•HCl that formed was filtered off and the filtrate was evaporated. The residual oily product was distilled under reduced pressure; yield: ~60%; bp 90–93 °C/0.5 Torr.

21.10.1.1.3.1.2 Method 2:
N-Carbamate Protection of Lactams

N-Acyl groups such as trifluoroacetyl, acetyl, or benzoyl are used as protecting groups for lactams in some cases. Carbamates can also be used as protecting groups, with *N*-*tert*-butoxycarbonyl (*N*-Boc) and *N*-benzyloxycarbonyl (*N*-Cbz) being the most commonly used. A simple procedure for preparing the *N*-*tert*-butoxycarbonyl derivatives involves the treatment of the lactam, e.g. **128**, with di-*tert*-butyl dicarbonate in dichloromethane (e.g., to give **130**, Scheme 57).^[161]

Scheme 57 *N*-*tert*-Butoxycarbonyl Protection of Pyrrolidin-2-one^[161]



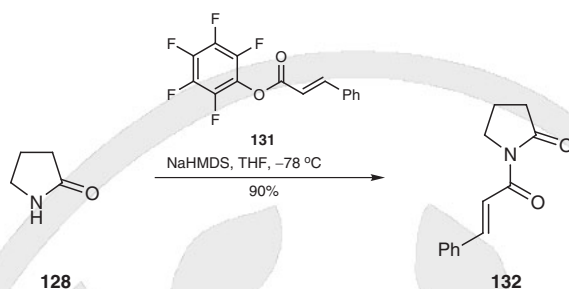
***N*-*tert*-Butoxycarbonylpyrrolidin-2-one (130); Typical Procedure:**^[161]

Et₃N (1.32 mL, 9.47 mmol), (Boc)₂O (4.13 g, 18.9 mmol), and DMAP (1.16 g, 9.5 mmol) were added to a 0.50 M soln of pyrrolidin-2-one (**128**; 0.81 g, 9.5 mmol) in CH₂Cl₂, and the soln was stirred for 6 h at 25 °C under argon. The volatiles were removed, and the residue was purified by rapid chromatography (silica gel, hexane/Et₂O 6:1); yield: 1.68 g (96%).

21.10.1.1.3.1.3 Method 3:
Acylation of Lactam Anions with Pentafluorophenyl Esters

Amide anions react with esters to form the *N*-substituted amide. Deprotonation of a lactam, followed by treatment with a pentafluorophenyl ester leads to the corresponding *N*-acyl lactam.^[162]

For example, treatment of the anion derived from pyrrolidin-2-one (**128**) and sodium hexamethyldisilazanide with the pentafluorophenyl 3-phenylprop-2-enoate (**131**) gives a 90% yield of the corresponding *N*-acyl lactam **132** (Scheme 58); no experimental details were reported.^[162]

Scheme 58 N-Acylation of Pyrrolidin-2-one with a Pentafluorophenyl Ester^[162]

Forming pentafluoro esters of sensitive acids is a useful alternative to generating the analogous acid chloride. Treatment of pyrrolidin-2-one with sodium hexamethyldisilazanide results in higher yields of the benzyloxycarbonyl- and *tert*-butoxycarbonyl-protected lactam pentafluorophenyl esters compared with deprotonation by other amide bases.

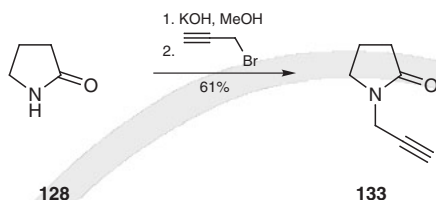
The use of butyllithium as a base significantly lowers the yield of the N-acylated lactam and butyl ketones are formed through the addition of the butyl group to the lactam carbonyl group. The pentafluorophenyl esters are prepared by coupling pentafluorophenol and the appropriate carboxylic acid with dicyclohexylcarbodiimide.

21.10.1.1.3.1.4 **Method 4: N-Alkylation**

In general, lactams are weak nucleophiles;^[163] however, the hydrogen on the nitrogen of a lactam is readily removed by an appropriate base to form an anion that is a much better nucleophile. A simple primary amide has a pK_a value of about 17,^[164] but the hydrogen attached to the lactam nitrogen (N—H) is less acidic than that of a primary amide. The pK_a of pyrrolidin-2-one was estimated to be 22.7, whereas that of piperidin-2-one was measured as 24.5.^[165] The pK_a values of hexahydro-2*H*-azepin-2-one and hexahydroazocin-2(1*H*)-one were determined to be 26.7 and 27.2, respectively.^[165] In earlier work, the pK_a values of piperidin-2-one, hexahydro-2*H*-azepin-2-one, and hexahydroazocin-2(1*H*)-one were measured as 30.7, 33, and 31.3, respectively.^[166] A lactam anion is a bidentate nucleophile as a result of delocalization of the electron density on nitrogen, which leads to significant weakening of the nucleophilic ability of the lactam nitrogen and the possibility of reaction at oxygen. This property can diminish the yield of N-alkylated products. Under most conditions, however, lactam anions react with alkyl halides to give N-alkyl lactams. A few reagents, such as dimethyl sulfate or Meerwein's reagent (triethyloxonium tetrafluoroborate)^[167] react with lactams to give the corresponding imino ethers (N=C—OMe), also known as lactim ethers.^[168]

21.10.1.1.3.1.4.1 **Variation 1: By Base-Mediated N-Alkylation**

Alkoxide bases are strong enough to deprotonate a lactam, and under equilibrium conditions with reactive alkyl halides, alkylation proceeds. For example, deprotonation of pyrrolidin-2-one (**128**) by heating with ethanolic potassium hydroxide, followed by addition of the reactive halide 3-bromoprop-1-yne, gives 1-(prop-2-ynyl)pyrrolidin-2-one (**133**) in 61% yield (Scheme 59).^[169]

Scheme 59 N-Alkylation of Pyrrolidin-2-one^[169]

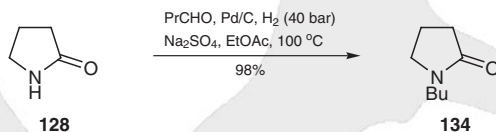
Other *N*-alkyl lactams can be prepared by this technique, although bases such as sodium hydride and lithium diisopropylamide are often used.^[170] A useful variation involves the use of ultrasound with aqueous potassium hydroxide under phase-transfer conditions.^[171] N-Alkylation of ethyl 5-oxo-L-prolinate (ethyl pyroglutamate) is readily accomplished by treatment with sodium hydride in dry tetrahydrofuran for 5 minutes followed by addition of the alkyl halide.^[172]

1-(Prop-2-ynyl)pyrrolidin-2-one (133); Typical Procedure:^[169]

A soln of KOH (28 g, 500 mmol) in dry MeOH (100 mL) was added to pyrrolidin-2-one (**128**; 45 g, 529 mmol). The solvent was slowly removed under reduced pressure from the stirred soln at an internal temperature not exceeding 25 °C. When solid began to separate, toluene (200 mL) was added, and toluene was continuously added during the course of all subsequent distillations. When 500 mL of toluene had distilled, the pressure was allowed to rise and distillation was continued at an internal temperature of 90 °C. Finally, 700 mL of toluene was collected at atmospheric pressure. The suspension was cooled and treated at 40 °C with 3-bromoprop-1-yne (60 g, 508 mmol) during 1 h. The mixture was then heated to 67 °C for 30 min, cooled, and filtered. The toluene was removed under reduced pressure and product was distilled; yield: 40 g (61%); bp 77 °C/0.05 Torr.

**21.10.1.1.3.1.4.2 Variation 2:
By Reductive Alkylation of Lactams with Aldehydes**

Lactams can be reductively alkylated by reaction with aldehydes under catalytic-hydrogenation conditions. The initial reaction with the lactam nitrogen generates an iminium intermediate that is hydrogenated to give the *N*-alkyl derivative. For example, treatment of pyrrolidin-2-one (**128**) with butanal and hydrogen gas in the presence of a palladium on carbon at 100 °C gives a 98% yield of 1-butylpyrrolidin-2-one (**134**) (Scheme 60).^[173]

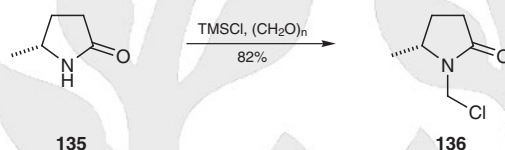
Scheme 60 Reductive Alkylation of Pyrrolidin-2-one^[173]**1-Butylpyrrolidin-2-one (134); Typical Procedure:**^[173]

A soln of pyrrolidin-2-one (**128**; 0.01 mol) and PrCHO (0.04 mol) in EtOAc (10 mL) was treated with 10% Pd/C (0.2 mmol) and Na₂SO₄ (0.01 mol). The mixture was stirred at 100 °C for 4 h under 4000 kPa of H₂. After the reaction, the soln was filtered off, the solvent was removed under reduced pressure, and the product was purified by distillation; yield: 98%; bp 205 °C (6 Torr).

21.10.1.1.3.1.4.3 Variation 3:
Functionalization of an *N*-Alkyl Group: Chloromethylation

The alkylation procedure can be modified to incorporate functional groups on the alkyl chain. Such functionalized alkyl units can be further functionalized, depending on the nature of the initial functional group. The hydroxymethyl intermediate from the reaction of an aldehyde and a lactam, for example, can be intercepted by other reagents. For example, when (5*R*)-5-methylpyrrolidin-2-one (**135**) is treated with paraformaldehyde and chlorotrimethylsilane, (5*R*)-1-(chloromethyl)-5-methylpyrrolidin-2-one (**136**) is obtained in 82% yield (Scheme 61).^[174] This compound reacts with alcohols or amines to form the corresponding *N*-alkoxymethyl- or *N*-alkylaminomethyl derivatives.

Scheme 61 Chloromethylation of (5*R*)-5-Methylpyrrolidin-2-one^[174]



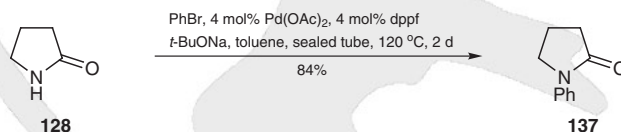
(+)-(5*R*)-1-Chloromethyl-5-methylpyrrolidin-2-one (136**):**^[174]

(5*R*)-5-Methylpyrrolidin-2-one (**135**; 1.10 g, 11.1 mmol) and paraformaldehyde (0.37 g, 12.2 mmol) were combined in TMSCl (5 mL) and refluxed for 2 h. The excess TMSCl and (TMS)₂ were removed in vacuo and the resulting oil was purified by Kugelrohr distillation (2 Torr, oven 120 °C) to give a colorless liquid; yield: 0.9 g (82%); bp 99 °C/6 Torr; [α]_D²⁰ +109.9 (*c* 0.032, CHCl₃).

21.10.1.1.3.1.5 Method 5:
***N*-Arylation**

The direct nucleophilic coupling of aryl halides and lactams to produce *N*-aryl derivatives is not generally feasible using traditional base reagents. Modern organometallic methodology provides a solution, particularly when organopalladium catalysts are used. Bromobenzene derivatives react with lactams in the presence of a palladium catalyst to give *N*-aryl lactams.^[175] For example, the reaction of pyrrolidin-2-one (**128**) and bromobenzene, in the presence of a palladium catalyst gives an 84% yield of 1-phenylpyrrolidin-2-one (**137**) (Scheme 62).^[175]

Scheme 62 Palladium-Catalyzed *N*-Phenylation of Pyrrolidin-2-one with Bromobenzene^[175]



In another example, intermolecular C—N bond-forming reactions between aryl halides and lactams are achieved by using a palladium catalyst with (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (Xantphos) as the ligand. Aryl trifluoromethanesulfonates, carbamates, and sulfonamides are viable substrates for the amidation, which proceeds at 45–110 °C with 1–4 mol% of the palladium catalyst in 66–99% yields.^[176]

1-Phenylpyrrolidin-2-one (137**):**^[175]

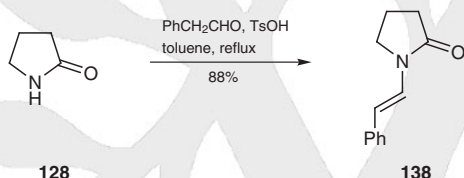
Pyrrolidin-2-one (**128**; 151 μL, 2.0 mmol), PhBr (316 μL, 3.0 mmol), dppt (66 mg, 0.12 mmol), Pd(OAc)₂ (22 mg, 0.10 mmol), and *t*-BuONa (0.29 g, 3.0 mmol) in toluene

(10 mL) under N_2 were heated in a sealed tube at 120 °C for 48 h. The mixture was cooled to rt and filtered through Celite, and the filtrate was concentrated onto silica gel. Flash chromatography (EtOAc/hexane 1:1) gave a white solid; yield: 0.27 g (84%); mp 66–67 °C.

21.10.1.1.3.1.6 Method 6: N-Alkenylation

N-Alkenyl lactams are useful for the synthesis of polymers and also for various synthetic applications, including the Diels–Alder reaction. 1-Vinylpyrrolidin-2-one, for example, is commercially available, and poly(1-vinylpyrrolidin-2-one) is a well-known and well-characterized polymer. There are several methods available for making other 1-alkenyl lactams, and most involve either high-pressure reactions of alkynes with the lactam in the presence of base or dehydrohalogenation of 1-(2-haloethyl)lactams.^[177–179] Based on earlier work involving the acid-catalyzed reaction of lactams and acetaldehyde,^[180,181] Smith and Zezza developed a straightforward alkenylation procedure in which a lactam and an aldehyde react in refluxing toluene in the presence of an acid catalyst.^[182] For example, the reaction of phenylacetaldehyde and pyrrolidin-2-one (**128**) in refluxing toluene containing an acid catalyst gives an 88% yield of 1-[(E)-2-phenylvinyl]pyrrolidin-2-one (**138**) (Scheme 63).^[182] This basic procedure can also be used to prepare 1-alkadienyl lactams from conjugated aldehydes.^[183]

Scheme 63 Condensation of an Aldehyde and a Lactam^[182]



1-[(E)-2-Phenylvinyl]pyrrolidin-2-one (**138**); Typical Procedure:^[182]

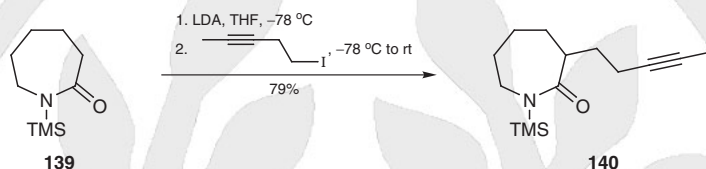
A mixture of pyrrolidin-2-one (**128**; 10 g, 117 mmol) and phenylacetaldehyde (14.1 g, 117 mmol) was dissolved in dry toluene (200 mL) and treated with $TsOH$ (~50 mg). The reaction flask was fitted with a Dean–Stark head and a condenser, and the soln was refluxed until a maximum amount of H_2O was produced (~12 h). The soln was cooled and washed with sat. aq $NaHCO_3$ (100 mL) and then H_2O (100 mL). The combined aqueous layers were extracted with Et_2O (3×100 mL) and the extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was recrystallized (Et_2O/CH_2Cl_2) to give white flakes; yield: 19.3 g (88%); mp 125–127 °C.

21.10.1.1.3.1.7 Method 7: α -Alkyl Lactams by Enolate Alkylation

The protons attached to the α -carbon of a lactam (C3) are slightly acidic, as expected with any carbonyl compound. Amides and lactams are significantly less acidic than ketones and aldehydes, but there is significant variation in the pK_a values of the α -protons. Kreshkov and co-workers used potentiometric titration to establish the pK_a of 1-methylpyrrolidin-2-one to be 25.6,^[184] whereas Bordwell and co-workers determined the pK_a in dimethyl sulfoxide to be 35,^[185] and Fraser and co-workers used NMR to establish the pK_a in tetrahydrofuran to be <33.8.^[186] Clearly, powerful bases such as the dialkylamides or organolithium reagents are required to deprotonate these weak acids. The proton attached to nitrogen is also acidic (see Section 21.10.1.1.3.1.4), and the formation of the enolate anion by removal of the α -proton usually requires reaction with N-alkyl or N-protected lactams.

The reaction of *N*-alkyl lactams with powerful bases such as lithium dialkylamides leads to the lactam enolate anion, and subsequent reaction with an alkyl halide gives the corresponding 3-alkyl lactam. Sodium amide can be used for enolate anion formation,^[187] but lithium diisopropylamide is the most common reagent. For example, treatment of 1-(trimethylsilyl)hexahydro-2*H*-azepin-2-one (**139**) with lithium diisopropylamide under more-or-less standard conditions generates the enolate anion. Subsequent reaction with 5-iodopent-2-yne gives a 79% yield of the alkylated product **140** (Scheme 64).

Scheme 64 α -Alkylation of Lactam Enolate Anions^[188]



Lactam enolate anions also undergo conjugate addition with α,β -unsaturated ketones, leading to more highly substituted α -alkylated lactams.^[189]

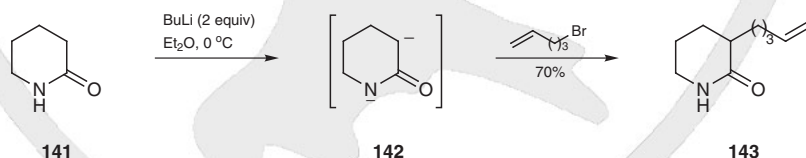
3-Pent-3-yn-1-yl(1-trimethylsilyl)hexahydro-2*H*-azepin-2-one (**140**):^[188]

A 2.3 M soln of BuLi in hexanes (17.6 mL, 40.5 mmol) was added to a soln of $i\text{Pr}_2\text{NH}$ (5.7 mL, 40.8 mmol) in THF (20 mL) at -78°C . After 15 min, a soln of 1-(trimethylsilyl)hexahydro-2*H*-azepin-2-one (**139**; 7.55 g, 40.8 mmol) in THF (20 mL) was added. The mixture was maintained at -78°C for 15 min and then added to a soln of 5-iodopent-2-yne (7.19 g, 37.1 mmol) in THF (40 mL) at -78°C . The mixture was allowed to warm to rt, diluted with Et_2O (250 mL), and washed with H_2O and brine. The organic fraction was dried (MgSO_4) and concentrated to give the crude product as a pale yellow solid that was recrystallized (hexane) as white needles; yield: 5.23 g (79%); mp $78\text{--}79^{\circ}\text{C}$.

21.10.1.1.3.1.7.1 Variation 1: Via the *N*, α -Dianion

Unprotected lactams can be converted into the corresponding dianions by treatment with at least 2 equivalents of a powerful base such as butyllithium. For example, piperidin-2-one (**141**) reacts with 2 equivalents of butyllithium in diethyl ether at 0°C to give dianion **142** (Scheme 65).^[190] Subsequent reaction with 5-bromopent-1-ene gives a 70% yield of the C3-alkylated lactam **143**.

Scheme 65 α -Alkylation of a Lactam Dianion^[190]



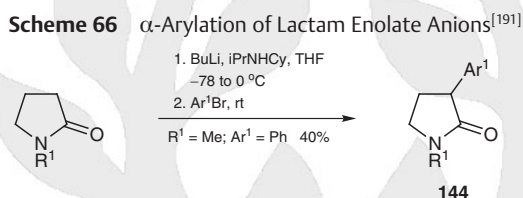
3-Pent-4-en-1-ylpiperidin-2-one (**143**):^[190]

A flame-dried, 1-L, three-necked flask equipped with a magnetic stirring bar, a pressure-equalizing addition funnel, and a N_2 inlet valve was charged with piperidin-2-one (**141**; 10.0 g, 101 mmol) and THF (500 mL). The mixture was stirred at 0°C for 1 h and then a 2.2 M soln of BuLi in hexane (92 mL, 202 mmol) was added dropwise. The resulting mixture was stirred for 1 h at 0°C , and then 5-bromopent-1-ene (16.0 g, 0.108 mol) was injected rapidly with stirring. The mixture was stirred for 1 h at 0°C then poured into sat. aq

NaCl (300 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to form a brown syrup that was purified by vacuum distillation to give colorless, irregular prisms; yield: 11.8 g (70%); mp 40–41 °C; bp 119–120 °C/0.1 Torr.

21.10.1.1.3.1.8 Method 8: Direct α -Arylation

Although N-arylation of lactams is difficult without the use of transition-metal catalysts, the α -arylation reaction of lactams is surprisingly straightforward. The reactions of dialkylamide bases, lactams, and aryl bromides at temperatures of 0–30 °C give the corresponding α -aryl lactams **144** (Scheme 66).^[191]



Temperature control is critical for successful arylation. Aryl lactams are not formed at low temperatures (–78 °C) and low yields are obtained at intermediate temperatures (up to –20 °C). Elevated temperatures (50–60 °C) cause condensation of the lactam, whereas 0–30 °C appears to be the optimal temperature range. The mechanism of this substitution reaction apparently involves benzyne intermediates.

The intramolecular arylation of a lactam can be accomplished through an oxidative phenol coupling reaction.^[192]

1-Methyl-3-phenylpyrrolidin-2-one (**144**, R¹ = Me; Ar¹ = Ph); Typical Procedure:^[191]

BuLi (32 mmol) in hexane was added from a syringe to a soln of cyclohexylisopropylamine (4.52 g, 32.0 mmol) in THF (30 mL) at –78 °C. After 20 min, the cold bath was removed and the flask was allowed to warm up to about 0 °C over 20 min. The flask was again cooled to –78 °C, and 1-methylpyrrolidin-2-one (1.98 g, 20.0 mmol) in THF (5 mL) was added dropwise over 2–4 min. The light yellow soln was stirred for 1 h (longer times do not affect the yield). The cold bath was removed, and the flask was allowed to warm unassisted to 20 °C, then a soln of PhBr (1.57 g, 10.0 mmol) in THF (10 mL) was added dropwise over 5 min. This gave a deep red soln that was stirred overnight at rt and then quenched with a mixture of Et₂O (50 mL) and H₂O (50 mL). 10% aq HCl (~200 mL) was added, followed by enough NaCl to saturate the aqueous layer. The soln was extracted with Et₂O (4 \times 50 mL) and the extracts were concentrated to give a light yellow oil (1.75 g). The oil was purified on the same day, to avoid a reduction in yield (~5%), by chromatography [silica gel (1.5 \times 70 cm), EtOAc] to give a product that crystallized on standing; yield: 0.70 g (40%); mp 58–59 °C.

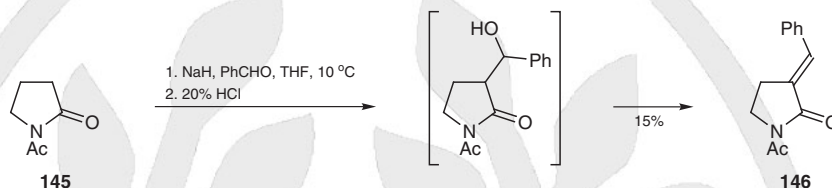
21.10.1.1.3.1.9 Method 9: α -Alkylidene Lactams by Addition to Aldehydes or Ketones

The enolate anion derived from a lactam can react with an aldehyde or ketone by acyl addition to form an α -alkylhydroxy product; however, such products readily lose water to form the corresponding α -alkylidene lactam, particularly when the substrate is an aromatic aldehyde.^[193] It has been claimed that success in this reaction depends upon protecting the lactam nitrogen with a sufficiently strong electron-withdrawing group, such

as acetyl.^[193] Such groups enhance the acidity of the hydrogen atoms α to the carbonyl group, as well as protecting the lactam nitrogen.

For example, addition of 1-acetylpyrrolidin-2-one (**145**) and benzaldehyde to a slurry of sodium hydride in tetrahydrofuran, followed by heating with 20% hydrochloric acid gives a 15% yield of the *E*-alkylidene lactam **146** (Scheme 67); clearly, this procedure as reported is not a very good one.^[194]

Scheme 67 Condensation of a Lactam Enolate Anion and an Aldehyde^[194]



The claim that an electron-withdrawing group is required may not be correct in all cases. For example, treatment of 1-methylpiperidin-2-one and benzaldehyde with sodium hydride followed by an acetic acid workup gives a 56% yield of (3*E*)-3-benzylidene-1-methylpiperidin-2-one (no experimental details reported).^[195] Sequential treatment of 1-methylpyrrolidin-2-one with lithium diisopropylamide and acetophenone in hexamethylphosphoric triamide gives a 64% yield of 3-(1-hydroxy-1-phenylethyl)-1-methylpyrrolidin-2-one (no experimental details reported).^[196]

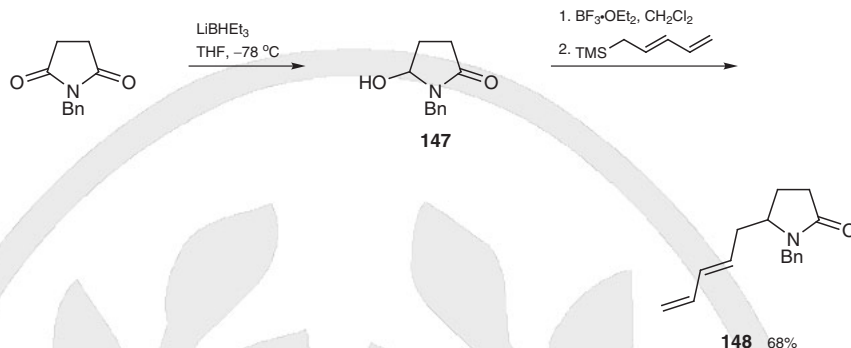
(3*E*)-1-Acetyl-3-benzylidenepyrrolidin-2-one (146**); Typical Procedure:**^[194]

A 3-L, three-necked flask equipped with a mechanical stirrer, a thermometer, and a 1-L pressure-equalizing dropping funnel was charged with a NaH dispersion (in mineral oil) in THF, and the resulting suspension was cooled to about 5–8 °C, but no lower. A soln of 1-acetylpyrrolidin-2-one in THF was added dropwise from the dropping funnel at a rate that maintained steady H₂ evolution and a temperature of 10–14 °C. The H₂ that evolved was removed through the top of the dropping funnel and was passed through a small flask containing THF so that the rate of evolution could be readily monitored. Constant attention was necessary, as the reaction appeared to require an induction period, and a vigorous exothermic reaction occurred after addition of about one-third of the soln, when the mixture turned yellow or brown. After addition was completed, the mixture was stirred at ice-bath temp for 1 h. A small quantity of a soln of MeOH in THF sufficient to decompose excess NaH was added and the mixture was poured into twice its volume of ice water. The mixture was acidified to pH 5 with 20% HCl and, after the mineral oil layer had separated, extracted with CHCl₃. The extracts were washed several times with sat. aq NaHCO₃, washed once with H₂O, dried, and evaporated to give a solid product which was then crystallized (EtOAc); yield: 15%; mp 172–173 °C.

21.10.1.1.3.1.10 Method 10:

Alkylation with Allylsilanes via *N*-Acyliminium Ion Intermediates

Imides are useful as synthetic precursors of 5-substituted lactams. Reduction to the 5-hydroxy compound (see Section 21.10.1.1.2.2.2.3) allows treatment with a Lewis acid to generate an *N*-acyliminium ion in situ. For example, trapping of the acyliminium ion from the hydroxylactam **147** with 1-(trimethylsilyl)penta-2,4-diene, gives 1-benzyl-5-[penta-2,4-dien-1-yl]pyrrolidin-2-one **148** (Scheme 68).^[197,198] Other trapping agents can be used to generate 5-substituted lactams.

Scheme 68 Alkylation of a 5-Hydroxypyrrolidin-2-one Derivative^[197]**1-Benzyl-5-penta-2,4-dien-1-ylpyrrolidin-2-one (148):**^[197]

A soln of LiBHEt_3H (4.6 mmol) in THF (4.6 mL) was added in one portion to a cooled (-78°C) soln of 1-benzylsuccinimide (0.51 g, 2.70 mmol) in dry THF to give the crude α -hydroxy lactam **147**. A soln of this hydroxy lactam in CH_2Cl_2 (30 mL) at -78°C was treated with $\text{BF}_3\cdot\text{OEt}_2$ (0.50 mL, 3.8 mmol) followed, after 15 min, with trimethyl(penta-2,4-dien-1-yl)silane (565 mg, 4.02 mmol). The mixture warmed slowly to rt over 6–12 h, then partitioned with sat. aq NaHCO_3 (2×10 mL) and sat. brine (10 mL). The THF was removed under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3×50 mL). The organic phase was dried (Na_2SO_4), concentrated, and the residue was purified by chromatography [silica gel (60–200 mesh), EtOAc] as a pale yellow oil; yield: 440 mg (68%).

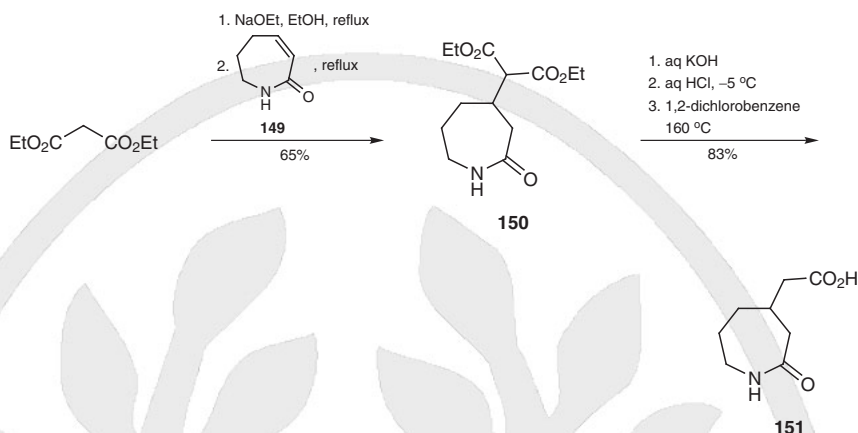
21.10.1.1.3.1.11 Method 11:
Alkylation at β - and More Remote Positions

It is possible to build substituents into lactam rings at positions other than the nitrogen atom or the α -carbon. With one exception, direct substitution is not feasible, so the lactam is constructed from precursors bearing the required functionality. The exception is the conjugate addition reaction of α,β -unsaturated lactams with suitable nucleophiles, such as malonate anions or organocuprates.

Substituents at other carbons are usually built into the molecule, or incorporated by modification of existing functionality. Ethyl 5-oxo-L-prolinate (ethyl pyroglutamate), for example, reacts with Grignard reagents to give 5-(1-hydroxyalkyl)pyrrolidin-2-one derivatives.^[199,200] 5-Oxo-L-prolinate derivatives with a ketone side chain [5-(1-oxoalkyl)pyrrolidin-2-ones] can be prepared by treatment with Grignard reagents or organolithium reagents.^[201–204]

21.10.1.1.3.1.11.1 Variation 1:
By Conjugate Addition to α,β -Unsaturated Lactams

Malonate anions are very suitable nucleophiles for the Michael addition to conjugated carbonyl compounds. Once they are incorporated in the molecule, sequential hydrolysis and decarboxylation then gives a 4-carboxymethyl-substituted lactam. For example, treatment of 1,5,6,7-tetrahydro-2H-azepin-2-one (**149**) with the diethyl malonate anion gives the 4-substituted derivative **150**, and hydrolysis followed by decarboxylation gives the carboxymethyl derivative **151** (Scheme 69).^[205]

Scheme 69 Malonate Addition to a Conjugated Lactam^[205]**Diethyl (2-Oxohexahydro-1H-azepin-4-yl)malonate (150):**^[205]

Clean Na (50.6 g, 2.2 mol) was allowed to react with abs EtOH (3 L). The resulting soln was refluxed and diethyl malonate (640.0 g, 4.0 mol) was added dropwise. The clear soln was refluxed for 3 h. A soln of the conjugated lactam prepared from 7-bromohexahydro-2H-azepin-2-one (**149**; 384.0 g, 2.0 mol) in benzene (**CAUTION: carcinogen**) was added dropwise. Refluxing was continued for 5 h. After cooling, the EtOH and benzene were removed and the resulting liquid was dissolved in Et_2O . The soln was washed with small portions of 4% aq HCl soln then with sat. aq NaHCO_3 until neutral, and finally with H_2O . The Et_2O soln was dried and the Et_2O and diethyl malonate were removed by distillation. The remaining oil was washed with petroleum ether until it solidified. The product was recrystallized (hexane); yield: 351 g (65% based on 7-bromohexahydro-2H-azepin-2-one); mp $49\text{--}50^\circ\text{C}$.

(2-Oxohexahydro-1H-azepin-4-yl)acetic Acid (151):^[205]

A soln of malonate ester **150** (351 g, 1.29 mol) in abs EtOH (500 mL) was added dropwise to a soln of KOH (175 g, 3.12 mol) in abs EtOH (1 L) and the mixture was refluxed for 6 h. The precipitate of dipotassium (2-oxohexahydro-1H-azepin-4-yl)malonate was filtered off and washed sequentially with dry EtOH and Et_2O ; yield: 378 g (quant).

This salt (378 g) was dissolved in H_2O (250 mL), and concd HCl (241 mL) was added dropwise at -5°C . The precipitated (2-oxohexahydro-1H-azepin-4-yl)malonic acid was filtered and washed with cool MeOH and Et_2O ; yield: 252 g (90%); mp 162°C (MeOH).

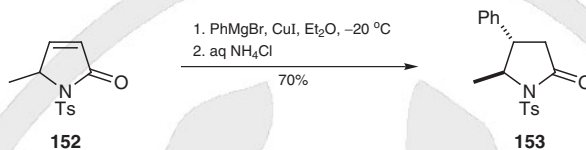
The acid (20 g) was added in small quantities to 1,2-dichlorobenzene at 160°C . When the evolution of CO_2 had ceased, the mixture was heated to 170°C . The (2-oxohexahydro-1H-azepin-4-yl)acetic acid (**151**) separated on cooling the clear soln to rt; yield: 18.4 g (92%); mp $193\text{--}194^\circ\text{C}$ (H_2O).

21.10.1.1.3.1.11.2 Variation 2: Addition of Organocuprates to Conjugated Lactams

Organocuprates react with α,β -unsaturated carbonyl compounds to give conjugate addition products in high yield. A similar reaction with α,β -unsaturated lactams is known, but the substituent on the nitrogen plays a crucial role. *N*-Alkyl α,β -unsaturated lactams do not necessarily give conjugate addition, but the nucleophilic reagents can deprotonate the γ -position, leading to a β,γ -unsaturated lactam.^[206] This problem can be overcome by converting the lactam into its *N*-tosyl derivative. For example, treatment of 5-methyl-1-tosyl-1,5-dihydro-2H-pyrrol-2-one (**152**) with the organocuprate reagent generated from phenylmagnesium bromide and copper(I) iodide gives a 70% yield of the 4-phenyl lactam

153, as a single diastereomer (Scheme 70).^[206] The conjugate addition is clearly *trans*-selective. Organocuprates also undergo conjugate addition to *N*-*tert*-butoxycarbonyl α,β -unsaturated lactams.^[207]

Scheme 70 Reaction of Organocuprates and Conjugated Lactams^[206]



Addition Reaction of Organocuprate Reagents with Conjugated Lactams; General Procedure:^[206]

CuI (19 mg, 0.1 mmol) was added to a soln of PhMgBr (3 mmol) in Et₂O at -5°C , and the mixture was stirred for 10–15 min. The soln was cooled to -20°C and the lactam (0.8 mmol) in Et₂O (2 mL) was added. After the soln had been stirred for 2.5 h at -20°C , excess PhMgBr was destroyed by adding aq NH₄Cl. The mixture was extracted with Et₂O and the combined extracts were washed with brine, dried (MgSO₄), and concentrated. The product was purified by chromatography (silica gel, hexane/Et₂O).

21.10.1.1.3.1.12

Method 12: α -Halogenation

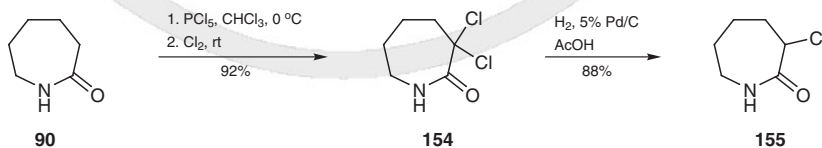
α -Halogenation of carbonyl compounds is well known, and usually occurs readily. In the case of lactams, α -halogenation is more difficult because the halo lactam products are usually labile. α -Halo lactams are prone to form α,α -dihalo derivatives. They also undergo elimination reactions, particularly in the case of pyrrolidin-2-one derivatives, which readily aromatize to the corresponding pyrroles. Success in the halogenation depends on the substituent on the nitrogen atom.

The most common direct halogenation method is to prepare an α,α -dihalo lactam and then reduce this to the monohalo lactam by a dehydrohalogenation technique.^[208] For example, hexahydro-2*H*-azepin-2-one (**90**) reacts with phosphorus pentachloride to give 3,3-dichlorohexahydro-2*H*-azepin-2-one (**154**) in 92% yield (Scheme 71).^[208] Hexahydro-2*H*-azepin-2-one (**90**) can also be converted into 3,3-dibromohexahydro-2*H*-azepin-2-one by reaction with phosphorus pentachloride followed by treatment with zinc(II) chloride and bromine. Hydrogenation of 3,3-dichlorohexahydro-2*H*-azepin-2-one (**154**) in acetic acid with 5% palladium/carbon gives 3-chlorohexahydro-2*H*-azepin-2-one (**155**) in 88% yield. Similar hydrogenation of the dibromo analogue gives a 95% yield of 3-bromohexahydro-2*H*-azepin-2-one.

Other halogenation techniques are available. 3-Bromo-1-methylpyrrolidin-2-one can be prepared in four steps from γ -butyrolactone.^[209]

α -Halo lactams are quite useful as synthetic intermediates, and can be converted into α -azido (and hence α -amino) lactams^[208] or α -cyanolactams.^[210]

Scheme 71 Dichlorination–Reductive Dehalogenation of a Lactam^[208]



3,3-Dichlorohexahydroazepin-2-one (154):^[208]

Hexahydro-2*H*-azepin-2-one (**90**; 11.3 g, 100 mmol) was dissolved in CHCl₃ (50 mL) and PCl₅ (22 g, 106 mmol) was added in small portions over 30 min, while maintaining the mixture at 0–6 °C by external cooling. The mixture was then warmed to rt, and Cl₂(g) was bubbled through as quickly as it could be absorbed. A small increase of temperature was noticed, but no cooling was applied. When no additional Cl₂ was absorbed, bubbling was stopped and the soln was stirred for 1 h. The CHCl₃ was removed under a reduced pressure at below 40 °C. The residue was poured into ice water and the solid product was collected, washed with a small volume of cold Et₂O, and dried in vacuo; yield: 16.6 g (92%); mp 126–127 °C (prisms, EtOH).

3-Chlorohexahydro-2*H*-azepin-2-one (155):^[208]

NaOAc (18 g, 220 mmol) and 5% Pd/charcoal (2 g) were added to a soln of 3,3-dichlorohexahydroazepin-2-one (**154**; 18.2 g, 100 mmol) in glacial AcOH (100 mL). The mixture was shaken under H₂ (2 atm initial pressure) until 1 equiv H₂ was absorbed. The catalyst and NaCl were removed by filtration and the filtrate was concentrated under reduced pressure (36 Torr) until most of the AcOH had been removed. The residue was then neutralized with aq NaHCO₃ soln and extracted with CHCl₃. The CHCl₃ extracts were concentrated until crystals began to separate, then hexane was added and a white crystalline solid (mp 92.5–93.5 °C) precipitated.

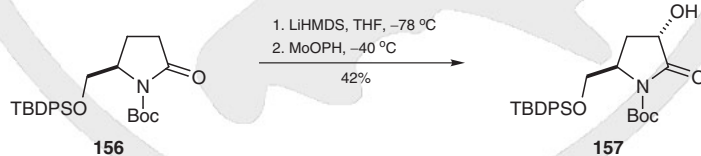
An additional portion of product (3.4 g; mp 84–88 °C) was obtained from the mother liquor; total yield: 12.98 g (88%).

**21.10.1.1.3.1.13 Method 13:
α-Hydroxylation**

Hydroxy lactams are useful synthetic intermediates, and hydroxy units can be incorporated at different positions on the ring by choosing an appropriate acyclic precursor. Direct hydroxylation is possible by using selected reagents. When the enolate anion of an *N*-*tert*-butoxycarbonyl lactam is formed by treatment with a dialkylamide base and then treated with (hexamethylphosphoric triamide)oxodiperoxy(pyridine-*N*)molybdenum(IV) (MoOPH), α-hydroxy lactams are formed in modest to good yields.^[211] For example, treatment of the *N*-*tert*-butoxycarbonyl-protected lactam **156** with lithium hexamethyldisilazide generates the enolate anion which, on treatment with (hexamethylphosphoric triamide)oxodiperoxy(pyridine-*N*)molybdenum(IV), gives a 42% yield of the 3-hydroxy lactam **157** (Scheme 72).^[212]

α,β-Unsaturated lactams can be converted into the corresponding 3,4-dihydroxy compounds by dihydroxylation with osmium(VIII) oxide.^[207,213,214]

Scheme 72 Hydroxylation of Lactam Enolate Anions^[212]


(3*S*,5*R*)-5-[(*tert*-Butyldiphenylsiloxy)methyl]-3-hydroxy-1-*tert*-butoxycarbonylpyrrolidin-2-one (157):^[212]

1.5 M BuLi in hexane (42.1 mL, 63.2 mmol) was added dropwise to a soln of (TMS)₂NH (13.3 mL, 63.2 mmol) in THF (50 mL) at –78 °C. The soln was stirred at –78 °C for 30 min. A soln of lactam **156** (9.55 g, 21.05 mmol) in THF (50 mL) was added during 5 min and the mixture was stirred for another 30 min at –78 °C, and then allowed warm to –40 °C during

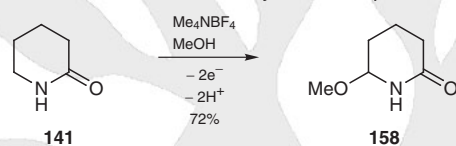
20 min before MoOPH (18.3 g, 42.1 mmol) was added in two portions. The green soln was stirred at -40 to -30°C for 45 min, and the reaction was then quenched by adding half-sat. aq NH_4Cl (150 mL). The THF was evaporated off and the aqueous phase was extracted with EtOAc (3 \times). The organic phases were combined, washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product (13.43 g), which was purified by chromatography (EtOAc/hexane, stepwise gradient 2:3 to 2:1) as a white solid; yield: 4.12 g (42%); mp 145 – 147°C .

The product was contaminated with 5% of the 3*R*,5*R*-isomer (^1H NMR).

21.10.1.1.3.1.14

Method 14:**Alkoxy Lactams by Electrochemical Oxidation of Lactams**

The methylene unit adjacent to the nitrogen in a lactam can be oxidized directly by electrochemical methods. The anodic oxidation of lactams, e.g. **141**, in the presence of methanol generates the corresponding α -methoxy lactam, e.g. **158** (Scheme 73).^[215] The alkoxy group can be exchanged by reaction with another alcohol and an acid catalyst. Treatment of several ω -methoxy and ethoxy lactams with benzyl alcohol in the presence of an acid catalyst leads to the corresponding benzyloxy lactam, whereas treatment with ethane-1-thiol leads to the ethylsulfanyl lactam.^[216]

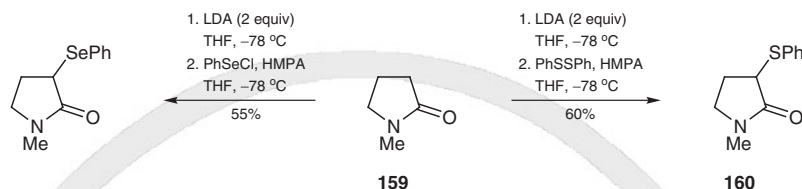
Scheme 73 Anodic Ethoxylation of Piperidin-2-one^[215]**6-Methoxypiperidin-2-one (158); Typical Procedure:**^[215]

Piperidin-2-one (**141**; 0.5–1.0 mol) was mixed with Me_4NBF_4 in MeOH and placed in an electrolytic cell equipped with Pt electrodes. A current of 1 – $2\text{ A}\cdot\text{dm}^{-2}$ was passed through the soln to a total of 2 F. The excess alcohol was removed under reduced pressure in a water bath maintained at 40 – 50°C . The product was isolated by vacuum distillation or recrystallization ($i\text{Pr}_2\text{O}$); yield: 72%; mp 110 – 112°C .

21.10.1.1.3.1.15

Method 15: **α -Sulfides and α -Selenides**

The conversion of a lactam into its enolate anion by treatment with lithium diisopropylamide or another suitable base, followed by reaction with diphenyl disulfide, leads to the corresponding α -phenylsulfanyl lactam. Similar treatment of the enolate anion with phenylselenenyl chloride or bromide gives the corresponding α -phenylselanyl lactam. Both of these compounds are useful for further functionalization of lactams. For example, sequential treatment of 1-methylpyrrolidin-2-one (**159**) with lithium diisopropylamide and diphenyl disulfide gives a 60% yield of 3-(phenylsulfanyl)-1-methylpyrrolidin-2-one (**160**) (Scheme 74).^[217] Oxidation to the sulfoxide allows *syn*-elimination to form the conjugated lactam, and other transformation are possible from this useful intermediate.

Scheme 74 Phenylsulfanyl and Phenylselanyl Lactams^[217]**1-Methyl-3-(phenylsulfanyl)pyrrolidin-2-one (160):**^[217]

CAUTION: Hexamethylphosphoric triamide is a possible human carcinogen and an eye and skin irritant.

A 250-mL, three-necked flask equipped with a N₂ inlet tube, an addition funnel, a serum cap, and a magnetic stirring bar was flamed, and deaerated with N₂. A soln of iPr₂NH (8.2 g, 81 mmol) in 50 mL of THF was added under N₂ and the reaction vessel was cooled to 0 °C. A 2.1 M soln of BuLi in hexane (38.5 mL, 81 mmol) was added with a syringe and the mixture was stirred at 0 °C for approximately 10 min. The mixture was then cooled with a dry ice/acetone bath to –78 °C and 1-methylpyrrolidin-2-one (4.0 g, 40 mmol) dissolved in THF (25 mL) was added dropwise during 15 min. The mixture was stirred at –78 °C for 35 min. PhSPh (8.8 g, 40 mmol) dissolved in THF (20 mL) containing HMPA (7.2 g, 40 mmol) was then added dropwise during 20 min and the mixture was stirred for an additional 35 min at –78 °C. The mixture was warmed to –20 °C over 30 min and then allowed to reach to rt before it was poured into H₂O (400 mL) and extracted with Et₂O (3 × 350 mL). The ethereal extracts were combined and washed consecutively with a 10% aq NaOH (150 mL), H₂O (150 mL), 10% HCl (150 mL), and H₂O (150 mL). The Et₂O soln was then dried (MgSO₄), filtered, and concentrated on a rotary evaporator to give a semisolid (8 g). The crude product was subjected to chromatography (silica gel G) to give an oil (6.7 g) that was further purified by chromatography (silica gel G, Et₂O); yield: 5.0 g (60%); bp 130–133 °C/0.05 Torr.

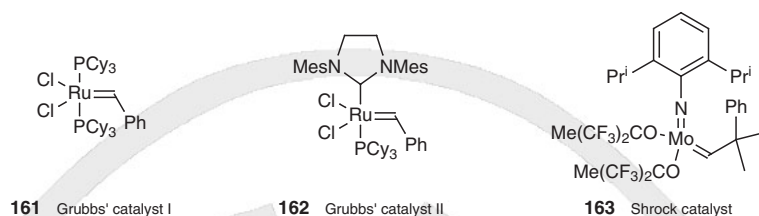
21.10.2 **Product Subclass 2:**
Unsaturated Lactams

21.10.2.1 **Synthesis of Product Subclass 2**

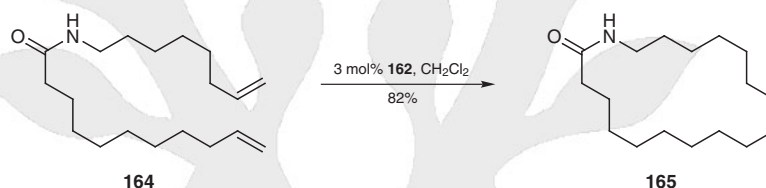
This section covers the more common methods for preparing lactams that contain unsaturation between ring carbon atoms.

21.10.2.1.1 **Method 1:**
Ring-Closing Metathesis

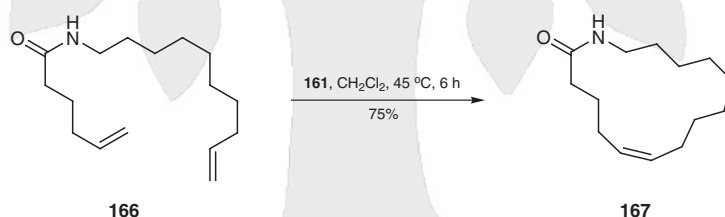
Metathesis reactions^[218–221] have been known for many years^[222,223] and are catalyzed by both homogeneous^[224–226] and heterogeneous^[227] catalysts. The development of Grubbs' catalysts (**161** and **162**)^[228] and the Shrock catalyst (**163**)^[229,230] (Scheme 75) has made ring-closing metathesis reactions feasible and dependable for the synthesis of ring compounds. These catalysts can be used to prepare a variety of lactams.

Scheme 75 Ring-Closing Metathesis Catalysts^[224–227]

Ring-closing metathesis can be applied to the formation of lactams by using either molybdenum catalysts, e.g., **163** (Scheme 75)^[231] or ruthenium catalysts.^[232] Of the two commonly used ruthenium catalysts, Grubbs' catalyst I **161** and Grubbs' catalyst II **162**, the latter is often more useful for metathesis reactions that generate lactams, but either catalyst can be used. Clearly, the position of the alkene units will dictate the final position of the C=C group in the lactam. For example, treatment of the dienyl amide **164** with 3% of Grubbs' catalyst II **162** in refluxing dichloromethane gives an 82% yield of the macrocyclic lactam **165** (Scheme 76).^[233]

Scheme 76 Macrocyclic Lactam by Metathesis Using Grubbs' Catalyst II^[233]

The ability to control the ring size as well as the position of the C=C unit is illustrated by the metathesis reaction of the dienyl amide **166** (Scheme 77), this time using Grubbs' catalyst I **161** to give the lactam **167** in 75% yield.^[234]

Scheme 77 Macrocyclic Lactam by Metathesis Using Grubbs' Catalyst I^[234]

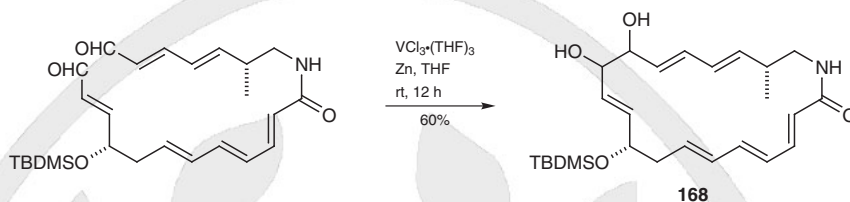
21.10.2.1.2

Method 2:**Metal-Mediated Coupling Reactions of Carbonyl Compounds**

Three excellent methods for generating rings are the acyloin condensation, the McMurry coupling, and pinacol coupling. In principle, the diester, dialdehyde, or diketone precursors used in these reactions can have an amide unit in the molecule, in which case ring closure gives a lactam. In fact, there are limitations to these ring-closure methods. For example, the formation of a C—C bond to give the twenty-membered ring system **168** is very difficult.^[235] The titanium-mediated and samarium-mediated pinacol-formation reactions and the McMurry reaction employing various titanium reagents all fail to give the required product. The use of a vanadium reagent $[\text{V}_2\text{Cl}_3 \bullet (\text{THF})_6][\text{Zn}_2\text{Cl}_6]$, prepared in situ from trichlorotris(tetrahydrofuran)vanadium and zinc in tetrahydrofuran as the solvent,

under high-dilution conditions affords the cyclic pinacol **168** in 60% yield (Scheme 78).^[235] No experimental details were reported.

Scheme 78 Macrocyclic Lactam via a Vanadium-Catalyzed Pinacol Coupling^[235]

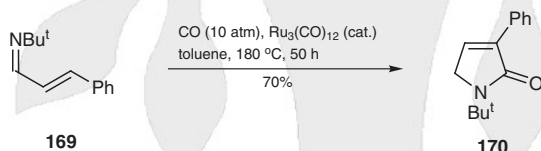


21.10.2.1.3

Method 3: Carbonylative [4 + 1] Cycloaddition

An interesting route to unsaturated lactams is the [4 + 1] cycloaddition of structurally simple α,β -unsaturated imines with carbon monoxide. The reaction of the α,β -unsaturated imine **169** [prepared by the reaction of (2*E*)-3-phenylacrylaldehyde with *tert*-butylamine] with carbon monoxide in toluene in the presence of a catalytic amount of dodecacarbonyltriruthenium gives 1-*tert*-butyl-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (**170**) in 36% isolated yield, with 47% of the imine being recovered as (2*E*)-3-phenylacrylaldehyde by silica gel column chromatography (Scheme 79).^[236] Prolongation of the reaction time (50 hours) increases the yield to 70%. No reaction is observed when other ruthenium complexes, such as tris(acetylacetonato)ruthenium or dicarbonyltris(triphenylphosphine)ruthenium, are used as catalysts. The standard reaction conditions established are 2 mol% of dodecacarbonyltriruthenium under 10 atm of carbon monoxide in toluene at 180 °C.

Scheme 79 Ruthenium-Catalyzed Carbonylation of a Conjugated Imine^[236]



1-*tert*-Butyl-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (**170**); Typical Procedure:^[236]

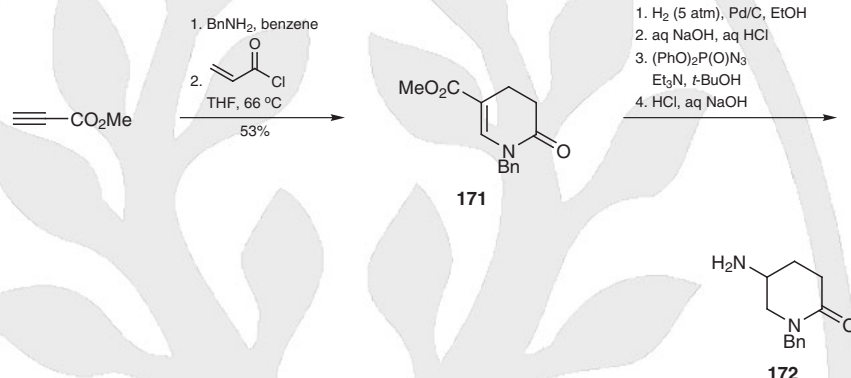
CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

A 50-mL stainless autoclave was charged with imine **169** (360 mg, 1.92 mmol), toluene (3 mL), and $\text{Ru}_3(\text{CO})_{12}$ (26 mg, 0.04 mmol). The system was flushed three times with 10 atm of CO, then pressured to 10 atm and immersed in an oil bath at 180 °C. After 50 h, the autoclave was removed from the oil bath and allowed to cool for 1 h before releasing the CO pressure. The contents were transferred to a round-bottomed flask with Et_2O and the volatiles were removed under reduced pressure. The residue was subjected to column chromatography (silica gel, hexane/ Et_2O 5:1) to give a white solid; yield: 291 mg (70%); mp 101–103 °C (hexane).

21.10.2.1.4

Method 4:
Conjugate Addition–Cyclization

The conjugate addition of an amine to an alkynoic acid derivative, followed by cyclization, generates unsaturated lactams. For example, conjugate addition of benzylamine to ethyl propynoate, followed by treatment with acryloyl chloride, gives the dihydropyridinone **171** in 53% yield (Scheme 80).^[237] The ester unit on the ring can be transformed into an amino unit, following the hydrogenation of the ring double bond, to give the aminopiperidinone **172**.

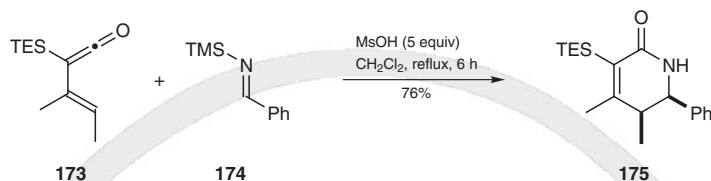
Scheme 80 Conjugate Addition–Cyclization with Alkynyl Esters^[237]**Methyl 1-Benzyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (171):**^[237]

BnNH_2 (10.72 g, 100 mmol) was added to a soln of $\text{HC}\equiv\text{CCO}_2\text{Me}$ (8.41 g, 100 mmol) in Et_2O (100 mL) at 0°C . The soln was warmed to rt and stirred for 12 h. The mixture was then concentrated, dissolved in THF (600 mL), and $\text{H}_2\text{C}=\text{CHCOCl}$ (9.92 g, 110 mmol) was added at rt. The soln was refluxed for 16 h and then washed sat. aq NaHCO_3 (200 mL). The aqueous layer was extracted with Et_2O (3×200 mL). The combined organic layers were dried (MgSO_4) and the product was purified by chromatography (petroleum ether/ Et_2O 7:3); yield: 13.12 g (53%); ^1H NMR (300 MHz, CDCl_3) δ : 2.61 (s, 4H), 3.68 (s, 3H), 4.71 (s, 2H), 7.19–7.35 (m, 6H).

21.10.2.1.5

Method 5:
Hetero [4 + 2] Cycloadditions of (Trialkylsilyl)vinylketenes

(Trialkylsilyl)vinylketenes undergo hetero [4 + 2]-cycloaddition reactions to form nitrogen heterocycles.^[238] The aza-Diels–Alder reactions of imino dienophiles are very useful in the synthesis of tetrahydropyridines, piperidin-4-ones, and other six-membered *N*-heterocycles.^[239,240] Especially valuable are the reactions of electron-deficient *N*-sulfonyl and *N*-acyl imines and immonium salts. Neutral, unactivated imines fail to undergo hetero [4 + 2] cycloadditions unless paired with electron-deficient dienes (inverse-electron-demand cycloadditions) or with highly electron-rich dienes in the presence of Lewis acids. Unactivated imines combine with (trialkylsilyl)vinylketenes to provide α,β -unsaturated piperidin-2-ones.^[238] For example, cycloaddition of the ketene **173** with the imine **174** gives a 76% yield of (5*R*,6*S*)-4,5-dimethyl-6-phenyl-3-(triethylsilyl)-5,6-dihydropyridin-2(1*H*)-one (**175**) (Scheme 81).^[238]

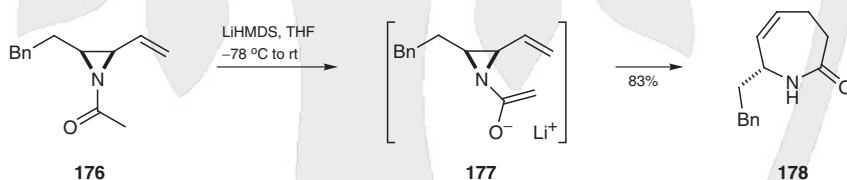
Scheme 81 [4 + 2] Cycloaddition of Vinylketenes and Imines^[238]**(5*R*,6*S*)-4,5-Dimethyl-6-phenyl-3-(triethylsilyl)-5,6-dihydropyridin-2(1*H*)-one (**175**); Typical Procedure:**^[238]

A 5-mL, pear-shaped flask equipped with a reflux condenser, a rubber septum, and an argon inlet needle was charged with ketene **173** (0.160 g, 0.76 mmol) and the imine **174** (0.202 g, 1.14 mmol). The mixture was refluxed for 6 h, and the resulting yellow oil was purified by column chromatography (silica gel, EtOAc/hexane 0–10%) to give a white solid; yield: 0.182 g (76%); mp 155 °C.

21.10.2.1.6

Method 6:**Aza-Claisen Rearrangement of Acylaziridines**

The Claisen rearrangement is a very useful method for generating rings when the 1,5-diene unit is anchored to another ring. When the 1,5-diene unit is anchored to a three-membered ring, sigmatropic rearrangement is accompanied by ring opening, and a new and larger ring is formed. An interesting variation on this reaction generates a diene unit that is anchored to an aziridine ring, and Claisen rearrangement generates a tetrahydroazepin-2-one.^[241] For example, treatment of the *N*-acyl aziridine **176** with lithium diisopropylamide generates the diene **177** (one C=C unit is an enolate anion); subsequent [3,3]-sigmatropic rearrangement generates the tetrahydrohydroazepin-2-one (**178**) in 83% yield (Scheme 82).^[241]

Scheme 82 Lactams by the Aza-Claisen Rearrangement^[241]**7-(2-Phenylethyl)-1,3,4,7-tetrahydro-2*H*-azepin-2-one (**178**); Typical Procedure:**^[241]

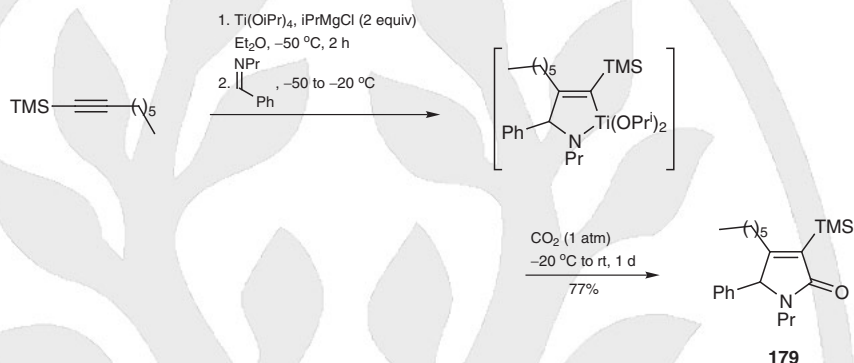
The acylvinylaziridine **176** [prepared by treatment of the corresponding vinylaziridine (9.2 mg, 0.053 mmol), with Et₃N, Ac₂O, and a catalytic amount of DMAP at -78 °C] was dissolved in THF (0.5 mL) and added to a 1.10 M soln of LiHMDS in hexanes (0.096 mL, 0.106 mmol) mixed with THF (0.5 mL) at -78 °C. After 20 min, the cooling bath was removed, and after 20 min at rt the reaction was quenched with phosphate buffer (pH 7). The mixture was diluted with Et₂O, and washed with H₂O and then brine. Drying (MgSO₄), concentration, and flash chromatography (3% iPrNH₂ in heptane/EtOAc 7:1) of the residue gave the lactam as a low-melting solid; yield: 9.5 mg (83% for two steps); [α]_D²⁰ +236 (c 0.87, CHCl₃).

21.10.2.1.7

Method 7:
Via Azametallocyclopentene Complexes

The sequential reaction of titanium complexes with an alkyne and an imine gives azatitanacyclopentene complexes that react with carbon dioxide at atmospheric pressure to form 1,5-dihydro-2H-pyrrol-2-one derivatives, e.g. **179** (Scheme 83).^[242] This procedure provides a one-pot technique for preparing a variety of dihydropyrrol-2-ones from alkynes.

Scheme 83 [4 + 2] Cycloaddition of an Aminotitanacyclopentene Complex^[242]

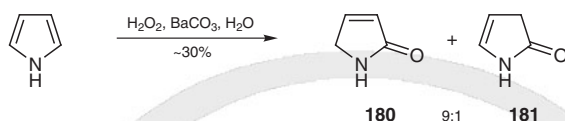

4-Hexyl-5-phenyl-1-propyl-3-(trimethylsilyl)-1,5-dihydro-2H-pyrrol-2-one (179); Typical Procedure:^[242]

A 1.16 M ethereal soln of *i*PrMgCl (1.45 mL, 1.68 mmol) was added to a stirred soln of Ti(O*i*Pr)₄ (239 mg, 0.84 mmol) and 1-trimethylsilyl-1-octyne (128 mg, 0.70 mmol) in Et₂O (6 mL) at –78 °C. The mixture was warmed to –50 °C over 0.5 h, stirred at the same temperature for 2 h, and then PhCH=NPr (82 mg, 0.56 mmol) was added. The mixture was stirred for a further 1 h at –50 °C and then gradually warmed to –20 °C over 2 h. The soln was then exposed to 1 atm of CO₂ at –20 °C for 0.5 h and allowed to react at rt for 24 h. The reaction was terminated by dropwise addition of H₂O (2 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were dried (MgSO₄) and concentrated to an oil that was purified by chromatography on silica gel; yield: 154 mg (77% from the imine).

21.10.2.1.8

Method 8:
Oxidation of Pyrroles

The direct oxidation of nitrogen heteroaromatic compounds is a potentially attractive route to unsaturated lactams. In practice, this approach is limited, but useful for specific compounds. The oxidation of pyrrole is well known, and a limited number of oxidants are available.^[243,244] Pyrrole and alkylpyrroles also undergo autoxidation, but this reaction has not been well studied.^[245,246] Although oxidation is not a general route to lactams, simple unsaturated pyrrolidin-2-ones can be quickly accessed. For example, the direct oxidation of a dilute solution of pyrrole with aqueous hydrogen peroxide, gives 1,5-dihydropyrrolidin-2-one (**180**) and 1,3-dihydropyrrolidin-2-one (**181**) in a ratio of 9:1 in about 30% yield (Scheme 84).^[247]

Scheme 84 Direct Oxidation of Pyrrole^[247]**1,5-Dihydropyrrolidin-2-one (180) and 1,3-Dihydropyrrolidin-2-one (181):**^[247]

Pyrrole (10 g, 0.15 mol) dissolved in H₂O (900 mL) containing BaCO₃ (3 g, 15 mmol) was refluxed with 36% H₂O₂ (14 g, 0.15 mol) in a 1-L round-bottomed flask for 4 h. The excess oxidant was eliminated by adding small amounts of finely ground PbO₂ to the boiling soln. The soln was then filtered and concentrated under reduced pressure, keeping the temperature below 40–50 °C, until it reached a syrupy consistency. After treatment with dioxane and filtration, the filtrate was evaporated under reduced pressure and the residue, a red liquid, was distilled at 0.5 Torr by heating in an air bath at 100–130 °C. Under optimal conditions, the yield of distilled product reached 30% of the pyrrole by weight. Smaller yields were obtained if the reaction time was longer than 4 h. After three subsequent distillations, a white, viscous, hygroscopic liquid was obtained that solidified on standing in a refrigerator at –25 °C. This product was very soluble in H₂O, EtOH, acetone, EtOAc, and dioxane; less soluble in CHCl₃; and insoluble in less-polar solvents. Paper chromatography showed one spot at R_f 0.76 (BuOH/AcOH/H₂O 12:3:5) and two spots at R_f 0.34 and 0.57 [CCl₄ (**CAUTION: toxic**)/EtOH 5:1] corresponding to 1,5-dihydropyrrolidin-2-one (**180**) and 1,3-dihydropyrrolidin-2-one (**181**), respectively; the ratio of these two compounds was >9:1 (¹H NMR).

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Product Class 11: Peptides

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General Introduction

Peptides are chains of amino acids linked by amide bonds. So-called “peptide” bonds are the most abundant examples of amides in nature. The remarkable biological and physical properties exhibited by natural peptides and proteins have stimulated great efforts to develop mild, functional group tolerant, high yielding, cost effective methodology for the synthesis of amide bonds. Moreover, because amide bond geometry and the dynamics of amide isomerization play significant roles in the folding and function of peptide and protein structures, chemists have strived to synthesize conformationally rigid amide surrogates and analogues possessing different barriers for amide isomerization in order to probe the importance of structure on peptide chemistry and biology.

Emil Fischer is credited with the birth of the field of peptide chemistry in 1901 with the synthesis of glycylglycine^[1] by an acylation reaction using an α -amino acid chloride. A year later, Theodore Curtius reported the application of α -amino acid azides for making peptide bonds.^[2] Although methods for preparing these reactive intermediates have changed over a century of research, α -amino acid chlorides and azides are still important contemporary reagents for assembling peptide bonds. Furthermore, the same principles for peptide construction by chemical methods are employed today. As the field has developed from dipeptides to the first total synthesis of a peptide hormone, oxytocin, by Du Vigneaud in 1953,^[3] to the synthesis of the 238 amino acid residue green fluorescent protein by the Sakakibara group in 1998,^[4] innovations in peptide and protein synthesis have been made to minimize the use and maximize the efficiency of protecting groups, to accelerate racemization-free amide bond formations, to facilitate deprotection without side products, and in particular to purify and characterize peptide products. Since the pioneering efforts of traditional organic chemists like Fischer and Curtius, peptide chemistry has advanced over the past 100 years by the discovery of novel chemical and biochemical approaches for amide bond synthesis. In spite of extensive improvements, stepwise synthesis of large peptides in solution remains a difficult challenge because of a diminished rate of amino acid coupling to longer peptides and the low solubility of larger protected peptide intermediates. Many impressive syntheses have been accomplished using solution-phase peptide synthesis, including oxytocin,^[3] insulin,^[5] and ribonuclease A.^[6] These examples illustrate the labor-intensive challenge of using solution-phase methods to construct pure peptides in acceptable yields.

The necessity for developing a simple, rapid process for peptide synthesis has given rise to new methodology involving building peptide chains linked to solid supports. This method was first demonstrated successfully by Bruce Merrifield in 1963^[7] by the synthesis of a tetrapeptide on a styrene–divinylbenzene copolymer. The unique feature of this strategy was the application of a polymeric support to facilitate the purification of the growing peptide chain prior to cleavage and isolation of the final peptide. Initially, the concept of solid-phase peptide synthesis received great criticism from the scientific community because it ran countercurrent to the traditional tenets of organic synthesis, which required purification and characterization of all intermediates leading to the final product. The merits of solid-phase synthesis have since proven such early concerns unreasonable.

Effective solid-phase methods now exist for synthesizing peptides as well as many other classes of organic compounds.

The solid-phase peptide synthesis protocol involves the attachment of the first amino acid residue onto the solid support and subsequent construction of the peptide chain, using terminal deprotection and coupling reactions, prior to cleavage of the final peptide from the solid support. The major advantage of this procedure is that a large excess of the coupling components and additive reagents can be employed to drive reactions to completion and subsequently separated easily from the polymer-bound peptide by simple filtration. This method revolutionized peptide chemistry when it proved amenable to automation; robotic synthesizers now produce routinely 100-mg quantities of pure peptides of 10–15 residues in length. Similarly, automated synthesizers possessing parallel reactor systems can now produce peptide libraries.

Solid-phase peptide synthesis and automation set the stage for tackling the synthesis of longer peptides and small proteins. Such challenges have demanded the development of new strategies for assembling amide bonds using larger peptide fragments. Among the innovations made to accomplish such goals, the method of Native Chemical Ligation has proven particularly effective for the synthesis of larger peptide structures because it can efficiently form amide bonds between fragments possessing diverse functional groups in aqueous media.^[8–10] The power of this method has been demonstrated by the synthesis of several large peptide/protein structures such as the anticoagulant microprotein S (116-mer),^[11] lymphotactin (93-mer),^[12] human matrix Gla protein (84-mer),^[13] and many others, as reviewed in 2005.^[14] Such methodology has given rise to a new age in peptide science in which larger, more complex polyamide structures are constructed and studied. As more difficult syntheses are attempted, the limitations of such methods have also become apparent and the need for new chemistry continues to expand in order to address new issues in the formation of amide bonds.

The purpose of this article is to provide a guide to effective methods commonly used in modern peptide synthesis. For the more interested reader, Vol. E 22 of *Houben–Weyl* is devoted to a detailed description of the developments in peptide science since the earliest discoveries of Fischer and Curtius and we strongly suggest its consultation for more in-depth reading. This review is thus meant to complement and often refers to articles in these volumes, whose Editor-in-Chief was Professor Murray Goodman.

21.11.1 Amino Acid Protection–Deprotection

Previously published information on protection strategies for this product class has been covered extensively in *Houben–Weyl*, Vol. E 22a, pp 39–423.

Since the first coupling of glycylglycine to the ethyl ester of leucine by Emil Fischer in 1902,^[15] two concepts have defined peptide synthesis. The first concept is that reactive functionality must be limited to the free amine of one residue and the carboxylate of the second residue; all other potentially reactive groups must be masked by protecting groups. The second concept is that the protection group strategy must enable selective deprotection of either the amino terminus (for synthesis in the C→N direction) or the carboxy terminus (for synthesis in the N→C direction) of the growing peptide chain without unmasking side chains and other protected functionalities. This orthogonality in the removal of protecting groups between the elongation and final deprotection steps is essential in modern peptide synthesis.^[16,17]

The first practical protecting group strategy to be developed for peptide synthesis in the solution and solid phases was the Boc/Bzl strategy, based on the differential acid lability of the α -amino *tert*-butoxycarbonyl (Boc) group and benzyl ester (Bzl, conventionally Bn) side-chain protecting groups (typically 1000:1).^[18,19] This strategy enables the acid deprotection of the terminal Boc group in trifluoroacetic acid, and the deprotection of all remaining protecting groups in a stronger acid such as anhydrous hydrogen fluoride or

hydrogen bromide. Although effective for the synthesis of a wide range of peptides, the Boc/Bzl strategy requires strong acid cleavage, which has limited its application due to safety issues in the handling of the necessary anhydrous acids. The second practical orthogonal protecting group strategy to be developed was the milder Fmoc/*t*-Bu strategy, this employs the 9-fluorenylmethoxycarbonyl (Fmoc) group, which is typically cleaved under basic conditions with a secondary amine, and the *tert*-butyl ester (*t*-Bu) side-chain protection, which is cleaved using trifluoroacetic acid. Alternative protecting groups have been developed for overcoming specific issues associated with the Boc/Bzl and the Fmoc/*t*-Bu protocols; however, the majority of peptides synthesized today are prepared by either the differential acid lability strategy or the orthogonal base/acid strategy.

The third major area of research on protecting groups for peptide synthesis has been the development of orthogonal protecting groups that are stable to the conditions of both Boc/Bzl synthesis and Fmoc/*t*-Bu synthesis. This protection can enable the site-specific modification of peptide side chains during synthesis, surmount issues with problematic side-chain functionalities (such as the imidazole of histidine), and restrict reactive groups after peptide synthesis (see Section 21.11.6 for examples).

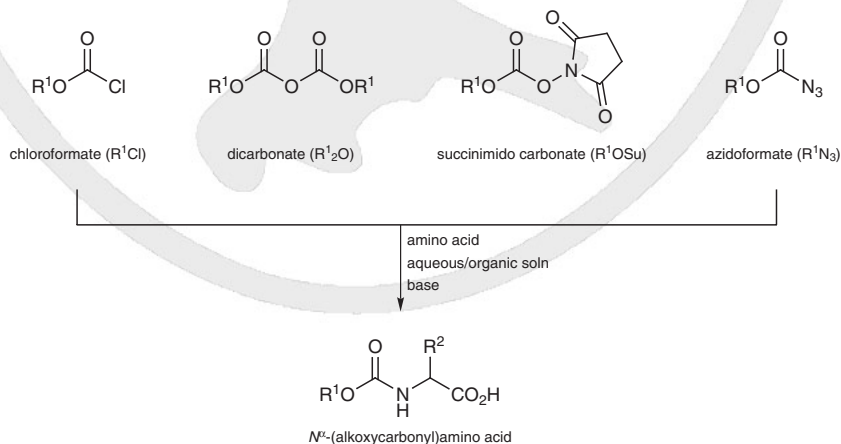
This section is not intended to survey all protecting groups used in peptide synthesis; readers interested in more detail are recommended to read *Houben–Weyl*, Vol. E 22a and more comprehensive reviews.^[20,21] This section will cover the most commonly used and efficacious protecting groups for peptide synthesis for both the Boc/Bzl and Fmoc/*t*-Bu protocols, as well as convenient orthogonal protecting groups that are employed in conjunction with both strategies.

21.11.1.1

Method 1: α -Amino Protection

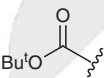
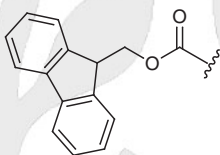
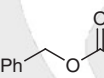
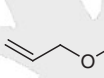
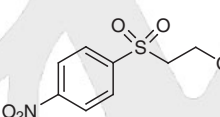
Many of the common amine protecting groups in use today have been developed to address issues in peptide science. Among the large number of amine protecting groups that have been employed in peptide synthesis, urethane-based protecting groups have been shown repeatedly to have superior properties with respect to their ease of handling, incorporation, and removal, as well as their ability to protect the α -amino acid configuration. Urethanes are typically introduced by coupling the amino acid to either a chloroformate, dicarbonate, succinimido carbonate, or an azidoformate in the presence of a base (Scheme 1), such as sodium carbonate, sodium hydrogen carbonate, or triethylamine, in a mixed solvent system such as dioxane/water or tetrahydrofuran/water, so-called Schotten–Baumann conditions.^[22,23]

Scheme 1 Urethane Protection of Amino Acids^[22,23]



The resulting carbamates have found wide application for amino acid protection (Table 1). In addition to α -amine protection, urethanes have proven successful in protection of the ω -amine functionality in lysine. Urethanes have also been used extensively for the temporary protection of the terminal amine during the installation of a variety of side-chain protecting groups (see Section 21.11.1.3 for examples).

Table 1 α -Amine Protecting Groups^[24–39]

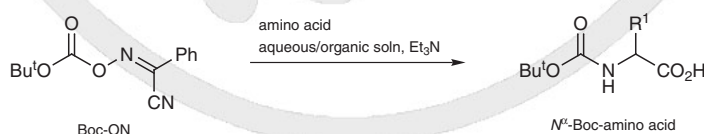
Group	Structure	Deprotection	Ref
<i>tert</i> -butoxycarbonyl (Boc)		TFA HCl/dioxane BF ₃ •OEt ₂	[24] [25] [27]
9-fluorenylmethoxycarbonyl (Fmoc)		20% piperidine/DMF 2% DBU/DMF 60% Et ₃ NH/DMF	[28] [29] [30]
benzyloxycarbonyl (Z)		H ₂ /Pd HBr/AcOH HF Et ₃ SiH, PdCl ₂	[31] [32] [33] [34]
allyloxycarbonyl (Aloc)		HBr/AcOH, Pd(0) HBr/AcOH, Pd(0), R ¹ ₂ NH HBr/AcOH, Pd(0), PhSiH ₃	[35] [36] [37]
2-[(4-nitrophenyl)sulfonyl]-ethoxycarbonyl (Nsc)		20% piperidine/DMF 20% piperidine/1% DBU/DMF	[38] [39]

21.11.1.1.1

Variation 1: *tert*-Butoxycarbonyl Group

Boc protection of amino acids and the related Boc/Bzl protection strategy have been covered in *Houben–Weyl*, Vol. 15/1, p 46, Vol. E 4, p 142, and Vol. E 22a, p 45 as well as in extensive reviews.^[21,40] Initial syntheses focused on amino acylation with *tert*-butyl chloroformate (Boc-Cl), a very reactive, relatively unstable reagent that was soon replaced by alternate acylating agents, namely di-*tert*-butyl dicarbonate [(Boc)₂O]^[42–44] and 2-[(*tert*-butoxycarbonyloxy)imino]-2-phenylacetonitrile (Boc-ON) (Scheme 2).^[41]

Scheme 2 *tert*-Butoxycarbonyl Protection Using 2-[(*tert*-Butoxycarbonyloxy)imino]-2-phenylacetonitrile^[41]



Boc-Cys-OMe; Typical Procedure for Acylation of Amino Acid Esters with (Boc)₂O:^[44]

A well-stirred slurry of H-Cys-OMe•HCl (1.72 g, 10 mmol) in CH₂Cl₂ (20 mL) was treated with Et₃N (1.01 g, 10 mmol), followed after 10 min by (Boc)₂O (2.18 g, 10 mmol), stirred for 16 h, washed with H₂O, dried, and concentrated to give the product as a colorless oil; yield: 2.29 g (97%); [α]_D²¹ +28.5 (c 0.075, CHCl₃).

Boc-Trp-OH; Typical Procedure for Acylation with Boc-ON:^[41]

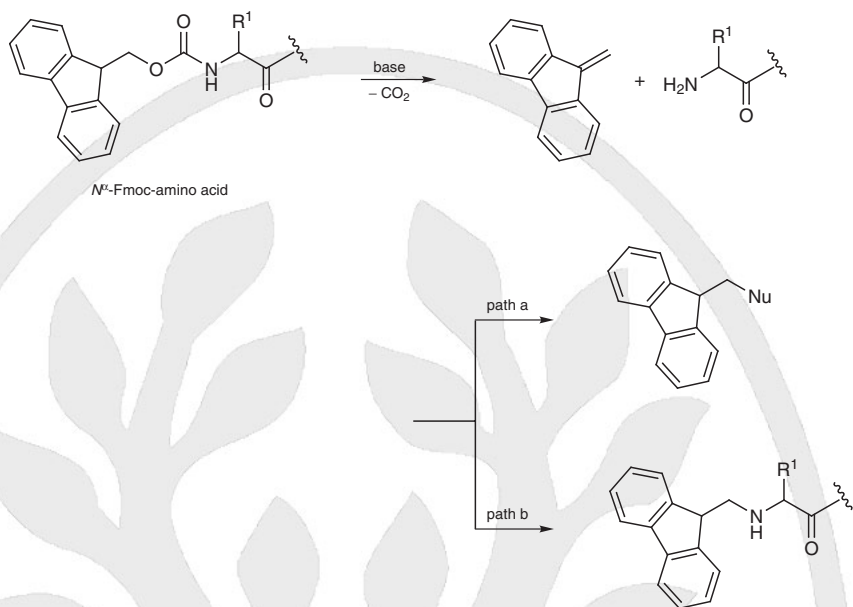
To a soln of H-Trp-OH (2.05 g, 10 mmol) and Et₃N (2.1 mL, 15 mmol) in H₂O (6 mL), dioxane (6 mL) and Boc-ON (2.71 g, 11 mmol) were added at rt. The mixture became homogenous within 1 h and was stirred for an additional 2 h. After addition of H₂O (15 mL) and EtOAc (20 mL), the aqueous layer was separated, washed with EtOAc (20 mL), acidified with 5% citric acid, and extracted with EtOAc. The organic extracts were combined and the solvents removed under reduced pressure; yield: 3.0 g (99%); mp 137–138 °C.

21.11.1.1.2

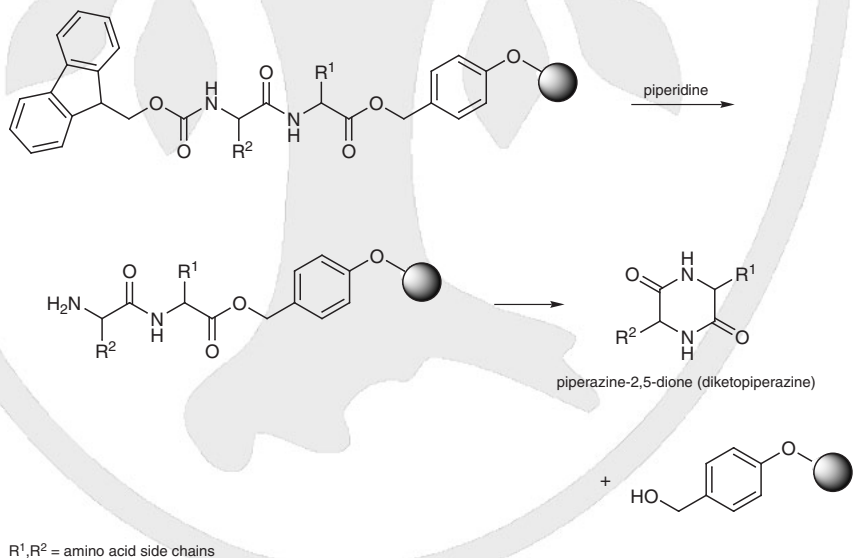
Variation 2:**9-Fluorenylmethoxycarbonyl Group**

Fmoc protection of amino acids and the related Fmoc/*t*-Bu strategy are discussed in *Houben–Weyl*, Vol. E 22a, p 57, and are the subjects of extensive reviews.^[20,45–50] The original method for the introduction of the Fmoc group was the reaction of the free amine with 9-fluorenylmethyl chloroformate (Fmoc-Cl),^[51] which is stable at room temperature yet can cause the formation of Fmoc-di- and Fmoc-tripeptides as side products in up to 20% yields during the protection step.^[52] These side products are avoided by using *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (9-fluorenylmethoxycarbonyl succinimido carbonate, Fmoc-OSu)^[52,53] or 9-fluorenylmethyl azidoformate (Fmoc-N₃).^[54]

Deprotection of the Fmoc group in the presence of a base has been conveniently monitored by observing the formation of the dibenzofulvene–piperidine adduct at 312 nm by UV spectroscopy (see also Section 21.11.5.5.1).^[55] Owing to the electrophilic nature of the dibenzofulvene adduct produced on Fmoc group removal, and the basic conditions for Fmoc removal, several problematic side reactions can occur upon cleavage (Scheme 3). In the absence of a nucleophile (e.g., piperidine or octanethiol) that can scavenge the liberated dibenzofulvene (path a), the dibenzofulvene can react with other nucleophiles such as the unprotected amine terminus and heteroatom side chains (path b). This is most frequently observed when alternate reagents such as 1,8-diazabicyclo[5.4.0]undec-7-ene are used for Fmoc removal.^[29]

Scheme 3 Dibenzofulvene Generation and Reactions^[55]

A second sequence-dependent problem is piperazine-2,5-dione (diketopiperazine) formation during solid-phase peptide synthesis at the dipeptide stage (Scheme 4). The terminal amine can displace the C-terminal ester linker. Peptides with C-terminal proline residues are particularly susceptible to piperazine-2,5-dione formation because of the lower barrier for isomerization of the amide of the N-terminal residue to proline.^[56–59]

Scheme 4 Piperazine-2,5-dione Formation^[56–59]

Fmoc-Trp-OH; Typical Procedure for N^{α} -Fmoc Protection of Amino Acids with Fmoc-Cl:^[60,61]

CAUTION: 9-Fluorenylmethyl chloroformate can evolve CO_2 (pressure!) upon prolonged storage; therefore, bottles should be opened carefully. Fmoc-Cl is harmful if swallowed, inhaled, or absorbed through skin, is corrosive, and is a strong lachrymator. Inhalation may be fatal.

H-Trp-OH (2.04 g, 10 mmol) was dissolved in 10% Na_2CO_3 in H_2O (26.5 mL, 25 mmol), treated with dioxane (15 mL), stirred in an ice-water bath, treated with small portions of Fmoc-Cl (2.6 g, 10 mmol), and left to stir at rt for 8 h. The mixture was poured into H_2O (600 mL) and extracted with Et_2O (2×100 mL). The aqueous soln was cooled in an ice-water bath and acidified under vigorous stirring with concd HCl to pH 5. The mixture was stored in the refrigerator overnight, filtered, and the solid material was thoroughly washed with H_2O and dried; yield: 4.0 g (94%); mp 182–185 °C. Recrystallization (MeNO_2) and a second recrystallization (CHCl_3 /hexane) yielded analytically pure material; yield: 3.9 g (91%); mp 185 °C (dec); $[\alpha]_{\text{D}}^{24} +6.4$ (c 1, EtOAc).

 N -(9-Fluorenylmethoxycarbonyloxy)succinimide (Fmoc-OSu):^[62]

A soln of Fmoc-Cl (129 g, 0.5 mmol) in dioxane (1.25 L) was treated with N -hydroxysuccinimide (HOSu; 63.3 g, 0.55 mmol), cooled in an ice bath with vigorous stirring, then treated slowly with Et_3N (70 mL, 0.5 mol) so as to maintain the temperature at 10–15 °C. After stirring at rt for 4 h, the precipitated $\text{Et}_3\text{N} \cdot \text{HCl}$ was removed by filtration. The filtrate was concentrated to 250 mL and poured slowly into Et_2O (2.5 L), with stirring. The product that crystallized was collected by filtration, washed (Et_2O), and dried; yield: 143–151 g (85–90%). The product can be used without further purification or recrystallized (CHCl_3 / Et_2O 4:1); mp 147–149 °C.

 N^{α} -Fmoc-Amino Acids; General Procedure Using Fmoc-OSu:^[63]

To a soln of the amino acid (0.10 mol) in H_2O (100 mL) and Et_3N (0.10 mol), Fmoc-OSu (90 mmol) in MeCN (100 mL) was added. The pH of the soln was brought to 8.5–9.0 with Et_3N and maintained until no further drop in the pH was detectable over 15 min. The mixture was filtered and the filtrate was concentrated. The residue was slowly added to vigorously stirred 1.5 M HCl (0.5 L). If a solid formed, it was filtered, washed with 1.5 M HCl and H_2O , and dissolved in EtOAc. When an oil precipitated, it was extracted with EtOAc (0.5 L). The respective organic layers were filtered through a porosity 4 sintered funnel to remove residual solids and the filtrate was washed with 1.5 M HCl (3×0.5 L), H_2O , and brine and then dried (MgSO_4). Crystallization of the product usually commenced during evaporation and was finished by trituration with petroleum ether (bp 40–60 °C) and dried; yield: 85–95%.

9-Fluorenylmethyl Azidoformate (Fmoc- N_3):^[54,60]

CAUTION: Sodium azide can explode on heating and is highly toxic. Contact of metal azides with acids liberates the highly toxic and explosive hydrazoic acid.

To an ice-cold, stirred soln of NaN_3 (6.9 g, 106 mmol) in H_2O (27 mL), a soln of Fmoc-Cl (18 g, 70 mmol) in acetone (33 mL) was added slowly. The mixture was stirred in the ice bath for 2 h and at rt for 2 h; then the solid was filtered, washed with H_2O , and recrystallized (acetone) to give the azide as colorless crystals; yield: 15.5 g (84%); mp 85 °C.

 N^{α} -Fmoc-Amino Acids; General Procedure Using Fmoc- N_3 :^[54]

To an ice-cold, stirring soln of the amino acid (25 mmol) in 10% Na_2CO_3 (66 mL), Fmoc- N_3 (23.5 mmol) in dioxane (65 mL) was added dropwise. After 2 h of stirring at 0 °C, the reaction was allowed to warm to rt and stirred for 5 d. The mixture was poured into H_2O

(300 mL), extracted (Et₂O), cooled, and acidified with concd HCl to pH 2.0. The white precipitate was filtered, washed with H₂O (3 ×), and dried. For example: Fmoc-Gly-OH, yield: 78%; mp 176–178 °C; Fmoc-Ala-OH, yield: 75%; mp 146–147 °C; [α]_D²⁰ –19.2 (c 1, DMF).

21.11.1.1.3

Variation 3:**Benzyloxycarbonyl Group**

The benzyloxycarbonyl (Z, conventionally Cbz) group, introduced by Bergmann and Zervas in 1932,^[31] was the first removable amine protecting group to enter popular use, because it can be efficiently removed using strongly acidic conditions^[32,33] as well as by hydrogenolysis.^[31] An effective method for introducing the Z group involves reacting the amino acid with benzyl chloroformate (Z-Cl) in a basic mixture of aqueous and organic solvents. Benzyl chloroformate is formed by the reaction of phosgene and benzyl alcohol.^[64] Benzyl chloroformate has limited stability relative to benzyl carbonates derived from benzyl chloroformate, such as dibenzyl dicarbonate (Z₂O) and *N*-(benzyloxycarbonyloxy)succinimide (benzyl succinimido carbonate, Z-OSu), which have been used in alternative protocols. *N*-(Benzyloxycarbonyloxy)succinimide has become the recommended reagent for introducing the Z group, because it reacts efficiently and is relatively more stable.

Z-Arg-OH; Typical Procedure Using Z-Cl:^[65,66]

A stirring ice-cold (0–3 °C) soln of 1 M NaOH (300 mL) was treated with H-Arg-OH•HCl (63.9 g, 300 mmol), followed by alternating portions of Z-Cl (55 mL, 390 mmol) and 2 M NaOH (165 mL), maintaining the temperature at 0 °C and the pH of the mixture between 9 and 10. After complete addition of the reactants, the suspension was stirred for 2 h. During this time, the pH dropped to 7–7.5. The precipitate was collected on a filter, washed with cold (10 °C) H₂O (150 mL), and recrystallized from boiling H₂O (ca. 400 mL). Crystallization was completed in the cold (ice-water bath). The product was collected, dried in air, and then suspended (as a powder) in acetone (150 mL), filtered, washed with acetone (60 mL) and with Et₂O (150 mL), and dried under reduced pressure at 50 °C; yield: 82.7 g (90%); mp 184 °C (dec); [α]_D²³ –9.3 (c 2, 1 M HCl). Other examples: Z-Pro-OH,^[67] Z-Leu-OH.^[66]

Dibenzyl Dicarbonate (Z₂O):^[68]

Benzyl alcohol (21.6 g, 200 mmol) was treated with NaH (4.8 g, 200 mmol) in refluxing THF (200 mL) for 2 h. The soln was cooled to rt and CO₂ was bubbled into the mixture under efficient stirring and with external cooling. After 1 h, Z-Cl (28.5 mL, 200 mmol) was added slowly. After stirring at rt for 3 h, the precipitate was removed by centrifugation. The supernatant was decanted and the solvents were removed under reduced pressure. The resulting oil crystallized in the cold. The crystalline mass was triturated with cold hexane, filtered, and dried; yield: 38.3 g (79%); mp 28 °C.

N^α-Z-Protected Amino Acids; General Procedure Using Z₂O:^[69]

To a soln of the amino acid (50 mmol) in 1 M NaOH (50 mL) and dioxane (50 mL), Z₂O (50 mmol) in dioxane (50 mL) was added dropwise while stirring. After 1 h at rt, the bulk of the dioxane was removed by evaporation. The resulting aqueous soln was acidified with 1 M H₂SO₄ to pH 2 and extracted with EtOAc or *t*-BuOMe (3 ×). The combined organic extracts were extracted with H₂O (3 ×), dried (Na₂SO₄), and the solvent was removed under reduced pressure. The product was isolated by crystallization (EtOAc/petroleum ether); yield: 83–95%.

N-(Benzyloxycarbonyloxy)succinimide (Z-OSu):^[52]

To a stirred soln of Z-Cl (54.4 mmol) in CHCl₃ (100 mL), HOSu•DCHA salt [obtained as a precipitate in acetone by mixing equimolar quantities of HOSu and DCHA (54.4 mmol

each)] was added in portions. After 12 h, the precipitate was filtered and washed with CHCl_3 . The filtrate and washes were combined, washed with one-third volumes each of 10% citric acid, 10% NaHCO_3 , and H_2O , dried, and concentrated to a residue that was recrystallized ($\text{CHCl}_3/\text{Et}_2\text{O}$); yield: 90%; mp 80–81 °C.

Z-Ser-OH; Typical Procedure Using Z-OSu:^[52]

To a stirred soln of H-Ser-OH (525 mg, 5 mmol) and NaHCO_3 (420 mg, 5 mmol) in a mixture of H_2O (7 mL) and acetone (7 mL), Z-OSu (1.24 g, 5 mmol) was added. The mixture was stirred overnight, acetone was removed under reduced pressure, and the soln was washed with CH_2Cl_2 (2×3 mL). The aqueous layer was acidified to pH 2.5 with concd HCl and extracted with EtOAc (3×5 mL). The combined organic layers were washed with H_2O , dried, concentrated, and recrystallized; yield: 78%; mp 120 °C; $[\alpha]_{\text{D}}^{20} +5.7$ (c 6, AcOH).

21.11.1.1.4 Variation 4: Allyloxycarbonyl Group

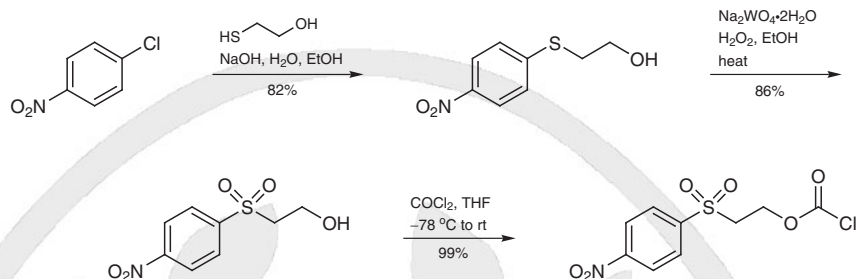
An amino protecting group that has found utility in both major peptide synthesis strategies is the allyloxycarbonyl (Aloc) group, which is cleaved under orthogonal palladium(0) conditions in the presence of a nucleophile or by strong acids (HF, HBr/AcOH). Stable to repetitive acid treatment (e.g., TFA), the Aloc group is also resistant to treatment with bases and nucleophiles. Aloc protection can be easily accomplished with allyl chloroformate (Aloc-Cl) as well as with diallyl dicarbonate [(Aloc) $_2\text{O}$].^[70]

N^α-Aloc-Amino Acids; General Procedure Using Aloc-Cl:^[71]

To a stirred soln of the amino acid (0.1 mol) in 4 M NaOH (25 mL) at 0 °C, Aloc-Cl (0.1 mol) and 4 M NaOH (25 mL) were added alternately in 8 portions within ~30 min, maintaining the soln at an alkaline pH. After an additional 15 min at rt, the mixture was extracted with Et_2O , and the aqueous layer was acidified with concd HCl. After cooling for several hours, crystals were collected, dried, and recrystallized. When the product was not crystalline, the cold soln was extracted with Et_2O , and the organic layers were concentrated to an oil. The DCHA salt was obtained by adding the amine (0.1 mol) to a soln of the oily Aloc derivative in EtOH or EtOAc and precipitation with Et_2O or Et_2O /petroleum ether; the yields are in the range 80–95%.^[72]

21.11.1.1.5 Variation 5: 2-[(4-Nitrophenyl)sulfonyl]ethoxycarbonyl Group

The 2-[(4-nitrophenyl)sulfonyl]ethoxycarbonyl (Nsc) group was developed as a base-labile alternative to the Fmoc group, in order to avoid the problem of dibenzofulvene adducts that may be formed during Fmoc deprotection. Similar to the Fmoc group, deprotection of the Nsc group can be monitored by UV spectroscopy; both Nsc-Cl and Nsc-protected amino acids are commercially available (Scheme 5).^[73,74]

Scheme 5 Synthesis of 2-[(4-Nitrophenyl)sulfonyl]ethyl Chloroformate^[73]**2-[(4-Nitrophenyl)sulfonyl]ethyl Chloroformate (Nsc-Cl):^[73]**

CAUTION: *Phosgene is a severe respiratory irritant and very toxic by inhalation.*

To a soln of 1-chloro-4-nitrobenzene (40.4 g, 256 mmol) in 2-sulfanylethanol (46 mL, 654 mmol), 4 M NaOH in H₂O (72 mL, 288 mmol) was added. The two-phase system was vigorously stirred at 70 °C for 3 h. During this period, the inner walls of the vessel were washed with EtOH (15 mL) to return crystalline 1-chloro-4-nitrobenzene to soln. The soln was cooled, extracted with CH₂Cl₂ (200 mL), and the organic layer was washed with 10% Na₂CO₃ (3 ×) and with aq KHSO₄. The organic layer was washed with H₂O until neutral, then dried (Na₂SO₄), concentrated, and crystallized (iPr₂O, 150 mL) to give 2-[(4-nitrophenyl)sulfanyl]ethanol; yield: 41.8 g (82%); mp 60 °C.

2-[(4-Nitrophenyl)sulfanyl]ethanol (5.0 g, 25 mmol) was dissolved in EtOH (25 mL), treated with 2% aq Na₂WO₄·2H₂O soln (3 mL), warmed to 40 °C, and treated slowly with 35% H₂O₂ (2 mL). The soln was warmed to 80 °C and treated again with 35% H₂O₂ (2 mL). The mixture was refluxed for 1 h to complete the oxidation and to decompose traces of H₂O₂. 2-[(4-Nitrophenyl)sulfonyl]ethanol crystallized upon cooling (4 °C); yield: 41.7 g (86%); mp 128 °C.

COCl₂ (57 mL) was condensed into a 100-mL three-necked flask at −78 °C and treated slowly with a soln of 2-[(4-nitrophenyl)sulfonyl]ethanol (10.0 g, 43 mmol) in THF (75 mL) while stirring at an internal temperature of −78 °C. The cooling bath was removed and the reaction flask was placed under a CaCl₂ drying tube and left in the hood at rt overnight. The following day, residual COCl₂ and HCl were removed by purging with N₂ for 1 h, after which time the solvent was removed; yield: 52.4 g (99%); mp 119–122 °C.

N^α-Nsc-Amino Acids; General Procedure:^[74]

To a soln of the amino acid (20 mmol) in CH₂Cl₂ (30 mL), Et₃N (40 mmol) and TMSCl (40 mmol) were added dropwise with stirring. The mixture was refluxed for 1.5 h, cooled (0 °C), treated with Nsc-Cl (17 mmol), and stirred at 0 °C for 30 min and at rt for 2 h, concentrated, and partitioned between Et₂O and 5% aq NaHCO₃. The aqueous layer was acidified to pH 2–2.5 with 2 M H₂SO₄, extracted with EtOAc, dried (Na₂SO₄), and concentrated. The residue was typically recrystallized from EtOAc/petroleum ether. For example: Nsc-Lys(Boc)-OH; yield: 83%; mp 110–112 °C; [α]_D²⁵ −11.3 (c 1, DMF); Nsc-Glu(Ot-Bu)-OH; yield: 90%; mp 94–96 °C; [α]_D²⁵ −17.0 (c 1, DMF).

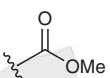
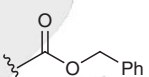
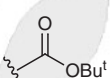
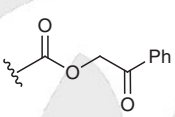
21.11.1.2**Method 2:
α-Carboxylic Acid Protection**

Previously published information on this set of protection strategies is discussed in *Houben-Weyl*, Vol. E 22a, pp 193–228.

The primary use of α-carboxylate protection has been solution-phase peptide synthesis (Table 2). α-Carboxylate protection has also found application in the protection of in-

intermediates during the introduction of protecting groups onto side-chain carboxylates or alcohols as well as solid-phase synthesis with residues linked through side chains.^[75–80]

Table 2 α -Carboxylic Acid Protecting Groups^[33,81–90]

Group	Ester Structure	Deprotection	Ref
methyl ester (OMe)		alkali, aqueous/organic solvent Bu ₄ NOH, aqueous/organic solvent, $\leq 0^\circ\text{C}$	[81] [82]
benzyl ester (OBzl)		H ₂ , Pd/C, aq EtOH, rt Na, liq NH ₃ HF, 0°C	[81] [83] [33]
<i>tert</i> -butyl ester (Ot-Bu)		TFA, CH ₂ Cl ₂ , rt 2 M HBr/AcOH ZnBr ₂ , CH ₂ Cl ₂	[84] [85] [86,87]
phenacyl ester (OPac)		Zn, AcOH, rt NaSPh, DMF, rt H ₂ , Pd/C, aq MeOH, rt	[88] [89] [90]

21.11.1.2.1

Variation 1: Methyl Ester

Methyl ester protection of α -carboxylates is effective, especially for solution-phase syntheses using the Boc/Bzl strategy, because of the generally orthogonal (basic) conditions required for its removal. However, hydrolysis may be difficult and may result in a number of side reactions; to reduce potential side reactions, tetrabutylammonium hydroxide has been recommended as the deprotection reagent.^[82]

Amino Acid Methyl Esters; General Procedure Using Me₂C(OMe)₂/HCl^[66,91]

The amino acid (10 mmol) was suspended in 2,2-dimethoxypropane (100–150 mL), treated with concd HCl (10 mL), and allowed to stand at rt overnight. The volatiles were removed under reduced pressure at a bath temperature not exceeding 60°C . The residue was dissolved in a minimum amount of anhyd MeOH and the soln was diluted with anhyd Et₂O (250 mL). The crystalline methyl ester hydrochloride was collected on a filter, washed with Et₂O, and dried under reduced pressure over NaOH pellets. Recrystallization (MeOH/Et₂O) afforded the analytically pure ester hydrochloride; yield: 80–95%.

H-Ser-OMe•HCl; Typical Procedure for Esterification Using MeOH/SOCl₂^[92,93]

CAUTION: Thionyl chloride reacts violently with water producing large volumes of corrosive gases. It is extremely destructive to all tissues.

Abs MeOH (100 mL) was cooled to -10°C and treated with freshly distilled SOCl₂ (26 mL) over 10 min. H-Ser-OH (10.5 g, 0.1 mol) was suspended in the mixture and stirred at rt until complete dissolution. After 24 h, the solvent was removed and the residue was recrystallized (MeOH/Et₂O 1:5); yield: 15.4 g (99%); mp 168°C ; $[\alpha]_{\text{D}}^{23} -2.5$ (c 1.8, DMF).

Z-Asp-OMe•DCHA; Typical Procedure for α -Carboxylate Methylation via an Internal Anhydride:^[94]

A mixture of freshly distilled Ac_2O (700 mL) and Z-Asp-OH (1.005 kg, 3.75 mol) was stirred at 45 °C for 4 h; the solvent was then removed. The solid residue was triturated with abs MeOH (4 L) and the resulting mixture was refluxed for another 4 h. After removal of the solvent, the oil was dissolved in Et_2O and extracted with several portions of aq NaHCO_3 ; each fraction was separately acidified and stored in the cold. Fractions in which the Z-Asp-OMe separated in crystalline form were combined and dissolved in Et_2O . Upon addition of DCHA (714 g, 3.94 mol), the DCHA salt was precipitated, filtered, and recrystallized (EtOH /petroleum ether); yield: 900 g (52%); mp 159–160 °C; $[\alpha]_{\text{D}}^{20} +14.9$ (c 1, EtOH).

**21.11.1.2.2 Variation 2:
Benzyl Ester**

Benzyl esters are effective and stable protecting groups for α -carboxylates and can be removed efficiently by catalytic hydrogenation or by treatment with strong acid; as a result, they are also suitable for solution-phase peptide syntheses using the Boc/Bzl strategy.

H-Gly-OBzl•TsOH; Typical Procedure for Esterification Using Bzl-OH/TsOH:^[95]

A mixture of H-Gly-OH (18.8 g, 0.25 mol) and TsOH• H_2O (48.5 g, 0.25 mol) in freshly distilled Bzl-OH (100 mL) and benzene (50 mL) (**CAUTION: carcinogen**) was refluxed and the H_2O formed in the reaction was azeotroped into a Dean–Stark receiver. When no more H_2O appeared in the distillate (2–5 h), the mixture was cooled to rt, diluted with benzene (250 mL) and Et_2O (400 mL), and cooled in an ice-water bath for 2 h. The crystalline product was filtered, washed with Et_2O (200 mL), and dried. The salt was recrystallized ($\text{MeOH}/\text{Et}_2\text{O}$); yield: 70.8 g (84%); mp 132–134 °C.

Boc-Asn-OBzl; Typical Procedure for Esterification of N-Protected Amino Acid Cesium Salts with Bzl-Br:^[96]

A soln of Boc-Asn-OH (11.0 g, 47.5 mmol) in MeOH (200 mL) and H_2O (20 mL) was neutralized with 20% aq Cs_2CO_3 (~55 mL) and concentrated to a residue that was dissolved in DMF (120 mL) and the solvent was removed under reduced pressure at 45 °C. The dry residue was resuspended in DMF (120 mL) and the evaporation was repeated. The solid was reacted in DMF (120 mL) with Bzl-Br (8.9 g, 52 mmol). After 6 h at rt, the solvent was removed and the residue was triturated with H_2O (500 mL). The solid was dissolved in EtOAc (150 mL). The organic layer was washed with H_2O , dried (Na_2SO_4), filtered, and concentrated to give the crude ester, which was recrystallized ($\text{EtOAc}/\text{hexane}$); yield: 13.8 g (90%); mp 120–122 °C; $[\alpha]_{\text{D}}^{25} -17.3$ (c 1, DMF).

**21.11.1.2.3 Variation 3:
tert-Butyl Ester**

tert-Butyl esters are stable and effective α -carboxylate protecting groups that have found wide application in solution-phase peptide synthesis by the Fmoc/*t*-Bu strategy. *tert*-Butyl esters can be efficiently cleaved by concentrated (>80%) or neat trifluoroacetic acid, but are stable to milder acidic conditions, such as those that cleave the trityl group. Alternatively, zinc(II) bromide in dichloromethane can be used to effect efficient removal of the *tert*-butyl group.^[86,87]

H-Tyr-OtBu; Typical Procedure for the Esterification of Unprotected Amino Acids with 2-Methylpropene:^[97]

Liq 2-methylpropene (25 mL) was slowly added to H-Tyr-OH (3 g, 16.6 mmol) in dioxane (25 mL) containing TsOH•H₂O (6 g, 31.5 mmol) in a 500-mL pressure bottle. The flask was stoppered and shaken at rt for 20 h. The soln was poured into an ice-cold mixture of EtOAc (100 mL) and 0.25 M NaOH (105 mL). The pH was adjusted to 9.1, and the *tert*-butyl ester was extracted into EtOAc (2 ×). The organic solvent was removed under reduced pressure. The product was recrystallized (EtOAc/petroleum ether); yield: 1.77 g (45%); mp 143–145 °C; $[\alpha]_{\text{D}}^{25} +24.4$ (c 2, EtOH).

 α -Amino Acid *tert*-Butyl Esters; General Procedure by Transesterification with *t*-BuOAc:^[98]

CAUTION: Commercially available perchloric acid (70–72%) can react explosively or violently with a range of organic and inorganic substances and is extremely destructive to all tissues.

The amino acid (10 mmol), *t*-BuOAc (150 mL), and 60% aq HClO₄ (11 mol) were mixed and stirred for 15 min until dissolution. After 4 d at rt, the mixture was cooled in an ice bath and extracted with 0.5 M HCl (4 × 25 mL). The aqueous extracts were immediately neutralized with solid NaHCO₃, combined, and extracted with Et₂O (4 × 100 mL). The pooled Et₂O extracts were dried (MgSO₄) and the solvent was removed under reduced pressure. Upon addition of anhyd HCl in Et₂O, the amino acid *tert*-butyl esters were isolated as hydrochlorides; yield: 40–75%, with the exception of H-Pro-Ot-Bu•HCl (19%).

Z-Xaa-Ot-Bu; General Procedure by Esterification of *N*-Z-Amino Acids with *t*-BuBr:^[99]

A soln of Z-Xaa-OH (10 mmol) and TEBAC (10 mmol) in DMA (75 mL) was treated with anhyd K₂CO₃ (0.26 mol), followed by *t*-BuBr (0.48 mol). The mixture was stirred at 55 °C for 24 h. After cooling, cold H₂O (1 L) was added, and the resulting precipitate was filtered and washed with H₂O. In the case of oily compounds, the oil was extracted into EtOAc (250 mL). The organic layer was separated, washed with H₂O (2 × 100 mL), dried (Na₂SO₄), concentrated, and recrystallized (Et₂O/hexane); yield: 80–100%.

21.11.1.2.4 Variation 4:
Phenacyl Ester

Phenacyl esters (Pac) are more stable to repetitive *N*^α-Boc deprotection cycles than benzyl esters, making them the ideal α -carboxylate protecting groups for longer solution-phase peptide syntheses using the Boc/Bzl strategy. They can be removed by catalytic hydrogenation or orthogonally by treatment with zinc powder in acetic acid.

Z-Glu-OPac•DCHA; Typical Procedure for Esterification with Phenacyl Bromide:^[88,100]

Pac-Br (2 g, 10 mmol) was added to a soln of Z-Glu-OH (2.8 g, 10 mmol) and Et₃N (1.4 mL, 10 mmol) in DMF (7 mL). After 48 h at rt the mixture was diluted with EtOAc (100 mL) and washed several times with H₂O. The organic layer was dried (Na₂SO₄) and concentrated to 50 mL. Upon addition of DCHA (4 mL) the product precipitated in the cold; yield: 3.13 g (54%); mp 149–151 °C; $[\alpha]_{\text{D}}^{14} -16.5$ (c 3, MeOH).

21.11.1.3 Method 3:
Acidic Side-Chain Protection

Development of side-chain carboxylate protection has been focused towards the selective deprotection of protecting groups at the end of peptide synthesis, either by treatment with stronger reagents (e.g., HF or TFOH as opposed to TFA) or by orthogonal cleavage (TFA as opposed to piperidine) (Table 3). Considerable effort has also been focused on

avoiding aspartimide formation (Scheme 6) during peptide synthesis.^[101–103] The primary difficulty with the use of side-chain carboxylate protection is the selective installation of different protecting groups at the side-chain carboxylate and the α -carboxylate.

Scheme 6 Aspartimide Formation upon Hydrogen Fluoride Cleavage^[101–103]

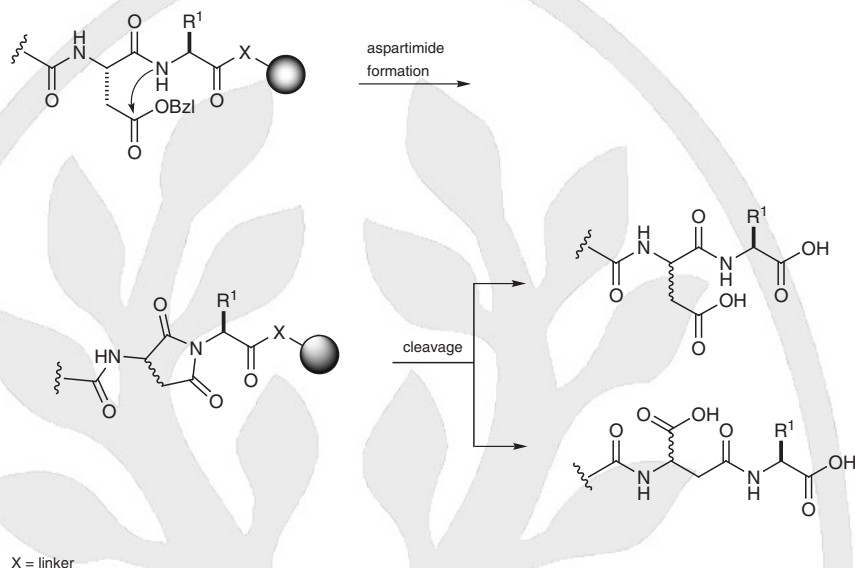


Table 3 Acidic Side-Chain Protecting Groups^[61,86,87,104–107]

Group	Structure	Deprotection	Ref
benzyl ester (OBzl)		HF (or strong acid) H ₂ , Pd/C TfOH, TFA	[105] [104] [106]
cyclohexyl ester (OCy)		HF (or strong acid) TfOH, TFA	[107] [108]
<i>tert</i> -butyl ester (Ot-Bu)		TFA ZnBr ₂ , CH ₂ Cl ₂	[61] [86,87]

21.11.1.3.1

Variation 1: Benzyl Ester

Typically employed in the Boc/Bzl peptide synthesis strategy for both α -carboxylate (see Section 21.11.1.2.3) and side-chain carboxylate protections, this protecting group can be cleaved under strongly acidic conditions or by catalytic hydrogenation. Occasional problems associated with α -carboxylate benzyl esters include deprotection with repetitive trifluoroacetic acid treatment, as well as aspartimide formation in the case of aspartic acid analogues.

H-Xaa(OBzl)-OH; General Procedure Using Bzl-OH/H₂SO₄:^[93,109]

Freshly distilled Bzl-OH (100 mL, 0.1 mol) was added to a mixture of anhyd Et₂O (100 mL) and concd H₂SO₄ (10 mL). The Et₂O was removed under reduced pressure and finely powdered H-Xaa-OH (0.1 mol) was added in small portions, with stirring. The resulting soln was kept at rt for ca. 1 day, diluted with 95% EtOH (200 mL), and neutralized by dropwise addition of pyridine (50 mL), with vigorous stirring. The mixture was stored overnight in the cold. The crystalline product was collected and washed (Et₂O). The ester was recrystallized from hot H₂O containing a few drops of pyridine. For example: H-Asp(OBzl)-OH; yield: 40–45%; mp 218–220 °C; [α]_D²⁰ +28.1 (c 1, 1 M HCl); H-Glu(OBzl)-OH; yield: 76%; mp 189 °C; [α]_D²⁰ +19.6 (c 6, AcOH).

H-Glu(OBzl)-OH; Typical Procedure Using Bzl-OH/HBF₄•OEt₂:^[110]

A suspension of finely powdered H-Glu-OH (2.0 g, 13.6 mmol) and anhyd Na₂SO₄ (2.0 g) in Bzl-OH (25 mL, 242 mmol) was treated with 54% HBF₄•OEt₂ (3.7 mL, 27.2 mmol) by means of a syringe. The suspension was stirred at rt for 15 h, diluted with anhyd THF (75 mL), and filtered through activated charcoal. The clear filtrate was neutralized with Et₃N (4.1 mL, 29.6 mmol) and concentrated under reduced pressure (14 Torr, with the bath temperature not exceeding 50–60 °C) until a slurry was formed. The viscous residue was triturated with EtOAc (100 mL) and the resulting solid was filtered off and washed with additional solvent; yield: 3.03 g (94%); mp 188–189 °C; [α]_D²⁰ +29.5 (c 2, 1 M HCl).

21.11.1.3.2

**Variation 2:
Cyclohexyl Ester**

The alternative protecting group to benzyl esters for side-chain carboxylates in the Boc/Bzl peptide synthesis strategy are cycloalkanes, which are more stable to acid than benzyl esters and more resistant to aspartimide formation. Stable to hydrogenation, cycloalkyl esters must be cleaved with a strong acid, typically anhydrous hydrogen fluoride. The most commonly used cycloalkyl ester is cyclohexyl.^[110,111]

H-Xaa(OCy)-OH; General Procedure Using CyOH/H₂SO₄:^[111]

CyOH (250 mL, 2.5 mol) was added to a mixture of anhyd Et₂O (250 mL) and concd H₂SO₄ (25 mL, 0.5 mol). H-Xaa-OH (0.25 mol) was added in small portions, with stirring. The resulting suspension was heated in a rotary evaporator at 70 °C for 2 h under reduced pressure. The bulk of the solvent was removed during this procedure. The resulting oil was partitioned between EtOAc (250 mL) and 5% aq KHCO₃ (300 mL). The pH was adjusted to 7.0 with 4 M NaOH and the aqueous layer was concentrated until precipitation occurred. The resulting suspension was chilled overnight and filtered. For example: H-Asp(OCy)-OH; yield: 60%; mp 220–223 °C; [α]_D²⁰ +20.1 (c 2, H₂O); H-Glu(OCy)-OH; yield: 49%; mp 195–198 °C.

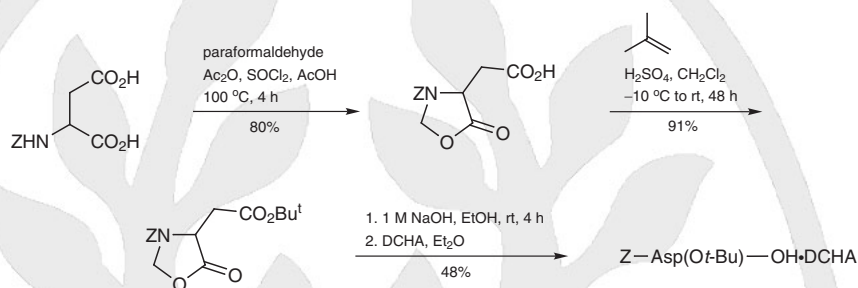
H-Glu(OCy)-OH; Typical Procedure for Using CyOH/HBF₄•OEt₂:^[110]

Finely powdered H-Glu-OH (4.4 g, 30 mmol) and anhyd Na₂SO₄ (4 g, 28 mmol) were suspended in CyOH (50 mL, 470 mmol) and 54% HBF₄•OEt₂ (8.2 mL, 60 mmol) was added by syringe. After stirring at rt for 15 h, the mixture was diluted with THF (100 mL). The Na₂SO₄ was removed by filtration and washed with CyOH. The filtrate was neutralized with Et₃N (9.2 mL, 66 mmol). The alcohol was removed by evaporation. The residue was triturated with EtOAc (200 mL) and the remaining solid was recrystallized (H₂O); yield: 3.16 g (45%); mp 175–176 °C; [α]_D²⁰ +29.8 (c 2, 1 M HCl).

21.11.1.3.3

Variation 3:
***tert*-Butyl Ester**

This common protecting group for side-chain carboxylates in the Fmoc/*t*-Bu peptide synthesis strategy is difficult to introduce regioselectively. As a result, α -carboxylate protection with an orthogonally labile group such as a benzyl ester or through an oxazolidinone intermediate is generally required prior to side-chain esterification (Scheme 7).^[66,112–115]

Scheme 7 Oxazolidinone Intermediate for Selective ω -*tert*-Butylation^[115]**H-Asp(Ot-Bu)-OH from Z-Asp-OBzl:**^[112]

To a cooled soln of Z-Asp-OBzl (4.92 g, 13.76 mmol) in CH_2Cl_2 (28 mL), 2-methylpropene (15 mL) and 17.75 M H_2SO_4 (0.14 mL, 2.47 mmol) were added and the mixture was left to stand at rt for 65 h. The mixture was cooled to 0 °C and neutralized carefully with cold H_2O (25 mL) containing 1 M Na_2CO_3 (4 mL). The excess 2-methylpropene was removed by evaporation under reduced pressure. The mixture was cooled and extracted with CH_2Cl_2 . Emulsions were avoided by the addition of EtOAc and sat. Na_2SO_4 . The organic layers were washed with H_2O until neutral, dried (MgSO_4), filtered, and concentrated. The resulting oil was dissolved in EtOAc, washed with cold aq NaHCO_3 and H_2O , dried (MgSO_4), and recrystallized (EtOAc/petroleum ether) to give Z-Asp(Ot-Bu)-OBzl; yield: 5.58 g (98%); mp 45–47.5 °C.

Z-Asp(Ot-Bu)-OBzl (323 mg, 1 mmol) was dissolved in MeOH (16 mL) and hydrogenated over 10% Pd/C (32 mg) for 3 h. The mixture was filtered and the filtrate was concentrated. The resulting oil was dissolved in MeOH. On addition of Et_2O , H-Asp(Ot-Bu)-OH precipitated as crystals; yield: 151 mg (80%); mp 189–190 °C; $[\alpha]_{\text{D}}^{23} +8.5$ (c 1.02, 90% AcOH).

H-Glu(Ot-Bu)-OH from Z-Glu-OBzl:^[66,113]

A cooled soln of Z-Glu-OBzl (H-Glu-OBzl can be derived from selective cleavage of the dibenzyl ester using HI/benzene and treatment with Bu_3N)^[114] (18.6 g, 50 mmol) in anhyd dioxane (55 mL) was placed in a thick-walled glass vessel, cooled to –10 °C, and treated with liq 2-methylpropene (210 mL) followed by concd H_2SO_4 (1 mL). The flask was stoppered, wrapped in a towel, and shaken at rt for about 20 h. Then H_2O (250 mL) was added and the excess 2-methylpropene was removed under reduced pressure. The residue was extracted with Et_2O (2 × 150 mL). The Et_2O extracts were combined, extracted with cold sat. aq NaHCO_3 (4 × 100 mL), washed with ice water until the washes were neutral, dried (MgSO_4), and concentrated to dryness. The residue, Z-Glu(Ot-Bu)-OBzl, crystallized on standing; yield: 13.5 g (63%); mp 40–44 °C.

Z-Glu(Ot-Bu)-OBzl (4.3 g, 10 mmol) was hydrogenated in MeOH (50 mL) and H_2O (25 mL) over 10% Pd/C (0.9 g). After completion of the reaction, the catalyst was filtered off and the filtrate was concentrated. The residue was triturated with acetone. Upon storage in the cold, the product solidified. The solid was collected and washed with acetone; yield: 1.08 g (89%); mp 182 °C; $[\alpha]_{\text{D}}^{20} +9.8$ (c 2, H_2O).

Z-Asp(Ot-Bu)-OH•DCHA via an Oxazolidinone Intermediate:^[115]

CAUTION: Thionyl chloride reacts violently with water producing large volumes of corrosive gases. It is extremely destructive to all tissues.

A mixture of Z-Asp-OH (5.35 g, 20 mmol), paraformaldehyde (1.8 g, 60 mmol), Ac₂O (4.0 g, 40 mmol), and SOCl₂ (0.3 mL, 4.1 mmol) in AcOH (80 mL) was heated at 100°C for 4 h. Removal of the AcOH gave an oily residue which was dissolved in EtOAc and extracted with 5% aq NaHCO₃. The aqueous layer was acidified with 6 M HCl with ice cooling and extracted with EtOAc. The extract was washed with H₂O, dried (MgSO₄), and concentrated to a pale yellow syrup. Purification by column chromatography (silica gel, CHCl₃/EtOAc 3:1) afforded pure [3-(benzyloxycarbonyl)-5-oxooxazolidin-4-yl]acetic acid; yield: 4.4 g (80%).

[3-(Benzyloxycarbonyl)-5-oxooxazolidin-4-yl]acetic acid (4.4 g, 15.8 mmol) was dissolved in anhyd CH₂Cl₂ (30 mL) containing concd H₂SO₄ (0.2 mL), cooled to –10°C, stirred, and treated with bubbling gaseous 2-methylpropene (ca. 15 g). The soln was kept in a stoppered flask at rt for 48 h. After addition of EtOAc (100 mL), the soln was washed with 5% aq NaHCO₃ and H₂O, dried (MgSO₄), and concentrated to give *tert*-butyl [3-(benzyloxycarbonyl)-5-oxooxazolidin-4-yl]acetate as a pale yellow syrup, which was used in further reactions without purification; yield: 4.9 g (91%).

A soln of *tert*-butyl [3-(benzyloxycarbonyl)-5-oxooxazolidin-4-yl]acetate (4.8 g, 14.4 mmol) in EtOH (20 mL) was treated with 1 M NaOH (7.1 mL) at rt for 4 h. The mixture was neutralized with 1 M HCl and the EtOH was removed under reduced pressure. The product was dissolved in EtOAc and extracted with 5% aq NaHCO₃. The aqueous phase was washed once with EtOAc, acidified with 6 M HCl, and extracted with EtOAc. The organic layer was washed with H₂O, dried (MgSO₄), and concentrated to give a syrup (2.8 g). A soln of the syrup in Et₂O was treated with DCHA (1.7 g, 9.4 mmol) and the crystalline DCHA salt was collected and subsequently recrystallized (H₂O); yield: 3.45 g (48%); mp 128–129°C; [α]_D²⁴ +6.5 (c 1.7, 90% AcOH).

21.11.1.4

**Method 4:
Basic Side-Chain Protection**

Effective protecting groups have been developed for the basic side chains of histidine, arginine, lysine, and tryptophan (Table 4). Lysine is usually protected using the orthogonal Fmoc and Boc groups. The side-chain guanidinium of arginine can be protected effectively by a variety of arylsulfonyl groups, which are typically more stable and cleaved more slowly than other protecting groups. The indole NH of tryptophan can be protected by formyl (Boc/Bzl strategy) or Boc (Fmoc/*t*-Bu strategy) groups or left unprotected. Protection of the histidine imidazole remains a particular challenge in the Boc/Bzl strategy: 2,4-dinitrophenyl (Dnp) is effective, but requires cleavage with a nucleophile; the benzyloxymethyl (Bom) group is also effective, but requires scavengers (e.g., resorcinol, cysteine) to prevent formaldehyde adducts; the Z group can be difficult to remove completely. Selective introduction of protection on side-chain amines generally requires either temporary or semipermanent protection of the α -nitrogen or coordination of the α -amino and carboxylate of the free amino acid in a copper(II) complex.

Table 4 Basic Side-Chain Protecting Groups^[32,33,66,107,116–126]

Group	Structure	Deprotection	Ref
benzyloxycarbonyl (Z)		HBr/AcOH HF (or strong acid)	[32] [33]
2-chlorobenzyloxycarbonyl [Z(2-Cl)]		HF (or strong acid)	[116]
2,4-dinitrophenyl (Dnp)		PhSH, DMF	[117]
benzyloxymethyl (Bom)		HF (or strong acid) + resorcinol	[118]
4-tolylsulfonyl, tosyl (Ts)		HF (or strong acid) Ac2O, pyridine HOBT	[119] [120] [121]
mesitylsulfonyl (Mts)		<i>hν</i> , H ₃ N•BH ₃ , dimethoxynaphthalene HF (or strong acid)	[122] [123]
2,2,5,7,8-pentamethyl-chroman-6-ylsulfonyl (Pmc)		TFA	[124]
formyl (For)		TfOH piperidine, DMF	[125] [107]
tert-butoxycarbonyl (Boc)		TFA	[66]
trityl (Trt)		TFA	[126]

21.11.1.4.1

**Variation 1:
Benzyloxycarbonyl Group and Derivatives**

The Z group, and derivatives with altered lability such as Z(2-Cl), have found application in protecting both the ω -amine of lysine and the imidazole ring of histidine in the Boc/Bzl peptide synthesis strategy (Scheme 8).^[116]

Scheme 8 Z(2-Cl) Side-Chain Protection of Lysine^[116]

native chemical ligation by an excess of thiol additives (see Section 21.11.6 for more details).^[117]

Boc-His(Dnp)-OH from Boc-His-OMe:^[117]

A soln of Boc-L-His-OMe (2.7 g, 10 mmol) in EtOH (20 mL) was treated with 1 M NaOH (10 mL), stirred for 45 min, neutralized at 0 °C with 1 M HCl, and concentrated under reduced pressure. The residue was first treated with a soln of NaHCO₃ (2.3 g) in H₂O (10 mL), then with 1-fluoro-2,4-dinitrobenzene (1.4 mL) in MeOH (15 mL) slowly over a period of 1 h. The mixture was allowed to react at rt for 10 h and the MeOH was concentrated under reduced pressure. The remaining aqueous phase was washed with Et₂O (3 × 20 mL), acidified to pH 3.5 with 1 M HCl at 0 °C, and extracted with EtOAc (3 × 20 mL). The extracts were washed with H₂O, dried (MgSO₄), and concentrated under reduced pressure. The oily residue was recrystallized three times [EtOH/petroleum ether (bp 30–60 °C)]; yield: 2.6 g (62%); mp 94 °C; [α]_D²⁰ +55.3 (c 1, EtOAc).

21.11.1.4.3

Variation 3: Benzyloxymethyl Group

The benzyloxymethyl (Bom) group is an effective and relatively stable protection for histidine in the Boc/Bzl strategy. Cleavage of the Bom group requires the presence of 2–4% resorcinol or another scavenger (e.g., cysteine) to prevent formaldehyde adducts.^[118,128]

Boc-His(Bom)-OH from Boc-His-OMe:^[118]

CAUTION: Chloromethyl ethers are carcinogenic irritants. Proper safety precautions and procedures should be adopted at all stages of their preparation and use.

A soln of Boc-L-His-OMe (32 g, 82 mmol) in CH₂Cl₂ (200 mL) was treated with BzlOCH₂Cl (18 mL, 130 mmol), left to stand at rt overnight, concentrated, dissolved in MeOH (30 mL), and treated with Et₂O (400 mL) to produce a slightly turbid soln from which Boc-L-His(Bom)-OMe•HCl crystallized overnight; yield: 24 g (69%); mp 152 °C; [α]_D²⁰ –19.1 (c 1, MeOH).

A soln of Boc-L-His(Bom)-OMe•HCl (22 g, 52 mmol) was dissolved in MeOH (50 mL) and was treated with 1 M NaOH (120 mL), stirred for 15 min, diluted with H₂O (1 L), and adjusted to pH 4.5 by the dropwise addition of 1 M HCl. The soln was extracted with CHCl₃ (3 × 100 mL) and the combined organic extracts were dried. Removal of the solvent gave an oil which was dissolved in EtOAc (50 mL). Evaporation gave Boc-L-His(Bom)-OH; yield: 17 g (87%); mp 155 °C; [α]_D²⁰ +6.9 (c 0.5, MeOH).

21.11.1.4.4

Variation 4: Arylsulfonyl Derivatives

The family of arylsulfonyl groups represents the most general approach to protection of the side-chain guanidine of arginine in both the Fmoc/*t*-Bu and Boc/Bzl strategies.^[129] Varying acid labilities are possible among the commonly used arylsulfonamides, including tosyl (Ts), mesitylsulfonyl (Mts), 2,2,5,7,8-pentamethylchroman-6-ylsulfonyl (Pmc), and 2,2,4,6,7-pentamethyldihydrobenzofuran-5-ylsulfonyl (Pbf). Arylsulfonyl groups are usually stable to hydrogenation and generally exhibit slow cleavage kinetics in acid; cleavage times (see Section 21.11.5) should be increased in direct proportion to the number of arylsulfonyl groups in a peptide.

H-Arg(SO₂Ar¹)-OH from Z-Arg-OH; General Procedure:^[129]

A vigorously stirred, ice-cold soln of Z-Arg-OH (180 mmol) in 4 M NaOH (180 mL) and acetone (1.3 L) was treated dropwise with a soln of the arenesulfonyl chloride (Ar¹SO₂Cl; 360 mmol) in acetone (300 mL) over a period of 30 min, agitated at 0 °C for 2 h, and at rt for an additional 2 h, acidified with citric acid, and concentrated. The aqueous layer was extracted with EtOAc and the combined extracts were washed with H₂O (2 ×) and then extracted with 5% NaHCO₃ (3 × 400 mL). After acidification of the aqueous extracts with citric acid, the precipitated oil was dissolved in EtOAc. The organic layer was washed with H₂O, dried (Na₂SO₄), and then concentrated to an oily residue that was dissolved in EtOAc (600 mL) and treated with DCHA (36 mL) or CyNH₂ (20.7 mL) to produce crystals upon standing in the cold; yield: 60–70%. For example, Z-Arg(Ts)-OH•DCHA; mp 110–112 °C; $[\alpha]_D^{23} + 5.1$ (c 1.35, MeOH); *R*_f 0.69 (EtOAc/pyridine/AcOH/H₂O 60:20:6:10).

Z-Arg(SO₂Ar¹)-OH•DCHA (20 mmol) was partitioned between EtOAc and 5% citric acid. After washing with H₂O, the organic layer was dried (Na₂SO₄) and concentrated. The residue was hydrogenated over Pd/C in MeOH. The catalyst was removed by filtration and the filtrate was concentrated. The product was precipitated with Et₂O and in some cases recrystallized (H₂O); yield: 80–95%. For example, H-Arg(Ts)-OH; mp 144–146 °C (dec); $[\alpha]_D^{23} - 6.1$ (c 0.71, MeOH); *R*_f 0.08 (EtOAc/pyridine/AcOH/H₂O 60:20:6:10).

21.11.1.4.5 **Variation 5:**
Formyl Group

The formyl (For) group is an effective protection against electrophilic attack of the indole NH of tryptophan in the Boc/Bzl strategy. Although the formyl group can be cleaved by nucleophilic bases or by weak nucleophiles in strongly acidic conditions, its incomplete deprotection has resulted in significant losses in the final yield of peptide.^[130] Because such losses can be greater than those due to side reactions in the course of the synthesis and cleavage of peptides possessing tryptophan, the formyl group is generally used in the Boc/Bzl strategy only when absolutely necessary to avoid significant side reactions.

H-Trp(For)-OH:^[66]

Anhyd HCl(g) was passed through a soln of H-Trp-OH (20.4 g, 100 mmol) in HCO₂H (300 mL) with hourly monitoring by UV at 278 and 298 nm. Formylation was deemed complete when no further increase in the UV maximum was observed at 298 nm (typically 3 h). Removal of the solvent and addition of Et₂O yielded the crystalline product; yield: 26.8 g (quant); mp 218–220 °C; $[\alpha]_D^{23} - 4.7$ (c 2, H₂O).

21.11.1.4.6 **Variation 6:**
***tert*-Butoxycarbonyl Group**

The Boc group (see Section 21.11.1.1.1) is frequently used to protect the ε-amine of lysine and the indole of tryptophan^[131] in the Fmoc/*t*-Bu strategy. Installed usually with reagents such as (Boc)₂O^[66] or Boc-ON,^[132] the Boc group has also been introduced as a protecting group on the τ-nitrogen of histidine using Boc-N₃.^[133] In the Fmoc/*t*-Bu strategy, the τ-Boc group of histidine has been observed to be partially removed during repetitive base treatments.^[134]

21.11.1.4.7 **Variation 7:**
Trityl Group and Derivatives

Protection of side-chain amino functionality with the *tert*-butyl group has been found to suffer from side reactions due to the reactivity of the liberated *tert*-butyl cation during cleavage, as well as incomplete deprotection. The more acid-labile trityl (Trt, convention-

allyl Trt) group has been proven generally more effective in the Fmoc/*t*-Bu strategy. The trityl group has been used as side-chain protection with histidine and arginine residues. The relatively more acid-labile methoxytrityl group has also been used to protect histidine and lysine residues.^[135] Introduction of both the trityl and methoxytrityl groups is usually accomplished by alkylation with trityl (or methoxytrityl) chloride.

H-His(τ -Trt)-OH from H-His-OH; Typical Procedure for the Protection of Histidine with Trityl Derivatives:^[126,135]

A stirred suspension of H-His-OH (1.55 g, 10 mmol) in CH₂Cl₂ (15 mL) was treated with Me₂SiCl₂ (1.21 mL, 10 mmol), refluxed for 4 h, treated with Et₃N (2.79 mL, 20 mmol), refluxed for an additional 15 min, treated with additional Et₃N (1.39 mL, 10 mmol) followed by a soln of Trt-Cl (2.79 g, 10 mmol) in CH₂Cl₂ (10 mL), and stirred at rt. After 2 h, an excess of MeOH was added to the mixture, which was then concentrated under reduced pressure. The residue was treated with H₂O, the pH was adjusted to 8–8.5 by dropwise addition of Et₃N, and the resulting slurry was shaken well with CHCl₃. The insoluble material was filtered off with suction. Further washing of the solid with H₂O and Et₂O provided H-His(Trt)-OH (negative Pauly test^[136,137]); yield: 3.85 g (97%); mp 218–220 °C. An analytical sample was prepared by recrystallization (THF/H₂O 1:1); mp 220–222 °C; [α]_D²⁵ –2.1 (c 1, THF/H₂O 1:1); IR ($\tilde{\nu}$): 3550–2200, 1650–1560, 750, 700 cm^{–1}.

21.11.1.5

Method 5: Alcoholic Side-Chain Protection

The alcoholic side chains of serine, threonine, tyrosine, and 4-hydroxyproline are typically protected by benzyl groups in the Boc/Bzl strategy and *tert*-butyl groups in the Fmoc/*t*-Bu strategy. Alternative protecting groups have been developed to (a) reduce alkylation of the tyrosine phenol ring during strong acid cleavage and (b) reduce the concentration of acid required for cleavage, especially within the Fmoc/*t*-Bu strategy (Table 5).

Table 5 Alcoholic Side-Chain Protecting Groups^[86,125,138–142]

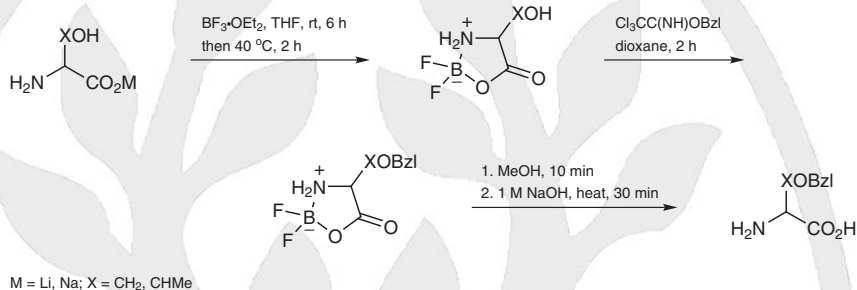
Group	Structure	Deprotection	Ref
benzyl (Bzl)		HF (or strong acid)	[125]
2-bromobenzyloxycarbonyl [Z(2-Br)]		HF (or strong acid)	[138]
<i>tert</i> -butyl (<i>t</i> -Bu)		TFA ZnBr ₂ , CH ₂ Cl ₂	[139] [86]
trityl (Trt)		1% TFA/CHCl ₃ TFA/TFE/CH ₂ Cl ₂ (5:5:90)	[142] [140]
2-chlorotrityl [Trt(2-Cl)]		1% TFA, 5% iPr ₃ SiH	[141]

21.11.1.5.1

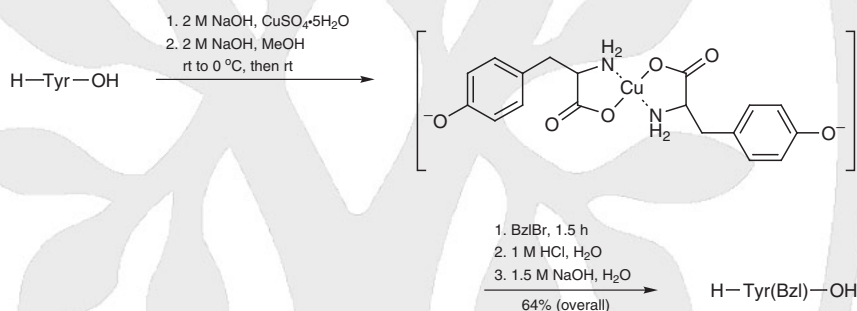
**Variation 1:
Benzyl Group**

Similar to their application as protecting groups for carboxylic acids (see Sections 21.11.1.2.2 and 21.11.1.3.1), benzyl groups have proven to be effective protecting groups for side-chain hydroxy groups, and can be cleaved under similar conditions (strong acids, hydrogenolysis) (Schemes 9 and 10).^[66,143,144]

Scheme 9 Selective Benzylation of Alcoholic Side Chains through a 4-Hydroxymethyl-Substituted 1,3,2-Oxazaborolidin-5-one Intermediate^[143]



Scheme 10 Benzyl Side-Chain Protection of Tyrosine^[66,144]



H-Ser(Bzl)-OH from H-Ser-O-Li or H-Thr(Bzl)-OH from H-Thr-O-Na via an Oxazaborolidin-5-one Intermediate:^[143]

To the salt of the amino acid (monolithium salt of Ser or monosodium salt of Thr, 10 mmol) suspended in THF (15 mL), BF₃•OEt₂ (6.0 mL) was added, stirred at rt for 6 h and then at 40–45 °C for an additional 2 h. A soln of the intermediate was produced quantitatively, concentrated under reduced pressure at rt to remove the solvent, and kept under reduced pressure (1.0 Torr) for an additional 0.5 h. Dioxane (30 mL) was added to the residue and the soln was stirred for 10 min, treated with benzyl trichloroacetimidate (2.15 mL, 11.5 mmol) over 10 min, stirred for 2 h, treated with anhyd MeOH (5 mL), stirred for 10 min, treated with 1 M aq NaOH (30 mL), and heated to 40–50 °C. After 30 min, the mixture was concentrated and the residue was dissolved in H₂O (200 mL). The resulting soln was washed with Et₂O (3 × 15 mL). The aqueous phase was adjusted to pH 6.0 and passed through a column (Amberlite XAD-4 resin, H₂O then 50% EtOH). The latter eluent containing the desired compound was collected and the solvent was removed under reduced pressure to give the product as a white solid; H-Ser(Bzl)-OH; yield: 1.85 g (95%); mp 219–221 °C (dec); [α]_D²⁵ +6.0 (c 1, 3 M HCl); H-Thr(Bzl)-OH; yield: 1.9 g (91%); mp 203–204 °C (dec); [α]_D²⁵ –30.8 (c 1, AcOH).

H-Tyr(Bzl)-OH from H-Tyr-OH:^[66,144]

H-Tyr-OH (18.1 g, 100 mmol) was dissolved in 2 M NaOH (100 mL) and treated with a soln of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (12.5 g, 50 mmol) in H_2O (50 mL). A precipitate formed and soon dissolved. The mixture was heated to 60 °C, cooled to rt, diluted with MeOH (350 mL), made more alkaline with 2 M NaOH (15 mL), treated with Bzl-Br (13 mL, 100 mmol), and stirred vigorously at rt for ca. 1.5 h. The purple-blue precipitate was collected on a filter, washed with a mixture of MeOH (50 mL) and H_2O (175 mL), then with MeOH (25 mL), and dried in air. The precipitate was ground, washed with 1 M HCl (5 × 50 mL), then distilled H_2O (2 × 25 mL), 1.5 M NaOH (5 × 25 mL), and H_2O (2 × 25 mL), followed by recrystallization (boiling AcOH); yield: 17.5 g (64%); mp 260–270 °C (dec); $[\alpha]_{\text{D}}^{20}$ –9.5 (c 1, 80% AcOH).

21.11.1.5.2

**Variation 2:
2-Bromobenzyloxycarbonyl Group**

The Z(2-Br) group provides superior protection of the phenol of tyrosine relative to benzyl ethers, because it can avoid side reactions encountered in the cleavage of benzyl ethers from Tyr(Bzl) residues using hydrogen fluoride.^[33] In the Boc/Bzl peptide synthesis strategy, the Z(2-Br) group has become the preferred protecting group for the tyrosine phenol because it is significantly more acid stable than the benzyl ether, but also more acid labile than the parent benzyloxycarbonyl group.^[125] However, because the Z(2-Br) group is generally stable to catalytic hydrogenolysis, it is typically removed under strongly acidic conditions.

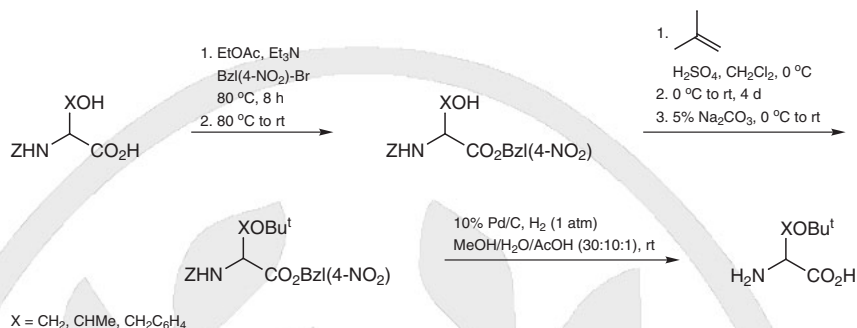
H-Tyr[Z(2-Br)]-OH from H-Tyr-OH:^[125]

A soln of tyrosine (13.9 g, 77 mmol) in 2 M NaOH (78 mL) was mixed with a soln of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (9.4 g) in H_2O (39 mL), heated to 60 °C, and then cooled to rt. The pH of the mixture was adjusted to ca. 5 with glacial AcOH. The solid which formed was collected on a filter and washed with H_2O and acetone. This solid was suspended in 70% aq DMF (1.1 L), treated with 4-nitrophenyl 2-bromobenzyl carbonate^[145] (41.5 g, 118 mmol) and NaHCO_3 (14.2 g) and stirred for 20 h. The insoluble product was collected on a filter and washed with 75% aq DMF, H_2O , and acetone, yielding a blue solid (21.4 g). This solid was stirred in 1 M HCl (300 mL) for 1 h, filtered, and washed with 1 M HCl (250 mL), H_2O , and acetone to yield the product as a colorless solid; yield: 15.9 g (50%). For analysis a sample was recrystallized (50% AcOH); mp 203–208 °C (dec); R_f 0.57 (BuOH/AcOH/ H_2O 4:1:1); $[\alpha]_{\text{D}}^{24}$ –4 (c 2, 80% AcOH).

21.11.1.5.3

**Variation 3:
tert-Butyl Group**

The *tert*-butyl group is generally stable to most conditions encountered in the Fmoc/*t*-Bu strategy. Protection is generally accomplished either through treatment of maximally protected amino acids with 2-methylpropene, or through treatment of an oxazaborolidin-5-one intermediate with 2-methylpropene (Scheme 11).^[143]

Scheme 11 *tert*-Butylation of Side-Chain Alcohols with Maximum Protection^[143]

Side-Chain *tert*-Butyl Protection of Alcoholic Side Chains (Ser, Thr, Tyr) from the Corresponding Z-Protected Amino Acids; General Procedure:^[146]

CAUTION: 4-Nitrobenzyl bromide is a serious irritant, is corrosive, and can liberate carbon monoxide and hydrogen bromide gases upon exposure to water. Handle only with full protective equipment inside a chemical safety hood.

The corresponding Z-protected amino acid (200 mmol) was dissolved in EtOAc (200 mL), then treated with Et₃N (300 mmol) and with 4-nitrobenzyl bromide (64.8 g, 300 mmol). The mixture was kept in a bath at 80 °C for about 8–9 h and then cooled to rt. The Et₃N•HBr was filtered off. The organic filtrate was extracted with 2 M HCl (200 mL), H₂O (200 mL), 10% NaHCO₃ (200 mL), and H₂O (200 mL), dried (Na₂SO₄), and the solvent was removed under reduced pressure. The residue was dissolved in a minimum volume of EtOAc and diluted with hexane until turbid. Crystals were collected, washed with a mixture of EtOAc and hexane, and dried to yield the 4-nitrobenzyl ester: Z-Thr-OBzl(4-NO₂); yield: 75.4 g (97%); mp 114–115 °C; [α]_D²⁰ –14.0 (c 2, MeOH); Z-Ser-OBzl(4-NO₂); yield: 73.3 g (98%); mp 115.5–116.6 °C, [α]_D²⁰ –11.87 (c 0.9, MeOH); Z-Tyr-OBzl(4-NO₂); yield: 84 g (95%); mp 117–119 °C; [α]_D²⁰ –11.16 (c 1, MeOH).

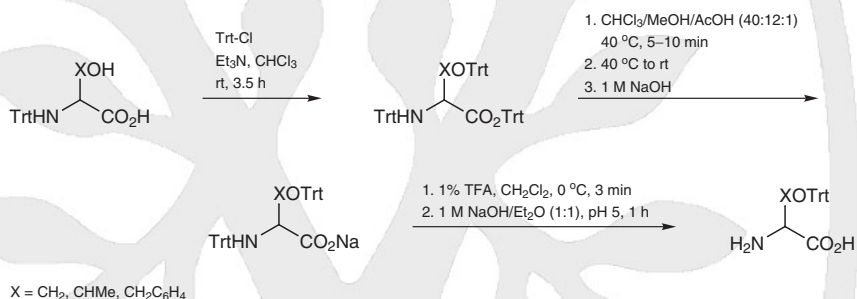
A soln of the 4-nitrobenzyl ester (100 mmol) in CH₂Cl₂ (400 mL) was placed in a thick-walled, round-bottomed flask, cooled in an ice-water bath to 0 °C, and treated with caution with 2-methylpropene (350 mL) and H₂SO₄ (5 mL). The flask was stoppered, wrapped in a towel, kept at rt for 4 d, and cooled to 0 °C. The final soln was extracted with ice-cold 5% aq Na₂CO₃ (3 × 200 mL). The aqueous extracts were washed with CH₂Cl₂ (2 × 100 mL), the organic phases were pooled, washed with H₂O until the washes were neutral, dried (P₂O₅), and concentrated under reduced pressure. The yellow, crystalline residue was dissolved in a minimum volume of EtOAc and diluted with hexane until a dark oil separated. The clear soln was decanted and diluted further with hexane. The *tert*-butyl ether crystallized: Z-Thr(*t*-Bu)-OBzl(4-NO₂); yield: 36 g (81%); mp 55–56.5 °C; *R*_f 0.5 (heptane/*t*-BuOH/pyridine 5:1:1); Z-Ser(*t*-Bu)-OBzl(4-NO₂); yield: 41 g (90%); mp 68–70.5 °C; *R*_f 0.49 (heptane/*t*-BuOH/pyridine 5:1:1); Z-Tyr(*t*-Bu)-OBzl(4-NO₂); yield: 35.9 g (80%); mp 73.5–74.5 °C; *R*_f 0.52 (heptane/*t*-BuOH/pyridine 5:1:1).

The fully protected amino ester (50 mmol) was dissolved in MeOH (150 mL) and diluted with H₂O (50 mL) and AcOH (4 mL). The soln was purged with N₂ bubbles and treated with 10% Pd/C (by wt). The reaction vessel was filled, vented, and filled with H₂ gas. The hydrogenation mixture was agitated at rt and 1 atm of H₂. After removal of the catalyst by filtration (under N₂), the filtrate was concentrated under reduced pressure to give a residue that was triturated with EtOH and recrystallized (MeOH/acetone) to furnish the *tert*-butyl protected amino acid: H-Thr(*t*-Bu)-OH; yield: 9.7 g (85%); mp 259–260 °C (dec); [α]_D²⁰ –42.1 (c 2, MeOH); H-Ser(*t*-Bu)-OH; yield: 6.9 g (90%); mp 250 °C (dec); [α]_D²⁰ –17.69 (c 2, H₂O); H-Tyr(*t*-Bu)-OH; yield: 8.3 g (87%); mp 248–249.5 °C (dec); [α]_D²⁰ –25.77 (c 1, H₂O).

21.11.1.5.4

**Variation 4:
Trityl Group and Derivatives**

Trityl protecting groups have often been employed as protection for the hydroxy groups of serine, threonine, and tyrosine residues in Fmoc-based peptide synthesis strategies (Scheme 12).^[140] The weaker electrophilicity of the trityl cation relative to the *tert*-butyl cation has been found to cause fewer side reactions with nucleophilic side chains such as those of methionine and tryptophan residues.^[141,147–150] The increased acid lability of the trityl group relative to the *tert*-butyl group enables its selective cleavage in the presence of other acid-labile protecting groups. This feature has been a key for effecting a variety of selective reactions,^[151,152] such as phosphorylation, glycosylation, and sulfation of specific residues during the synthesis of peptide analogues possessing posttranslational modifications. The 2-chlorotrityl group is relatively more acid labile than the trityl group, and can be removed with 1% trifluoroacetic acid and 5% triisopropylsilane in dichloromethane. Trityl protection can be accomplished by complete tritylation and selective deprotection of the trityl ester and *N*^α-trityl protection; urethanes such as the Fmoc group can then be introduced under typical conditions.

Scheme 12 Tritylation of Side-Chain Alcohols by Selective Deprotection^[140,142]**Side-Chain Trityl Protection of Alcoholic Side Chains (Ser, Thr, Tyr) from the Corresponding *N*^α-Trt-Protected Amino Acids; General Procedure^[140,142]**

CAUTION: Hexamethylphosphoric triamide is a known human carcinogen^[153] and an eye and skin irritant and adequate protections must be taken to avoid exposure to this compound.

A soln of the corresponding *N*^α-Trt-protected amino acid (58 mmol) in CHCl₃ (115 mL) was treated with Et₃N (50 mmol) and Trt-Cl (61 mmol), stirred for 20 min at rt, treated with additional Et₃N (50 mmol) and Trt-Cl (61 mmol), and stirred at rt for 3 h. The resulting soln was concentrated under reduced pressure. The product was resuspended in Et₂O/5% citric acid (1:1) and agitated for 10 min. The resulting precipitate was filtered, washed with equal portions of H₂O, MeOH, and Et₂O, and dried under reduced pressure to yield the *N*^α,*O*-ditritylamino acid trityl ester, Trt-Ser(Trt)-OTrt: yield: 91%; mp 201–202 °C; [α]_D²⁰ –43.4 (c 2, CHCl₃).

A suspension of the respective *N*^α,*O*-ditritylamino acid trityl ester (52.5 mmol) in CHCl₃ (80 mL), MeOH (25 mL), and AcOH (2 mL) was warmed to 40–45 °C and stirred for 5–10 min until all of the ester dissolved. After cooling to rt, methyl trityl ether crystallized out of the soln, which was filtered. The filtrate was concentrated under reduced pressure and resuspended in Et₂O/5% citric acid (1:1). The organic phase was separated and washed with H₂O. On treatment of the organic phase with 1 M NaOH the sodium salt of the *N*^α,*O*-ditritylamino acid precipitated. After filtration and washing with 1 M NaOH, H₂O, and Et₂O, the precipitate was dried under reduced pressure at 40 °C for 12 h. Recrystallization (acetone) yielded the sodium salt of the *N*^α,*O*-ditritylamino acid, Trt-Ser(Trt)-ONa; yield: 72%; mp 209 °C; [α]_D²⁰ 32.3 (c 2, CHCl₃).

The sodium salt of the N^α , O -ditritylamino acid (5 mmol) was dissolved in an ice-cold soln of 1% TFA/ CH_2Cl_2 (20–50 mL), stirred for 3 min, and concentrated under reduced pressure at 0 °C. The remaining residue was triturated with Et_2O /petroleum ether (1:1). The resulting solid was filtered off, washed with Et_2O , and dried under reduced pressure to yield the TFA salt of the O -tritylamino acid. The TFA salt was added to 1 M NaOH/ Et_2O (1:1). The phases were separated and the aqueous phase was treated with AcOH until pH 4.8–5. After standing for 1 h, the O -tritylamino acid precipitated from the aqueous phase and was washed with H_2O , acetone, and Et_2O , and recrystallized ($\text{EtOH}/\text{H}_2\text{O}$). For example, H-Ser(Trt)-OH; yield: 66%; mp 192 °C; $[\alpha]_{\text{D}}^{20}$ –4.6 (c 2, 1 M NaOH/HMPA 1:1).

21.11.1.6

Method 6: Amide Side-Chain Protection

Protection of the side chains of asparagine and glutamine has often been used to avoid a variety of possible side reactions during amino acid activation and cleavage (Table 6), including dehydration leading to nitrile formation^[154,155] and pyroglutamate formation^[156] (Scheme 13). Base-catalyzed aspartimide formation is another side reaction that is largely sequence dependent and most commonly observed at Asn-Gly and Asp-Gly junctions.^[157,158]

Scheme 13 Side Reactions of Asparagine and Glutamine During Peptide Synthesis^[154–156]

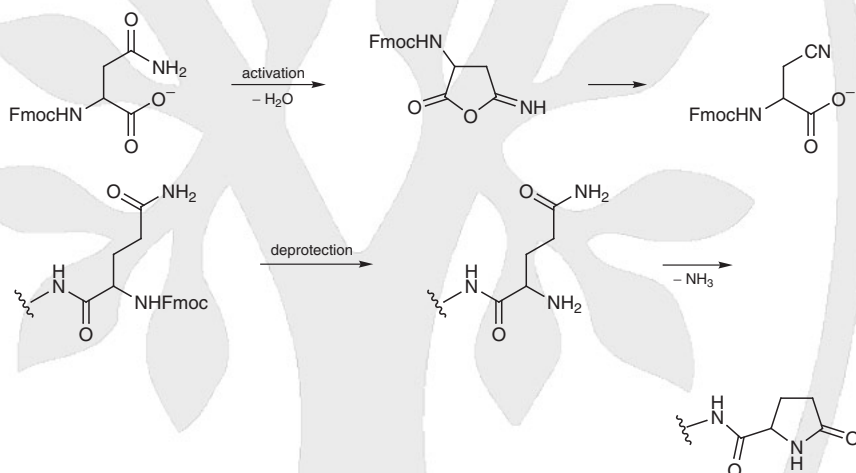


Table 6 Amide Side-Chain Protecting Groups^[159–161]

Group	Structure	Deprotection	Ref
9H-xanthen-9-yl (Xan)		TFA	[159]
2,4,6-trimethoxybenzyl (Tmb)		TFA	[160]
trityl (Trt)		TFA	[161]

21.11.1.6.1

**Variation 1:
9H-Xanthen-9-yl Group**

The acid-labile 9H-xanthen-9-yl (Xan) group can be cleaved in trifluoroacetic acid and has found application as both a temporary protecting group^[162] for asparagine and glutamine residues in the Boc/Bzl strategy as well as a longer term protection for such residues in the Fmoc/*t*-Bu strategy.

H-Gln(Xan)-OH from Z-Gln-OH:^[163]

Z-L-Gln-OH was dissolved in glacial AcOH and an equimolar amount of Xan-OH was added. Z-Gln(Xan)-OH was obtained; yield: 80%; mp 182–183 °C; $[\alpha]_D^{17}$ –5.7 (c 5.7, DMF). This was hydrogenated in EtOH with 10% Pd/C (by wt) to yield H-Gln(Xan)-OH; mp 222 °C (dec).

21.11.1.6.2

**Variation 2:
2,4,6-Trimethoxybenzyl Group**

A common protecting group for Fmoc synthesis of asparagine or glutamine, the 2,4,6-trimethoxybenzyl (Tmb) group prevents dehydration and nitrile formation. Scavengers are required during its cleavage if tryptophan is present in the peptide.^[164] Starting with fully *N*^o-amino and α -carboxylic acid protected aspartic acid or glutamic acid, the Tmb amides are prepared by coupling to 2,4,6-trimethoxybenzylamine. Cleavage of the Tmb protecting group is performed under acidic conditions (TFA) to unmask the asparagine and glutamine residues.

Z(OMe)-Asn(Tmb)-OBzl from Z(OMe)-Asp-OBzl; Typical Procedure:^[160]

Z(OMe)-Asp-OBzl (4.73 g, 12.2 mmol) and HOSu (2.10 g, 18.2 mmol) were dissolved in CH₂Cl₂ (35 mL), cooled to 0 °C, treated with a soln of DCC (2.78 g, 13.5 mmol) in CH₂Cl₂ (10 mL), stirred at 0 °C for 1 h, treated with 2,4,6-trimethoxybenzylamine (2.65 g, 13.5 mmol), and left stirring overnight. The next day, the resulting DCU was filtered off and the soln was extracted with 10% citric acid (2 \times), 10% aq NaHCO₃ (2 \times), and H₂O (2 \times). The organic phase was concentrated and the resulting product was recrystallized (CHCl₃/petroleum ether); yield: 6.1 g (87%); mp 159 °C; $[\alpha]_{546}^{22}$ –3.2 (c 3, CHCl₃).

21.11.1.6.3

**Variation 3:
Trityl Group**

As with the protection of basic (Section 21.11.1.4.7) and alcoholic side chains (Section 21.11.1.5.4), the trityl group is an effective protection for side-chain amides in the Fmoc/*t*-Bu strategy.

H-Asn(Trt)-OH•0.5H₂O from H-Asn-OH:^[161]

A soln of H-Asn-OH (13.2 g, 100 mmol) in glacial AcOH (300 mL) was treated with Trt-OH (52 g, 200 mmol), Ac₂O (18.9 mL, 200 mmol), and concd H₂SO₄ (6.1 mL, 115 mmol), heated to 60 °C, stirred for 75 min, and then added slowly to cold H₂O (600 mL). The pH was adjusted to 6 by addition of 10 M NaOH. The soln was transferred to an ice bath; crystals formed rapidly. After 1 h at 0 °C the crystals were filtered and thoroughly washed with H₂O, then with toluene, and dried; yield: 28.7 g (75%); mp >240 °C (dec); $[\alpha]_D^{20}$ –3.7 (c 1, 1 M NaOH).

H-Gln(Trt)-OH•0.5H₂O from Z-Gln-OH:^[161]

A soln of Z-Gln-OH (27.9 g, 100 mmol) in glacial AcOH (300 mL) was treated with Trt-OH (52 g, 200 mmol), Ac₂O (18.9 mL, 200 mmol), and concd H₂SO₄ (0.5 mL, 9 mmol), heated to 50 °C, stirred for 1 h, and then slowly added to cold H₂O (3 L). The precipitate was filtered

off, dissolved in EtOAc (800 mL), washed with H₂O, dried, concentrated, and crystallized (EtOAc/hexane) to yield Z-Gln(Trt)-OH; yield: 35 g (67%); mp 161–162 °C; $[\alpha]_D^{20}$ –4.5 (c 1, MeOH).

Z-Gln(Trt)-OH (24 g, 46 mmol) was subsequently hydrogenated in 90% MeOH (240 mL) and 1 M HCl (46 mL) with 10% Pd/C (1.2 g). After 90 min, the starting material was completely dissolved; after 2.5 h, the catalyst was filtered off, the soln was concentrated to 200 mL, and Et₃N (6.4 mL) was added. After stirring at 0 °C for 1 h, the crystals were removed by filtration, washed with H₂O, and dried; yield: 17 g (93%); mp >220 °C (dec); $[\alpha]_D^{20}$ +9.2 (c 1, 1 M NaOH).

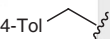
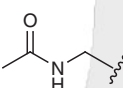



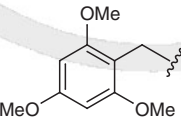
21.11.1.7

Method 7: Thiol Side-Chain Protection

Previously published information on protection strategies for this product class is covered extensively in *Houben–Weyl*, Vol. E 22a, pp 384–417.

Protection of thiol groups during peptide synthesis is necessary to avoid nucleophilic cross reactivity. The structural role of thiol groups in forming disulfide bonds in peptides and proteins, as well as the unique chemistry of the cysteine thiolate, such as in chemo-selective ligation (see Section 21.11.6), has resulted in the development of multiple orthogonal protection strategies aimed at enabling selective deprotection for oxidation during the course of the synthesis, as well as preventing removal during global deprotection. Special consideration needs to be given to the conditions used for effecting deprotection, as well as subsequent oxidation to prevent handling and purification difficulties. Most thiol protecting groups are stable to trifluoroacetic acid but labile to thallium(III) trifluoroacetate/trifluoroacetic acid (Table 7). For example, the 4-methylbenzyl [Bzl(4-Me)] and acetamidomethyl (Acm) groups can be cleaved by thallium (III) trifluoroacetate/trifluoroacetic acid; however, the Bzl(4-Me) group can be cleaved under strong acid conditions (e.g., anhyd HF), in which the Acm group is not labile. Sequential protection–deprotection strategies of the Cys thiol have been reviewed extensively.^[165–168]

Table 7 Thiol Side-Chain Protecting Groups^[66,105,167,169–180]

Group	Structure	Deprotection	Ref
4-methylbenzyl [Bzl(4-Me)]		HF (or strong acid) Tl(COCF ₃) ₃ , TFA	[169] [105]
acetamidomethyl (Acm)		Hg(OAc) ₂ I ₂ Tl(COCF ₃) ₃ , TFA	[170] [66] [171]
trityl (Trt)		Hg(OAc) ₂ TFA (+ scavengers) Tl(COCF ₃) ₃ , TFA	[172] [173] [174]
tert-butyl (t-Bu)		Hg(OAc) ₂ Tl(COCF ₃) ₃ , TFA	[175,176] [174]
tert-butylsulfanyl (St-Bu)		thiol reduction phosphine reduction	[177,178] [179]
2,4,6-trimethoxybenzyl (Tmb)		dil TFA (+ scavengers) I ₂ Tl(COCF ₃) ₃ , TFA	[180] [167] [167]

21.11.1.7.1

**Variation 1:
4-Methylbenzyl Group**

The 4-methylbenzyl group [Bzl(4-Me)] is commonly used in the Boc/Bzl synthetic strategy because of its relative stability to trifluoroacetic acid and reagents used to cleave other thiol protections, but lability to strong acids, such as anhydrous hydrogen fluoride, and thallium(III) trifluoroacetate.

H-Cys[Bzl(4-Me)]-OH from H-Cys-OH:^[169]

Et₃N (7.75 mL, 55.5 mmol) and 4-methylbenzyl bromide (3.42 g, 18.5 mmol) were added to a soln of H-Cys-OH•HCl•H₂O (3.25 g, 18.5 mmol) in EtOH/H₂O (2:1, 30 mL). The mixture was stirred at rt for 12 h and filtered. The filter cake was washed well with H₂O and crystallized from EtOH/H₂O (3:2) to provide the product as a white solid; yield: not reported but probably quant; mp 209–211 °C (dec); *R*_f 0.19 (CHCl₃/MeOH/AcOH 17:2:1).

21.11.1.7.2

**Variation 2:
Acetamidomethyl Group**

The acetamidomethyl (Acm) group is a very stable cysteine protecting group, which is not cleaved by exposure to trifluoroacetic acid or anhydrous hydrogen fluoride. The Acm group can be cleaved by mercury(II)^[170] or thallium(III) salts,^[171] or by treatment with iodine.^[66] Because of its chemical stability, the Acm group has been particularly useful for protecting cysteines during multiple oxidation and ligation strategies.

H-Cys(Acm)-OH•HCl from H-Cys-OH•HCl:^[66,170,181]

H-Cys-OH•HCl (1.58 g, 10 mmol) and *N*-(hydroxymethyl)acetamide (0.89 g, 10 mmol) in TFA (10 mL) were stirred at rt for 30 min and concentrated to dryness; the residue was dissolved in 1 M HCl and concentrated to dryness. The treatment with HCl was repeated to give a residue which, after recrystallization (iPrOH), washing with Et₂O, and drying, yielded the product; yield: 1.62 g (71%); mp 166–168 °C (dec); [α]_D –33.2 (c 1, H₂O).

21.11.1.7.3

**Variation 3:
Trityl Group**

Among the most acid sensitive of the cysteine protecting groups, the trityl group is cleaved with trifluoroacetic acid under normal Fmoc/*t*-Bu cleavage conditions. The trityl group is thus recommended for general protection of cysteine residues in the Fmoc/*t*-Bu strategy. Moreover, *S*-tritylcysteine residues are simultaneously cleaved and oxidized by treatment with iodine^[182,183] to form disulfides prior to other protected cysteines, such as Cys(Acm) residues, which can enable sequential oxidation. Scavengers, such as trialkylsilanes, are generally necessary during cleavage of *S*-trityl groups to prevent alkylation of unprotected cysteine, methionine, or tryptophan residues^[180,184,185] by the trityl carbocation.

H-Cys(Trt)-OH from H-Cys-OH•HCl:^[186]

Into a 200-mL Erlenmeyer flask was placed H-L-Cys-OH•HCl (1.58 g, 10 mmol) and Trt-OH (2.60 g, 10 mmol) dissolved in glacial AcOH (10 mL). The soln was treated with BF₃•OEt₂ (1.40 mL, 11 mmol). The mixture was warmed for 30 min on a steam bath, kept at rt for 45 min, and transferred to a beaker containing EtOH (15 mL). The soln was treated with H₂O (5 mL) and powdered anhyd NaOAc (3 g). The addition of H₂O (40 mL) provided a gum that solidified when triturated with cold H₂O. After successive washings with H₂O, acetone, and Et₂O, the product was dried under reduced pressure over P₂O₅ and NaOH to yield the crude product; yield: 3.08 g (85%); mp 181–182 °C (dec). One recrystallization

(DMF/H₂O) raised the mp to 183.5 °C (dec); $[\alpha]_D^{24} +114 \pm 2$ (c 0.832, 0.04 M HCl/EtOH); reported^[173] mp 181–182 °C; $[\alpha]_D^{24} +108$ (c 1.45, 0.04 M HCl/EtOH).

21.11.1.7.4 Variation 4: tert-Butyl Group

The *tert*-butyl group is a relatively acid-stable protecting group for thiol groups, requiring orthogonal cleavage with mercury(II) or thallium(III) salts for efficient removal. Cleavage of *tert*-butyl sulfides with hydrogen fluoride at 0 °C in the presence of scavengers is possible, but can fail to go to completion.^[125,187–189]

H-Cys(*t*-Bu)-OH•HCl from H-Cys-OH•HCl:^[190,191]

A soln of H-Cys-OH•HCl (175.6 g, 1 mol) in a mixture of 2 M HCl (450 mL) and *t*-BuOH (123 mL, 1.3 mol) was refluxed for 10–12 h. Some 2-methylpropene was evolved. The soln was concentrated under reduced pressure and the crystalline product was filtered off and washed with anhyd acetone; yield: 209 g (90%); mp 198–200 °C. Recrystallization (4 M HCl) gave pure material; mp 204 °C; $[\alpha]_D^{20} +6.35$ (c 2, 5 M HCl); *R*_f 0.5 (BuOH/AcOH/H₂O 4:2:1).

21.11.1.7.5 Variation 5: tert-Butylsulfanyl Group

Stable to trifluoroacetic acid and relatively stable to hydrogen fluoride (at ≤0 °C), the *tert*-butylsulfanyl (*St*-Bu) group can be easily removed by reduction with thiols or with phosphines.

H-Cys(*St*-Bu)-OH from H-Cys-OH:^[177,178,192]

A soln of H-Cys-OH (48 g, 396 mmol) in 2 M NaOH (200 mL) was diluted with dioxane (300 mL), treated with *t*-BuSH (36 g, 346 mmol), and stirred vigorously (open to the air) for 12 h. Air was subsequently bubbled through the mixture until oxidation was complete, as monitored by the disappearance of free Cys on TLC plates. At worst, this oxidation takes 5–7 d; however, this process can be accelerated by the addition of more *t*-BuSH. After complete conversion was observed by TLC, the soln was acidified with glacial AcOH (50 mL) and concentrated under reduced pressure at 30 °C. The resulting residue was triturated with H₂O (50 mL) and digested subsequently into volumes of 50% aq AcOH (2 × 300 mL). The volumes were combined, concentrated to 100 mL in a rotary evaporator, and treated with H₂O (500 mL). The soln was left overnight at 0 °C and shiny needle-like crystals were obtained (65 g); another crop of crystals could be obtained from the mother liquor (5 g); yield: 70 g (85%); $[\alpha]_D^{20} -84 \pm 1$; $[\alpha]_{546}^{20} -100$ (c 1, 1 M HCl).

21.11.1.7.6 Variation 6: 2,4,6-Trimethoxybenzyl Group

The 2,4,6-trimethoxybenzyl (Tmb) group is among the most acid labile of the thiol protecting groups and is cleaved by as little as 6% trifluoroacetic acid in dichloromethane in the presence of 0.5% triisopropylsilane.^[180] The Tmb group is thus suitable for inclusion in the synthesis of acid-sensitive sequences by the Fmoc/*t*-Bu strategy.

H-Cys(Tmb)-OH•TFA from H-Cys-OH:^[180]

A suspension of L-cysteine (0.9 g, 7.4 mmol) in CH₂Cl₂ (60 mL) was stirred at <5 °C, treated dropwise with TFA (12.0 mL, 156 mmol) to completely dissolve the amino acid, treated dropwise with a soln of Tmb-OH^[180] (1.5 g, 7.5 mmol) in CH₂Cl₂ (30 mL) over 10 min, and concentrated under reduced pressure. The residue was triturated with anhyd Et₂O

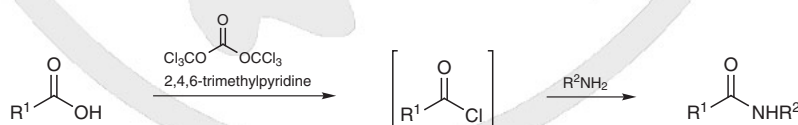
(50 mL), followed by Et₂O (200 mL), and filtered to provide a white solid; yield: 2.9 g (84%); mp 175–185 °C; *R*_f 0.72 (BuOH/pyridine/AcOH/H₂O 15:10:3:12); [α]_D –64.5 (*c* 1.0, H₂O).

21.11.2 Amino Acid Activation

21.11.2.1 Method 1: α -Amino Acid Halides

The acid halide mode of activation has been one of the most common approaches for peptide bond formation since Fischer used acid chloride activation to synthesize a dipeptide in 1903.^[193] Acid halides are used routinely in solution- and solid-phase peptide synthesis. They are often the method of choice for coupling hindered and weakly nucleophilic systems. Their high activity has, however, prevented the application of acid halides with certain *N* α - and side-chain protecting groups. For example, the *N* α -benzyloxycarbonyl- (Z) and *N* α -*tert*-butoxycarbonyl- (Boc) protected amino acid chlorides tend to react intramolecularly to form *N*-carboxyanhydrides and oxazol-5(4*H*)-ones.^[194,195] Amino acid chlorides bearing acid-labile side-chain protecting groups, such as *tert*-butyl esters, undergo cyclic anhydride formation and possess limited shelf life. *N* α -9-Fluorenylmethoxycarbonyl (Fmoc) acid chlorides, by contrast, are generally more stable and do not exhibit such side reactions. Furthermore, *N* α -Fmoc-amino acid chlorides have been used successfully in step-wise peptide synthesis both in solution and on solid phase. Additives, such as silver(I) cyanide and ammonium and potassium salts of 1*H*-benzotriazol-1-ol (HOBt), have also been used to prevent the formation of the oxazol-5(4*H*)-ones, which may occur in the presence of a tertiary amine. Alternatively, *N* α -Fmoc-amino acid chlorides may be generated and utilized in situ without side reactions in the absence of any additive by using reagents such as bis(trichloromethyl) carbonate (triphosgene) (Scheme 14).^[196] Generating the *N* α -Fmoc-amino acid chlorides in situ using bis(trichloromethyl) carbonate has also been performed with acid-labile side-chain protecting groups such as *t*-Bu, Trt, Boc, Ot-Bu, and Pmc.^[196] In contrast to *N* α -Fmoc-amino acid chlorides, *N* α -Fmoc-amino acid fluorides show a slow rate of oxazol-5(4*H*)-one formation in the presence of a tertiary amine, even in the case of amino acids bearing *t*-Bu, Boc, or *N*-Trt side-chain protection. *N* α -Fmoc-amino acid fluorides have served as common intermediates for both solution-^[197,198] and solid-phase peptide synthesis.^[197–201] Furthermore, *N* α -Z-amino acid fluorides and *N* α -Boc-amino acid fluorides, as well as other *N*-protected and side-chain protected acid halides, have been prepared and used for specific applications, as reviewed in *Houben–Weyl*, Vol. E 22a.^[202] α -Amino acid bromides are exceptionally active and thus are not employed routinely in peptide synthesis. However, when the appropriate *N* α -protecting group (e.g., oNbs,^[203] N₃^[204]) is employed, the amino acid bromides can be generated in situ and used efficiently for the solution preparation of peptides with extremely difficult sequences [e.g., L-Val(α Me) homopeptide].^[205]

Scheme 14 In Situ Preparation of α -Amino Acid Chlorides with Bis(trichloromethyl) Carbonate and Peptide Bond Formation^[196]

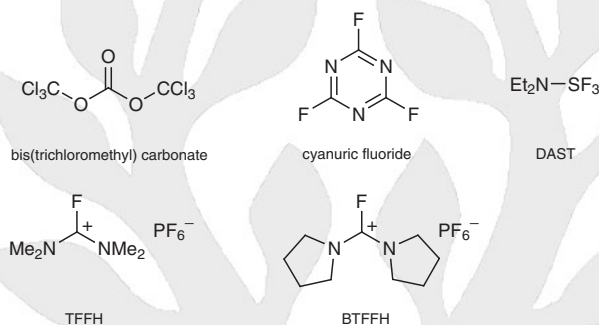


21.11.2.1.1

Variation 1:***N*^α-9-Fluorenylmethoxycarbonyl Amino Acid Chlorides**

Stable crystalline *N*-Fmoc-amino acid chlorides can be prepared from Fmoc-protected amino acids by treatment with thionyl chloride and by the reaction of the *N*-Fmoc-amino acid mixed anhydride with hydrogen chloride. These solids can be added together with the appropriate base to the coupling reaction. Alternatively, the acid chlorides can be generated and utilized in situ using the *N*-Fmoc-amino acid and an activating reagent, such as thionyl chloride,^[206] oxalyl chloride,^[207] bis(trichloromethyl) carbonate,^[196] 1-chloro-*N,N*,2-trimethylprop-1-en-1-amine,^[208] or other reagents^[209–211] (Scheme 15).

Scheme 15 Common Reagents Used for the Preparation of α -Amino Acid Chlorides and α -Amino Acid Fluorides^[196,206–208]

 **α,α -Dialkyl-Substituted *N*-Fmoc-Amino Acid Chlorides; General Procedure:^[212]**

CAUTION: Thionyl chloride reacts violently with water producing large volumes of corrosive gases. It is extremely destructive to all tissues.

A soln of the α,α -dialkyl-substituted *N*-Fmoc-amino acid (10 mmol) in CH_2Cl_2 (15 mL) was treated with freshly redistilled SOCl_2 (1.5 mL) and the mixture was stirred at rt for 10–12 h. The soln was concentrated and the residue was recrystallized (CH_2Cl_2 /hexane); yield: 75–87%.

Dipeptides Containing Sterically Hindered α,α -Dialkyl-Substituted Amino Acids; General Procedure Using *N*-Fmoc-Amino Acid Chlorides and KOBT:^[212,213]

To a soln of the amino ester hydrochloride (1 mmol) and KOBT (1 mmol) in CH_2Cl_2 (3 mL) was added a soln of α,α -dialkyl-substituted *N*-Fmoc-amino acid chloride (1 mmol) and KOBT (1 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 3–4 h, then washed with 5% NaHCO_3 , 5% HCl, H_2O , and brine (3 mL each). The organic layer was dried and concentrated to an oily residue, which was recrystallized (CH_2Cl_2 /hexane); yield: 70–80%.

H-Lys-Pro-Lys-Pro-Gly-Gly-Phe-Phe-Gly-Leu-Nle- NH_2 ; Typical Procedure for Solid-Phase Peptide Synthesis Using *N*-Fmoc-Amino Acid Chlorides:^[214]

CAUTION: DCC and other carbodiimides are acute skin irritants and allergenic in susceptible individuals. The carbodiimides should be handled with gloves in a fumehood. Since DCC has a low melting point (mp 34–35 °C), it can also be handled as a liquid after gentle warming in a water bath.

CAUTION: Anhydrous HF is colorless and extremely hazardous; exposure to trace amounts of HF can easily result in death or permanent injury. Anhydrous HF should only be handled with the utmost caution by appropriately trained personnel with HF-specific reaction equipment such as a Teflon vacuum line.^[215]

A norleucine resin was prepared by coupling Boc-Nle-OH to 4-methylbenzhydrylamine (MeBHA) resin using DCC/HOBt (3 equiv) in DMF. The Boc group was removed with 4 M HCl in dioxane for 30 min and the resin was neutralized with 10% Et₃N in CHCl₃ and washed with CH₂Cl₂ to afford the amine resin. The synthesis of the peptide was performed on the Nle (norleucine) resin (100 mg), which was treated with a soln of HOBt (0.3 mmol) and iPr₂NEt (0.3 mmol) in DMF (0.5 mL), followed by a soln of the *N*-Fmoc-amino acid chloride (0.3 mmol) in DMF (0.5 mL). Couplings were performed for 10 min, except in the case of Gly (3 × 10 min), Lys(Z) (2 × 10 min), and Pro (2 × 10 min). Completion of coupling was checked by the ninhydrin test (see Section 21.11.5.6.1).^[216] After incorporation of the last amino acid, the Fmoc group was removed and the resin was washed with DMF, CH₂Cl₂, AcOH, MeOH, and CH₂Cl₂. After drying, the resin was treated with HF (10 mL) containing DMS (0.5 mL) and anisole (0.5 mL) at 0 °C for 1 h; yield: 165 mg; amino acid analysis: Pro 1.9 (2), Gly 3.0 (3), Lys 1.8 (2), Phe 1.8 (2), Nle 1.0 (1), Leu 0.8 (1).

In Situ Generation and Utilization of *N*-Fmoc-Amino Acid Chlorides; General Procedure Using Bis(trichloromethyl) Carbonate:^[196]

The *N*-Fmoc-amino acid or *N*-Fmoc-*N*-methylamino acid (5 equiv, 0.275 mmol) and (Cl₃CO)₂CO (1.65 equiv, 0.09 mmol) were dissolved in THF (or dioxane, diglyme, or 1,3-dichloropropane) to give a 0.15 M soln and treated with 2,4,6-trimethylpyridine (14 equiv, 0.75 mmol) to yield a white suspension. After 1 min, the suspension was poured into the *N*-methylamino peptidyl resin, which was prewashed and swollen with the appropriate solvent, and preheated to 50 °C. The mixture was shaken at 50 °C for 1 h and filtered. In cases using *N*-Fmoc-amino acids and amino peptidyl resin, only 3 equiv of *N*-Fmoc-amino acid, 1 equiv of (Cl₃CO)₂CO, and 8 equiv of 2,4,6-trimethylpyridine were used in dioxane at rt for 1 h. The peptidyl resin was washed with CH₂Cl₂, swollen with the appropriate reaction solvent, and repeated in the case of difficult couplings; yield: not reported.

21.11.2.1.2

Variation 2:

***N*^α-9-Fluorenylmethoxycarbonyl Amino Acid Fluorides**

N-Fmoc-amino acid fluorides can be prepared from the corresponding *N*-Fmoc-amino acids using cyanuric fluoride or alternatively with *N,N*-diethylaminosulfur trifluoride (DAST), which permits the facile isolation of the acid fluorides from the water-soluble by-products. Similar to the acid chlorides, acid fluorides are added as solids together with a base to a solution of the desired amino ester or peptidyl resin in the coupling reaction. Analogously to acid chlorides, acid fluorides can also be prepared and utilized in situ using various reagents: fluoro-*N,N,N',N'*-tetramethylformimidamidium hexafluorophosphate (TFFH),^[217] fluoro-*N,N,N',N'*-bis(tetramethylene)formimidamidium hexafluorophosphate (BTFH),^[217] or 2-fluoro-1,3-dimethylpyridinium 4-toluenesulfonate (see Scheme 15).^[218]

***N*-Fmoc-Amino Acid Fluorides; General Procedure Using Cyanuric Fluoride:**^[198]

A soln of the *N*-Fmoc-amino acid (1 equiv), pyridine (1 equiv), and cyanuric fluoride (1 equiv) in CH₂Cl₂ was stirred at rt for 3–4 h, treated with ice water, and filtered to remove precipitated cyanuric acid. The organic phase was dried and evaporated to furnish the acid fluoride as a crystalline solid; yield: 70–96%. Specific physical properties and yields of different *N*^α-protected amino acid fluorides have been described.^[198]

Fmoc-Val-F; Typical Procedure Using Cyanuric Fluoride:^[197,213]

A soln of Fmoc-Val-OH (339 mg, 1 mmol), cyanic fluoride (700 μL, 8 mmol), and pyridine (81 μL, 1 mmol) in CH₂Cl₂ (5 mL) was heated at reflux under N₂ for 2 h. The mixture, from which a white water-soluble precipitate had settled, was extracted with ice water (2 ×

15 mL), dried (MgSO_4), and concentrated to a white solid that was recrystallized (CH_2Cl_2 /hexane); yield: 239 mg (70%); mp 113–114 °C.

Fmoc-Val-F; Typical Procedure Using DAST:^[213,219]

To a stirred soln of Fmoc-Val-OH (339 mg, 1 mmol) in CH_2Cl_2 (10 mL), DAST (1.2 mmol) was added at rt. After 10 min, the mixture was extracted with ice water. The organic layer was dried first with MgSO_4 and then with molecular sieves (10 Å). The solvent was removed under reduced pressure and the residue was recrystallized (CH_2Cl_2); yield: 259 mg (76%); mp 113–114 °C.

H-Ala-Asn-Lys-Gly-Phe-Leu-Glu-Glu-Val-OH; Typical Procedure:^[197]

Prothrombin (1–9) was assembled manually on a batch synthesizer in DMF soln using a TFA-sensitive polyamide resin (1 g) bearing Fmoc-Val ($0.1 \text{ mmol} \cdot \text{g}^{-1}$). The *N*-Fmoc-amino acid fluorides of Glu(*Ot*-Bu) (82 mg, 0.4 mmol), Leu (53 mg, 0.4 mmol), Phe (67 mg, 0.4 mmol), Gly (31 mg, 0.4 mmol), Lys(Boc) (99 mg, 0.4 mmol), and Ala (36 mg, 0.4 mmol) were introduced as 0.08 M solns in DMF containing iPr_2NEt (4 equiv); Asn was introduced as a Pfp ester. Removal of the Fmoc protection was performed using 20% piperidine in DMF ($2 \times 4 \text{ min}$). All washing steps employed DMF. Resin samples were removed after each 10 min coupling period and tested by the ninhydrin method (see Section 21.11.5.6.1). All couplings were complete after this time except for the Phe-to-Leu coupling, which required 25 min. Final deblocking and removal from the resin (950 mg; at each coupling stage, 5–10 mg of resin was lost due to the ninhydrin tests) was achieved with TFA (30 mL) containing 5% H_2O and 5% *m*-cresol at 20 °C for 2 h to give the peptide as the TFA salt; yield: 74 mg (63%); this coeluted with an authentic sample; MS/FAB: 1006 (MH^+); calcd 1005 (M).

21.11.2.2

Method 2:

α -Amino Acid Anhydrides

Peptide bond formation using α -amino acid anhydrides is routinely employed in both solution- and solid-phase peptide synthesis. Amino acid anhydrides can be generally divided into linear and cyclic analogues. Linear anhydrides can be further separated into mixed and symmetrical anhydrides. Cyclic anhydrides are formed from intermolecular reactions and include *N*-carboxyanhydrides (NCAs, Leuch's anhydrides), *N*-thiocarboxyanhydrides, *N*-substituted *N*-carboxyanhydrides, and urethane-protected *N*-carboxyanhydrides (UNCAs). The last anhydride is perhaps the best suited for solution- and solid-phase peptide synthesis, because coupling reactions using UNCAs proceed rapidly in various solvents without detectable racemization or formation of byproducts.

21.11.2.2.1

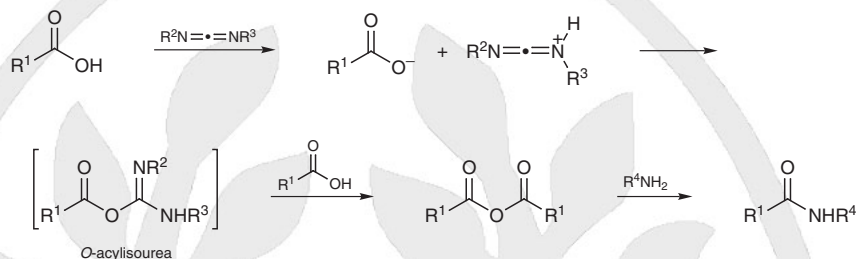
Variation 1:

Symmetrical Anhydrides

Symmetrical anhydrides are formed from the condensation of 2 equivalents of the same *N*-protected amino acid. They have been prepared by many methods, including the disproportionation of mixed anhydrides and reactions of 2 equivalents of the *N*-protected amino acid with 1 equivalent of a coupling agent such as ethoxyacetylene, diethyl(prop-1-ynyl)amine, and 1,1'-carbonyldiimidazole. The method most routinely used employs the reaction of 2 equivalents of *N*-protected amino acid with 1 equivalent of a carbodiimide, such as *N,N'*-dicyclohexylcarbodiimide (DCC), *N,N'*-diisopropylcarbodiimide (DIC), or *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (EDC) (Scheme 16). Symmetrical anhydrides are often used in solid-phase peptide synthesis (SPPS), because they give higher yields of peptides having greater purity than that achieved using carbodiimide procedures.^[220–223] In solution, however, the symmetrical anhydrides do not ex-

hibit significant advantages relative to the standard carbodiimide, mixed anhydride, or active ester methods with regard to yield and purity. Furthermore, because only one of the two amino acid equivalents is capable of peptide coupling, symmetrical anhydrides are not routinely applied in solution-phase synthesis.

Scheme 16 α -Amino Acid Symmetrical Anhydride Formation with Carbodiimides and Their Aminolysis^[220–223]



***N*-(Alkoxy carbonyl)amino Acid Anhydrides; General Procedure:**^[224]

CAUTION: Carbodiimides are severe eye, skin, and respiratory tract irritants, and skin sensitizers. They should only be handled with gloves in a fumehood.

A soln of the *N*-Z- or *N*-Boc-amino acid (2 mmol) and EDC (1 mmol) in CH_2Cl_2 (20 mL) was stirred at rt for 1 h (*N*-Z-amino acids; 0 °C for 2 h with *N*-Boc-amino acids). The solvent was removed at 0 °C to give a residue that was dissolved in EtOAc (25 mL). The soln was washed successively with ice-cold solns (2 × 10 mL) of citric acid (10%), brine, sat. NaHCO_3 , and brine. The organic phase was dried (MgSO_4), filtered, and concentrated at 0 °C. Crystals appeared immediately, or after storing at –5 °C. The crystals were washed with petroleum ether/ Et_2O (20:1); yield: 77–90% (*Z* anhydrides) or 50–86% (*Boc* anhydrides). The anhydrides showed characteristic IR absorptions (KBr or liq film) at ~1830 and 1750 cm^{-1} . Their ^1H NMR spectra (CDCl_3) were nearly identical to those of the starting acid except for the absence of the acidic proton at $\delta \sim 10$.

Symmetrical Anhydrides of *N*-Fmoc-Amino Acids for SPPS; General Procedure:^[225]

CAUTION: *N,N'*-Dicyclohexylcarbodiimide is a severe eye, skin, and respiratory tract irritant, and a skin sensitizer. Since it has a low melting point (34–35 °C), it can also be handled as a liquid after gentle warming in a water bath.

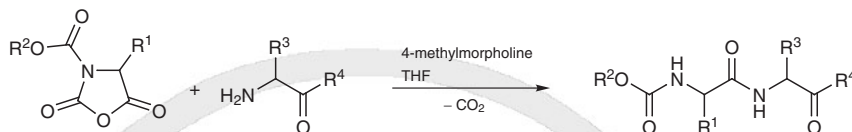
The *N*-Fmoc-amino acids (3.2 mmol) in CH_2Cl_2 /DMF (2:1, 6 mL) were reacted with DCC (1.6 mmol) in CH_2Cl_2 (4 mL) at 0 °C. After 30 min the DCU was filtered off and washed with CH_2Cl_2 /DMF (2:1, 2 mL). The combined filtrates and washings were used directly for coupling.

21.11.2.2.2

Variation 2:

Urethane-Protected Amino Acid *N*-Carboxyanhydrides

These cyclic anhydrides are the most routinely used anhydrides in both solution- and solid-phase peptide synthesis. UNCAs have been favored because they react rapidly in coupling reactions to give high yields of the pure product without detectable racemization or byproducts other than carbon dioxide (Scheme 17). Various UNCAs are conveniently prepared by condensing the appropriate chloroformate with the desired amino acid *N*-carboxyanhydride using the base 4-methylmorpholine as a promoter. UNCAs are generally stable, crystalline compounds that can be stored for a prolonged time at 0 °C.

Scheme 17 Peptide Bond Formation with Urethane-Protected *N*-Carboxyanhydrides**Asn-NCA from Boc-Asn-OH Using Thionyl Chloride:**^[226,227]

CAUTION: Thionyl chloride reacts violently with water producing large volumes of corrosive gases. It is extremely destructive to all tissues.

To a suspension of Boc-Asn-OH (88.4 g, 0.38 mol) in THF (1.0 L) at 0–5 °C, SOCl₂ (45.3 g, 0.38 mol) was added dropwise over 1 h, and stirring was continued at 0–5 °C for 2 h and at rt for 1 h. The precipitate was collected by filtration, washed with Et₂O (4 × 200 mL), and dried; a second crop was isolated from the mother liquors by concentration; yield: 55.9 g (93%); IR (THF) $\tilde{\nu}_{\text{max}}$: 1860, 1790, 1694 (C=O) cm⁻¹.

***N*-Fmoc-Amino Acid NCAs; General Procedure:**^[228]

The amino acid NCA (20 mmol) was dissolved in THF (67 mL) (dried over 4-Å molecular sieves) under N₂ and cooled to about 2 °C, with stirring, in an ice bath. Fmoc-Cl (22 mmol) was added all at once, followed by the slow addition of anhyd 4-methylmorpholine (29 mmol). The resulting suspension was stirred at 2–5 °C for 2 h, after which time 4 M HCl in dioxane was added slowly until a pH of 4–5 (sample diluted in H₂O) was obtained. The solids were removed by filtration and washed with anhyd THF. The combined THF solns were concentrated under reduced pressure and the resulting oil was dissolved in a minimum volume of anhyd iPr₂O. Anhyd hexane was added until the mixture went cloudy, and the soln was kept at –20 °C overnight. The resulting crystalline product was collected by filtration, washed with anhyd hexane, and dried under high reduced pressure; yield: 50–70%.

Acyl Carrier Decapeptide (65–74, VQAADYING); Typical Procedure Using UNCAs on a Solid Support:^[228]

CAUTION: When using phosphonium reagents containing the tris(dimethylamino) residue, hexamethylphosphoric triamide (HMPA) is produced. HMPA is a known human carcinogen^[153] and an eye and skin irritant and adequate precautions must be taken to avoid exposure to this compound.

In a flow reactor, a column was charged with Fmoc-glycine resin (0.8 g, 0.36 mequiv·g⁻¹) and equilibrated with anhyd DMF (all solvents were dried by being passed through a column of 4-Å molecular sieves) at a flow rate of 11 mL·min⁻¹. The resin was allowed to react sequentially with a threefold excess of each of the *N*-Fmoc-amino acid NCAs according to the following protocol: (1) Fmoc deprotection (10% piperidine in DMF) for 10 min at 11 mL·min⁻¹; (2) washing (DMF) for 5 min at 11 mL·min⁻¹; (3) coupling (0.15 M UNCA in DMF) for 45 min at 11 mL·min⁻¹; (4) washing (DMF) for 5 min at 11 mL·min⁻¹; (5) repeat steps 1–4. Fmoc-Tyr(*t*-Bu)-OH was coupled using the benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) reagent^[229] to demonstrate compatibility of the Fmoc-NCA procedure with standard peptide synthesis procedures. After deprotection of the terminal protecting group, the resin was removed from the column, washed with anhyd CH₂Cl₂, and dried under reduced pressure. The peptide was cleaved from the resin on treatment for 1 h with 50% TFA in anhyd CH₂Cl₂ containing 2.5% anisole and 2.5% pentamethylbenzene. After removal of solvents under reduced pressure and lyophilization, the crude acyl carrier peptide (65–74) was obtained; yield: 0.223 g (73%); amino

acid analysis: Val 1.00 (1.00), Gln 1.02 (1.00), Ala 2.08 (2.00), Ile 2.05 (2.00), Asp+Asn 2.20 (2.00), Tyr 1.05 (1.00), Gly 1.00 (1.00); FAB MS (MH^+): calcd 1064, found 1064.

21.11.2.2.3 Variation 3: Mixed Anhydrides

The term “mixed anhydride” applies generally to anhydrides that are not symmetrical. The most common mixed anhydrides in peptide chemistry are carboxylic acid–carbonic acid anhydrides, which are mainly employed in solution, where they react rapidly at low temperature to give pure product in high yield. Because mixed anhydrides are prone to racemization, they are used under stringent conditions.^[230] Mixed anhydrides have not found general use in solid-phase peptide synthesis (SPPS), mainly because of their limited stability at room temperature. In addition, in the case of mixed carboxylic-carbonic acid anhydrides, reaction at the carbonic acid carbonyl terminates the peptide chain elongation. Alternative mixed anhydrides derived from inorganic acids, such as phosphorus and sulfur, have also been used in peptide synthesis^[231,232] but have not yet gained general applicability.

Bz-Leu-Gly-OEt ; Typical Procedure Using a Mixed Carboxylic Acid–Carbonic Acid Anhydride:^[230]

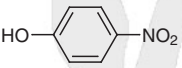
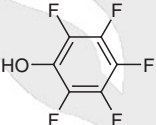
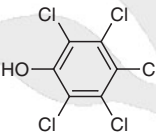
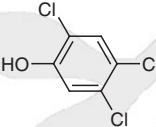
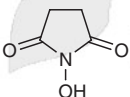
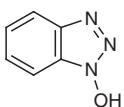
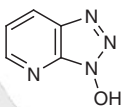
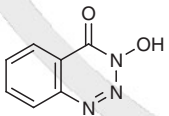
A stirred, chilled ($-15\text{ }^{\circ}\text{C}$) soln of Bz-L-Leu-OH (2.35 g, 10 mmol) in dry THF (50 mL) was treated with 4-methylmorpholine (1.10 mL, 10 mmol), followed by isobutyl chloroformate (1.39 mL, 10.5 mmol), stirred for 4 min, and treated with H-Gly-OEt (1.11 mL, 10.5 mmol). After 1 min, the bath was removed and the mixture was allowed to stand at rt for 0.5 h. The solvent was removed under reduced pressure, and the residue was redissolved in a mixture of CHCl_3 (15 mL), EtOAc (85 mL), and H_2O (10 mL). The aqueous layer was removed and the organic layer was washed successively with sat. NaHCO_3 , H_2O , 1 M HCl, and H_2O (10 mL each), dried (Na_2SO_4), and concentrated under reduced pressure. The crystalline residue was washed out of the flask with warm Et_2O (20 mL), followed by an Et_2O wash to give the title compound (2.90 g). A second crop could be obtained by concentration of the Et_2O extracts and recrystallization of the residue (warm $\text{EtOH}/\text{H}_2\text{O}$); yield: 2.99 g (93%); mp $157\text{--}158\text{ }^{\circ}\text{C}$; $[\alpha]_D^{25} -32.5 \pm 0.5$ (c 3, EtOH).

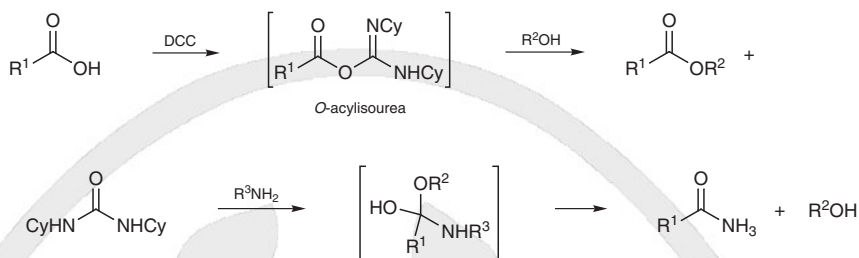
21.11.2.3 Method 3: Active Esters

Activated amino acid derivatives can be formed by condensation of an N-protected amino acid and an electron-deficient hydroxy compound. The hydroxy components that are most commonly used for this purpose (Table 8) are substituted phenols, such as 4-nitrophenol,^[233] pentafluorophenol,^[234] pentachlorophenol,^[235] and trichlorophenol,^[236] as well as substituted hydroxylamines such as N-hydroxysuccinimide,^[237–240] 1H-benzotriazol-1-ol (HOBt),^[241] 7-aza-1H-benzotriazol-1-ol (HOAt),^[242] and 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HODhbt).^[243] These active esters are typically synthesized by forming a more reactive carboxylate intermediate and reacting it with the hydroxy component. For example, activation of the carboxylate moiety has been performed with carbodiimides to give O-acylisoureas (Scheme 18) as well as thionyl chloride to generate acid chlorides, both of which react in situ with the hydroxy compound to provide active esters. The carboxylate can also be acylated with a suitable carbonate to prepare a mixed carboxylic acid–carbonic acid anhydride that reacts with the displaced hydroxy component to form the active ester, carbon dioxide, and another hydroxy derivative. Peptide bond formation occurs by aminolysis of the active ester via a tetrahedral intermediate, the breakdown of which is usually rate limiting (Scheme 18). The rates of aminolysis of substituted phenyl esters are directly related to the relative acidity of the parting phenol: pentafluorophenol > penta-

chlorophenol > 2,4,5-trichlorophenol > 4-nitrophenol.^[234–236] HODhbt esters have been shown to be five times as reactive as pentafluorophenyl esters.^[244] Active esters are used routinely for single residue extensions of peptides in solution. Active esters, such as 4-nitrophenyl, pentafluorophenyl, and HODhbt esters, have also been used successfully in solid-phase peptide synthesis. Furthermore, the above-mentioned hydroxy compounds, specifically *N*-hydroxysuccinimide (HOSu),^[237–240] HOBt,^[241] HODhbt,^[243] and HOAt,^[242,245] are commonly used as additives in carbodiimide-mediated reactions for the purpose of suppressing side reactions and epimerization.

Table 8 Commonly Used Hydroxy Moieties in Active Ester Formation^[233–237,241–243]

HOR ²	Abbreviation	Ref
	HONp	[233]
	HOPfp	[234]
	HOPcp	[235]
	HOTcp	[236]
	HOSu	[237]
	HOBt	[241]
	HOAt	[242]
	HODhbt	[243]

Scheme 18 Active Ester Synthesis with *N,N'*-Dicyclohexylcarbodiimide and Aminolysis

21.11.2.3.1

**Variation 1:
Halogenated Phenyl Esters**

For amide bond synthesis, the most commonly used halogenated phenyl esters are 2,4,5-trichlorophenyl,^[236] pentachlorophenyl,^[235] and pentafluorophenyl.^[234] These halogenated aryl esters have replaced 4-nitrophenyl esters^[233] in peptide chemistry because of their greater reactivity. Such *N*-Boc-protected α -amino acid phenyl esters have been used successfully in solution-phase synthesis. Their Fmoc counterparts are commonly employed in solid-phase peptide synthesis. Halogenated phenyl esters are usually prepared from the substituted phenol and an *N*-protected α -amino acid which is activated with a carbodiimide, mixed carbonate, or thionyl chloride.

Fmoc-Xaa-OPfp; General Procedure Using DCC:^[246,247]

CAUTION: DCC is a severe eye, skin, and respiratory tract irritant, and a skin sensitizer. Since it has a low melting point (34–35 °C), it can also be handled as a liquid after gentle warming in a water bath.

To a stirred, ice-cooled soln of Fmoc-Xaa-OH (2 mmol) and HOPfp (2 mmol) in dry dioxane, EtOAc, or a mixture of one of these solvents with DMF (5–10 mL), DCC (2 mmol) was added and stirring was continued at 0 °C for 1 h and at rt for 1 h. The DCU was removed by filtration, the filtrate was concentrated, and the residue was triturated with hexane. The active ester product was recrystallized (EtOAc or EtOAc/hexane); yield: 61–99%.

Fmoc-Xaa-OPfp; General Procedure Using Thionyl Chloride:^[247,248]

CAUTION: Thionyl chloride reacts violently with water producing large volumes of corrosive gases. It is extremely destructive to all tissues.

A mixture of Fmoc-Xaa-OH (2 mmol) and SOCl₂ (20 mmol) in CH₂Cl₂ (12 mL) was refluxed until complete conversion into the acid chloride was indicated by TLC analysis [an aliquot was diluted with dry MeOH to give the derived methyl ester that was analyzed by TLC using petroleum ether/EtOAc/AcOH (15:5:1) as eluent]. Residual SOCl₂ was removed under reduced pressure. The Fmoc-Xaa-Cl was dissolved in THF (10 mL), treated with HOPfp (2.1 mmol), cooled in an ice bath, and treated with pyridine (3 mmol), with stirring. The soln was diluted with THF (40 mL) and washed with cold brine (2 ×), dried (MgSO₄), and concentrated to a residue that was triturated with petroleum ether to afford a crude product contaminated with the starting Fmoc-Xaa-OH, which was typically removed by recrystallization; yield: 81–93%.

Fmoc-Asp(Ot-Bu)-Phe-NH₂; Typical Procedure Using the Pentafluorophenyl Ester:^[246]

To a stirred suspension of H-Phe-NH₂•HBr (1.67 g, 6.8 mmol) and Et₃N (1.90 mL, 13.6 mmol) in DMF (10 mL), Fmoc-Asp(Ot-Bu)-OPfp (3.92 g, 6.8 mmol) was added and stir-

ring was continued for 10 min. The mixture was then concentrated. The residue was dissolved in CHCl_3 (50 mL), washed with 1 M HCl (3×15 mL), then 5% NaHCO_3 (3×15 mL), dried (Na_2SO_4), and concentrated to a residue that was recrystallized (MeOH, 10 mL); yield: 2.94 g (77%); mp 174–175 °C.

21.11.2.3.2

**Variation 2:
Hydroxylamine-Derived Esters**

A series of useful active esters has been conceived by amplifying the electrophilicity of *O*-acylhydroxylamines on placement of the nitrogen in an electron-deficient heterocycle, including succinimido,^[237–240] benzotriazolyl,^[241] and 4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl esters.^[243] The succinimido esters have been routinely used because of their facile preparation and purification, their high reactivity, and the ease of removal of the liberated *N*-hydroxysuccinimide, which is soluble in water. They are used mainly for the stepwise synthesis of peptide segments in solution, yet are not generally employed in solid-phase peptide synthesis, where the more reactive benzotriazolyl and 4-oxo-3,4-dihydro-1,2,3-benzotriazin-3-yl esters are generally used without isolation. The hydroxylamine-derived esters can be prepared by the carbodiimide, mixed carbonate, or thionyl chloride methods.

Z-Gly-OSu; Typical Procedure Using DCC:^[237]

CAUTION: DCC is a severe eye, skin, and respiratory tract irritant, and a skin sensitizer. Since it has a low melting point (34–35 °C), it can also be handled as a liquid after gentle warming in a water bath.

A cooled soln of Z-Gly-OH (26.3 g, 126 mmol) and HOSu (14.5 g, 126 mmol) in dioxane (250 mL) was treated with DCC (26 g, 126 mmol) and allowed to stand in the refrigerator overnight. The formed DCU was filtered and washed with dioxane. The filtrate was concentrated under reduced pressure to yield a yellow oil that crystallized. The solid was triturated with Et_2O and filtered to give the ester; yield: 37.5 g (97%); mp 108–111 °C. Recrystallization (CH_2Cl_2 /petroleum ether) gave the pure ester; yield: 33 g (86%); mp 113–114 °C.

N-Protected Xaa-OSu ; General Procedure Using the Mixed Carbonate Method:^[247,249]

A mixture of the *N*-protected amino acid (0.5 mmol), isopropenyl succinimido carbonate (0.5 mmol), and DMAP (6.1 mg, 0.05 mmol) in MeCN (3 mL) was stirred at rt for 4 h and concentrated under reduced pressure to a residue that was dissolved in EtOAc (100 mL), washed successively with 1 M HCl (50 mL), H_2O (50 mL), 5% NaHCO_3 (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was generally crystallized from MeCN or dioxane; yield: 88–98%.

Z-Pro-Gly-OH; Typical Procedure Using the *N*-Hydroxysuccinimide Ester:^[237]

A soln of Z-Pro-OSu (1.73 g, 5 mmol) in EtOH (17 mL) was added to a soln of H-Gly-OH (380 mg, 5 mmol) and NaHCO_3 (840 mg, 100 mmol) in H_2O (12 mL). After 18 h, the soln was concentrated under reduced pressure. Acidification to pH 2 with concd HCl gave an oil that crystallized on cooling. The solid was collected and dried (1.4 g); mp 116–124 °C. Recrystallization (EtOAc/petroleum ether) gave the pure product; yield: 1.12 g (72%); mp 124–125 °C.

21.11.2.3.3

**Variation 3:
4-Nitrophenyl Esters**

4-Nitrophenyl esters^[233] are usually crystalline solids that can be prepared using the carbodiimide and mixed carbonate methods. The 4-nitrophenyl esters of N-protected glutamine and asparagine are particularly important because they can circumvent the amide dehydration, which may occur during their DCC-mediated coupling.

Fmoc-Xaa-ONp; General Procedure Using DCC:^[250]

CAUTION: DCC is a severe eye, skin, and respiratory tract irritant, and a skin sensitizer. Since it has a low melting point (34–35 °C), it can also be handled as a liquid after gentle warming in a water bath.

A 0.3 M soln of Fmoc-Xaa-OH (1 equiv) in EtOAc was treated with HONp (1.2 equiv), cooled and stirred in an ice-water bath, treated with DCC (1 equiv), and stirred at 0 °C for 30 min and at rt for an additional 2 h. The consumption of DCC was monitored by the disappearance of the IR band at 2100 cm⁻¹, and if necessary, more time was allowed for the completion of the reaction. The precipitated DCU was removed by filtration and the solvent was removed under reduced pressure. The residue was recrystallized (95% EtOH/AcOH 99:1). Certain N-Fmoc-amino acids that were not sufficiently soluble in EtOAc were esterified in different solvents, e.g. Fmoc-L-Pro in EtOAc/THF (1:1); yield: 38–94%.

Boc-Gln-Asn-Cys(EC)-Pro-OH; Typical Procedure Using Boc-Gln-ONp:^[251]

Boc-Asn-Cys(EC)-Pro-OH (EC = ethylcarbamoyl; 2.1 g, 4.0 mmol) was treated with TFA (20 mL) for 20 min and the TFA was removed by rotary evaporation. The residue was triturated with Et₂O, washed with Et₂O, and dried under reduced pressure. The peptide salt was dissolved in DMF (13 mL) and neutralized to pH 7.5 with iPr₂NEt (1.0 mL, 6.0 mmol). Boc-Gln-ONp (1.7 g, 4.8 mmol) was added to the mixture. The reaction progress was monitored using the ninhydrin test (see Section 21.11.5.6.1). After 20 h, the pH was adjusted back up to 6.5 with iPr₂NEt (0.5 mL, 3 mmol) and the reaction was continued for 2 h. The soln was cooled to 0 °C, treated with TFA (0.7 mL, 9.5 mmol), and added slowly to EtOAc (150 mL), with rapid stirring. During the addition the product precipitated and the resulting suspension was stored at 8 °C for 2 h. The precipitate was collected by filtration, washed with EtOAc and Et₂O, and dried under reduced pressure (2.58 g); mp 119–124 °C. This material was triturated in boiling EtOAc (50 mL), cooled to 8 °C, and the precipitate was collected by filtration, washed with EtOAc and Et₂O, and dried under reduced pressure to furnish the title peptide; yield: 2.37 g (94%); mp 133–135 °C; [α]_D²² –51.2 (c 0.88, DMF).

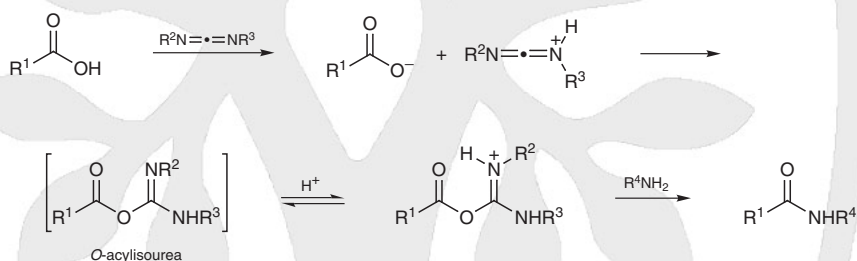
21.11.2.4

**Method 4:
Carbodiimides**

Carbodiimides are one of the most frequently used reagents for amide bond formation in both solution- and solid-phase peptide syntheses. Introduced in 1955 by Sheehan and Hess^[252] for the preparation of esters and amides of amino acids and peptides, carbodiimide methods gained popularity due to their efficiency, high reaction rate, tolerance to a variety of solvents, and low cost. Commercially available reagents include dicyclohexylcarbodiimide,^[253] diisopropylcarbodiimide,^[253] N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide, and its corresponding hydrochloride salt (Table 9).^[254–256] The carbodiimide method suffers, however, from several drawbacks, which lead to the formation of side products and racemization. Furthermore, DCC and other carbodiimides are acute skin irritants and allergenic in susceptible individuals. The major byproduct generated from carbodiimide-mediated coupling is the corresponding urea from the hydration of the carbo-

diimide reagent (Scheme 19). Ureas such as *N,N'*-dicyclohexylurea (DCU) are generally insoluble in most organic solvents and may be removed by filtration. Alternatively, water-soluble carbodiimides such as EDC furnish ureas that can be separated by aqueous extraction.^[254–256] *N*-Acy lurea formation may be a significant side product from carbodiimide activation and results from intramolecular rearrangement of the *O*-acylisourea intermediate by an *O*→*N* acyl group migration (Scheme 20).^[257] *N*-Acy lurea formation reduces coupling yields by decreasing the amount of reactive carboxy component. In addition, *N*-acylureas can exhibit similar solubility to the desired amide products and may thus be difficult to separate. Water-soluble carbodiimides, such as EDC, can facilitate removal of *N*-acylurea which becomes water soluble. Activation of glutamine and asparagine using carbodiimides can cause side-chain dehydration to afford the corresponding ω -nitriles. Dehydration can be minimized by using amide protecting groups such as ω -trityl^[161] and ω -9*H*-xanthen-9-yl^[258] (see Section 21.11.1.6), as well as nucleophiles such as HOBT.^[243] Racemization during carbodiimide-mediated coupling can occur by proton abstraction from oxazol-5(4*H*)-one and *O*-acylisourea intermediates (see also Section 21.11.3). Racemization may be suppressed by auxiliary nucleophiles or additives, such as HOBT,^[243] HOAt,^[242] HOSu,^[259] and HODhbt,^[243] which can convert the *O*-acylisourea intermediate into less reactive active esters (see Section 21.11.2.3). Carbamate- and 2-nitrophenylsulfanyl-protected amino acids^[260] are also less susceptible to racemization. In addition to their use in peptide bond formation, carbodiimides are also extensively utilized for the preparation of symmetrical anhydrides (see Section 21.11.2.2) and active esters (see Section 21.11.2.3).

Scheme 19 Peptide Bond Formation Using Carbodiimides^[253–256]



Scheme 20 *N*-Acy lurea Formation^[257]

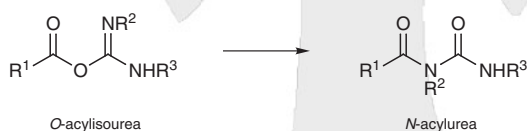


Table 9 Commonly Used Carbodiimides, $R^2-N=C=N-R^3$ ^[252,253,256]

R^2	R^3	Abbreviation	Solubility	Ref
Cy	Cy	DCC	CH_2Cl_2 , THF, MeCN, DMF	[252,253]
iPr	iPr	DIC	DMF	[253]
Et	$(CH_2)_3NMe_2 \cdot HCl$	EDC	H_2O , CH_2Cl_2 , DMF, THF	[256]

21.11.2.4.1

Variation 1:

Synthesis of Peptides in Solution Using Carbodiimides

Peptide synthesis in solution is commonly performed using various carbodiimides contingent on the coupling participants and potential byproducts. Although carbodiimides can be used without auxiliary nucleophiles or additives when coupling suitably *N*-protected

amino acids and peptide fragments bearing a glycine or proline residue at the C-terminus, additives such as HOBt^[243] or HOSu^[259] are frequently used because they suppress side reactions such as the formation of N-acylureas.

Boc-Val-Dpg-OMe Using DCC Without Additional Additives:^[261]

CAUTION: DCC and other carbodiimides are acute skin irritants and allergenic in susceptible individuals. The carbodiimides should be handled with gloves in a fumehood. Since DCC has a low melting point (mp 34–35 °C), it can also be handled as a liquid after gentle warming in a water bath.

A soln of Boc-Val-OH (4.3 g, 20.0 mmol) in CH₂Cl₂ (20 mL) was treated with H-Dpg-OMe (Dpg = C^{α,α}-dipropylglycine; 5.20 g, 30 mmol) (obtained from free-basing its ester hydrochloride) followed by DCC (4.0 g, 20.0 mmol). The mixture was stirred at rt for 48 h. The solvent was removed under reduced pressure and EtOAc (~25 mL) was added to the residue. Insoluble DCU was removed by filtration and the filtrate was washed with brine, 2 M HCl (2 × 50 mL), 1 M Na₂CO₃ (2 × 50 mL), and brine, dried (Na₂SO₄), filtered, and the solvent was removed under reduced pressure to give the title dipeptide as a gum; yield: 6.0 g (80%).

Boc-Leu-Ala-Val-Leu-Aib-Val-OMe Using DCC/HOBt:^[262]

CAUTION: HOBt is commercially available with or without water of crystallization; the hydrated form can be used for peptide coupling by the DCC/HOBt method. However, when water-free material is required, drying should be carried out carefully, as HOBt (and HOAt) decompose in a rapid exothermal reaction above 180 °C. Water-free HOBt can also be obtained by recrystallization from EtOH or EtOH/Et₂O.

HCO₂H (9 mL) was added to Boc-Leu-Aib-Val-OMe (Aib = α-aminoisobutyric acid; 0.98 g, 2.28 mmol). The Boc group removal was monitored by TLC until complete deprotection, and the HCO₂H was removed under reduced pressure. The residue was taken up in H₂O (10 mL) and washed with Et₂O (2 × 20 mL). The aqueous layer was adjusted to ca. pH 8 with Na₂CO₃ and extracted with EtOAc (4 × 30 mL). The EtOAc extracts were pooled, dried (Na₂SO₄), filtered, and concentrated to about 5 mL; this sample was ninhydrin positive. The free-based tripeptide was added to an ice-cooled soln of Boc-Leu-Ala-Val-OH (1.18 g, 2.94 mmol), DCC (0.6 g, 2.94 mmol), and HOBt (0.4 g, 2.94 mmol) in DMF (10 mL), stirred, and allowed to warm to rt for 4 d. After this period, EtOAc (15 mL) was added to the mixture and DCU was removed by filtration. The organic filtrate was washed with 2 M HCl (3 × 30 mL), 1 M Na₂CO₃ (3 × 30 mL), and brine (3 × 30 mL), dried (Na₂SO₄), and concentrated to yield the hexapeptide as a white solid; yield: 1.49 g (76%); mp 175–178 °C.

21.11.2.4.2

Variation 2:

Solid-Phase Peptide Synthesis Using Carbodiimides

Solid-phase peptide synthesis is generally performed in one of two chemical pathways: the Boc/Bzl and Fmoc/*t*-Bu approaches. In the Boc/Bzl strategy, DCC is the carbodiimide of choice, because the formed *N,N'*-dicyclohexylurea (DCU) can be effectively filtered with the trifluoroacetic acid/dichloromethane mixture employed in the Boc cleavage steps. In the Fmoc/*t*-Bu approach, DIC is generally utilized as the activating agent owing to the high solubility of the byproducts in the solvents used in this strategy. In both approaches the amino acid is preactivated with the carbodiimide before addition to the solid support to form the corresponding symmetrical anhydride or active ester; the latter is formed by a preactivation step in the presence of an additive such as HOBt. The urea byproducts may be removed by filtration and the solvent may be changed from dichloro-

methane to dimethylformamide or dichloromethane/dimethylformamide mixtures, prior to the reaction with the solid support.

SPPS with *N*-Boc-Amino Acid Symmetrical Anhydrides:^[263,264]

CAUTION: DCC is a severe eye, skin, and respiratory tract irritant, and a skin sensitizer. Since it has a low melting point (34–35 °C), it can also be handled as a liquid after gentle warming in a water bath.

A soln of the *N*-Boc-amino acid (8 equiv) in CH₂Cl₂ at 4 °C was treated with DCC (4 equiv), left for 5–15 min, filtered, and the filtrate was diluted with DMF and added to the resin-bound amino component. After 30 min, the resin was filtered and washed with DMF; yield: not reported.

SPPS with *N*-Fmoc-Amino Acid Active Esters:^[263,264]

CAUTION: Carbodiimides are severe eye, skin, and respiratory tract irritants, and skin sensitizers. They should only be handled with gloves in a fumehood.

CAUTION: HOBt is commercially available with or without water of crystallization; the hydrated form can be used for peptide coupling by the DCC/HOBt method. However, when water-free material is required, drying should be carried out carefully, as HOBt (and HOAt) decompose in a rapid exothermal reaction above 180 °C. Water-free HOBt can also be obtained by recrystallization from EtOH or EtOH/Et₂O.

The *N*-Fmoc-amino acid (4 equiv) was dissolved in CH₂Cl₂ at 4 °C with a minimum amount of DMF, treated with HOAt or HOBt (4 equiv) and DIC (4 equiv), left for 5–15 min at 4 °C, diluted with DMF, and added to the resin-bound amino component. After 30 min the resin was filtered and washed with DMF; yield: not reported.

21.11.2.5

Method 5: Phosphonium and Uronium/Guanidinium Salts

These coupling reagents are among the most widely used in both solution- and solid-phase peptide syntheses; many variants are commercially available. In general, these reagents are based on a similar structure in which a central atom (phosphorus or carbon) is linked to a series of electron-withdrawing substituents that stabilize a cationic charge which is usually neutralized by a hexafluorophosphate or tetrafluoroborate counterion (Table 10). In accordance with their structural similarity, these reagents function by a similar mechanism for peptide bond formation (Schemes 21 and 22). First, the carboxylate ion, generated usually from the reaction of the carboxylic acid with a tertiary amine, attacks the cationic center with consequent release of an *N*-hydroxy substituent to furnish a highly reactive intermediate (i.e., acyloxyphosphonium^[265] or acyluronium ion^[266]), which may acylate the amine component or react with the displaced *N*-hydroxy component to provide an active ester. The active ester has been suggested to be the predominant species undergoing aminolysis.^[265,267,268] In the case of halophosphonium^[265] or haloformamidinium^[269] reagents, the intermediate acyloxyphosphonium or acyluronium ions may react with the acid to give a symmetric anhydride intermediate or undergo intramolecular cyclization to an oxazolone, both of which may then be aminolyzed.

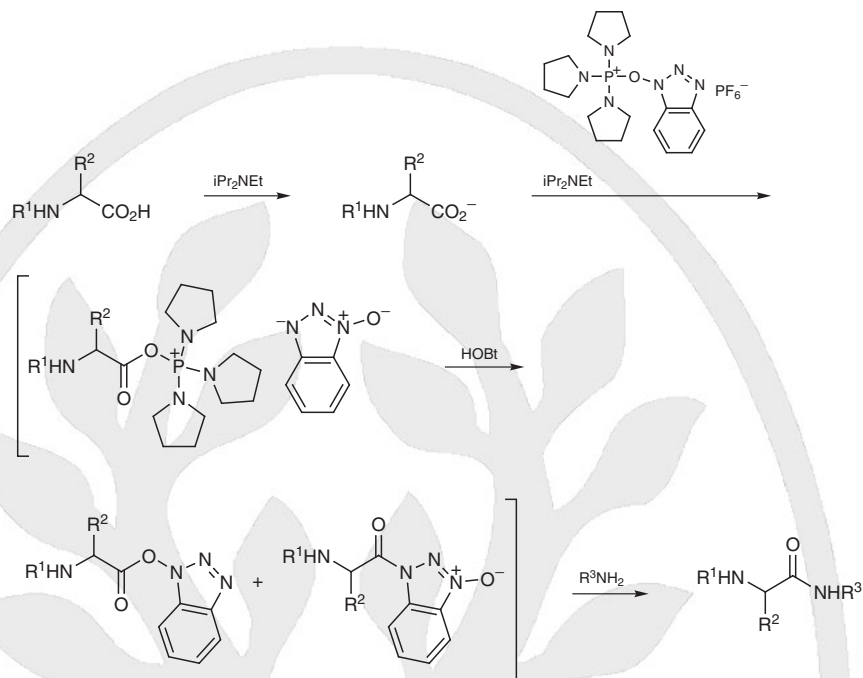
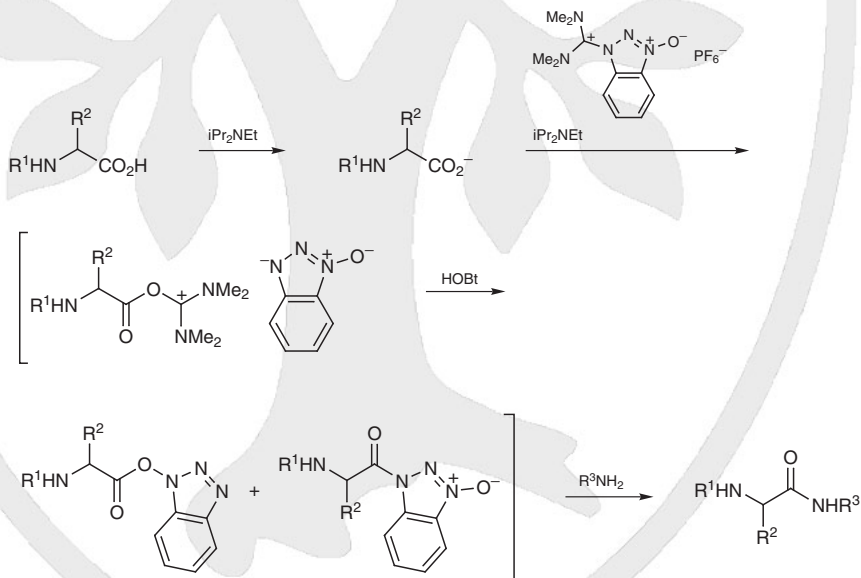
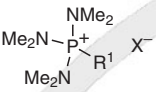
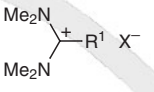
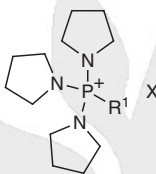
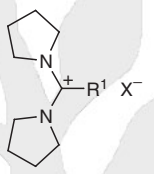
Scheme 21 Peptide Bond Formation with the Phosphonium Salt PyBOP^[265]**Scheme 22** Peptide Bond Formation with the Uronium/Guanidinium Salt HBTU^[266]

Table 10 Structures of Phosphonium and Uronium/Guanidinium Salts^[229,242,245,265,266,270–281]

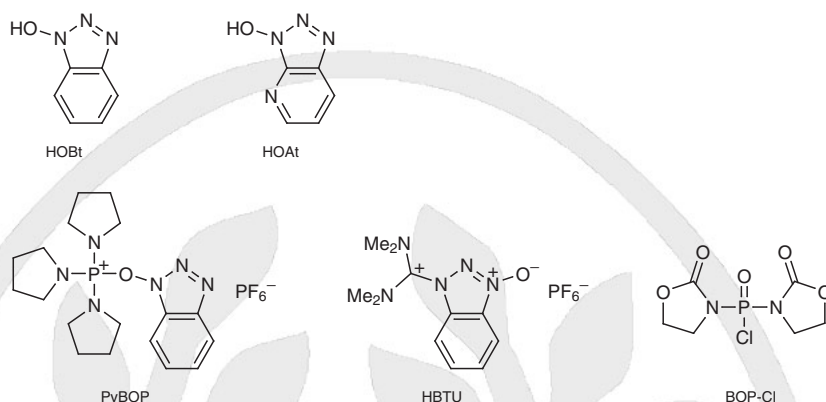
Phosphonium Salts				Uronium/Guanidinium Salts			
R ¹	X	Abbreviation	Ref	R ¹	X	Abbreviation	Ref
							
OBt	PF ₆	BOP	[229,273,274]	OBt	PF ₆	HBTU	[266,275]
OAt	PF ₆	AOP	[276]	OBt	BF ₄	TBTU	[277]
Br	PF ₆	BroP	[278]	OAt	PF ₆	HATU	[276]
							
OBt	PF ₆	PyBOP	[279,280]	OBt	PF ₆	HBPyU	[272]
OAt	PF ₆	PyAOP	[281]	OBt	BF ₄	TBPyU	[270,271]
Br	PF ₆	PyBroP	[265]	OAt	PF ₆	HAPyU	[242,245]
Cl	PF ₆	PyCloP	[265]	OAt	PF ₆	4-HAPyU ^a	[242,245]

^a 4-HAPyU = O-(4-azabenzotriazol-1-yl)-N,N,N',N'-bis(tetramethylene)uronium hexafluorophosphate.

21.11.2.5.1

**Variation 1:
Phosphonium Salts**

Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP)^[229,273,274] was the first phosphonium salt based coupling reagent to achieve wide use in peptide chemistry. Although very effective, BOP has drawbacks because the synthesis and use of BOP necessitates the handling of hexamethylphosphoric triamide, a known carcinogen.^[153] Several closely related phosphonium coupling reagents were later developed (Table 10); some of which circumvent working with the known carcinogen hexamethylphosphoric triamide (e.g., PyBOP, PyAOP, PyBroP, PyCloP). For example, the tri-pyrrolidino analogue benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) (Table 10, Scheme 23) was found to give comparable results to BOP.^[279] Later, 7-azabenzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (AOP) and 7-azabenzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyAOP),^[276] the azabenzotriazole analogues of BOP and PyBOP, were prepared and found to be more effective in couplings with hindered amino acids.^[280] The halophosphonium analogues bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP), and chlorotris(pyrrolidino)phosphonium hexafluorophosphate (PyCloP) have been particularly utilized in coupling *N*-methylamino acids and α,α -disubstituted amino acids.^[265,278,281,282] Bis(2-oxo-oxazolidin-3-yl)phosphinic chloride (BOP-Cl) (Scheme 23) has also been used effectively in solution for the acylation of *N*-methylamino acids^[283,284] and hindered amino acids, such as (2*S*,5*R*)-5-*tert*-butylproline.^[285,286]

Scheme 23 Selected Coupling Reagents and Additives

Activation and coupling are typically performed in a one-pot reaction into which the base is added last, because phosphonium salts do not usually react with the amine component in the reaction mixture.^[265,268,287] A separate activation step is not required and has been reported to increase the chance of epimerization.^[288,289] The most common solvents used in the coupling reaction are dichloromethane, dimethylformamide, 1-methylpyrrolidin-2-one, and dimethyl sulfoxide, into which the solid phosphonium reagents exhibit high solubility, such that high concentrations of reactants and reagents can be employed. The bases of choice are generally *N,N*-diisopropylethylamine, 4-methylmorpholine, and 2,4,6-trimethylpyridine. Additives such as HOBT^[290] and HOAt^[242] may also enhance the efficiency of couplings with BOP, PyBOP, AOP, and PyAOP, and thereby decrease the levels of epimerized product.^[291,292] These reagents have proven useful in fragment condensations of racemization-prone sequences. One possible side reaction in phosphonium salt mediated peptide couplings has been esterification of unprotected hydroxy group side chains. In practice, BOP has been used to mediate esterifications of carboxylic acids.^[293,294] However, because ester formation is slower than amide formation,^[295] side-chain unprotected serine, threonine, and tyrosine can be effectively used in solution^[229] and solid-phase peptide syntheses^[296,297] with phosphonium salts when less than 10 coupling cycles are performed after their incorporation.

Boc-Pro-Aib-OMe; Typical Procedure Using PyBOP:^[281]

CAUTION: Thionyl chloride reacts violently with water producing large volumes of corrosive gases. It is extremely destructive to all tissues.

A soln of Boc-Pro-OH (0.43 g, 2 mmol), HCl•H-Aib-OMe (0.34 g, 2.2 mmol), and PyBOP (1.04 g, 2 mmol) in CH₂Cl₂ (2 mL) was treated with iPr₂NEt (1.04 mL, 6 mmol), stirred at rt for 1 h, and concentrated. The residue was dissolved in EtOAc (20 mL), washed successively with 5% KHSO₄ (3 ×), brine, 5% NaHCO₃ (3 ×), and brine again, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc 1:1). Evaporation of the collected fractions furnished the title peptide; yield: 0.55 g (88%); mp 78 °C; *R*_f 0.4 (hexane/EtOAc 1:1); [α]_D −56 (c 1, EtOH).

Ac-Lys-Arg-Trp-Phe-Phe-Glu-NH₂; Typical Procedure Using Fmoc Chemistry and PyBOP on Solid Phase:^[298]

The peptide was prepared on Rink amide 4-methylbenzhydrylamine (MeBHA) resin (0.5 mmol·g^{−1}) using an automated solid-phase multiple peptide synthesizer. Side-chain protecting groups were: Boc for Lys and Trp, *t*-Bu for Glu, and 2,2,4,6,7-pentamethyl-2H-benzofuran-5-ylsulfonyl (Pbf) for Arg. Fmoc deprotection was performed with 20%

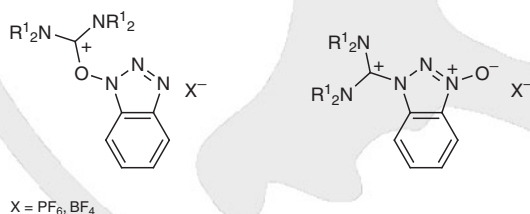
piperidine in DMF (1×10 min + 1×20 min). The resin was washed with DMF (3×2 min), CH_2Cl_2 (2×2 min), and DMF (2×2 min). Couplings were performed in DMF using the *N*-Fmoc-amino acid (100 μmol , 4 equiv), PyBOP (100 μmol , 4 equiv), and 4-methylmorpholine (200 μmol , 8 equiv), for 20–45 min at rt, and repeated twice. The resin was washed after each coupling cycle as described above. Acetylation of the terminal amino group was performed prior to cleavage by reacting the peptidyl resin twice with a soln of Ac_2O (10%) and $i\text{Pr}_2\text{NEt}$ (0.5%) in DMF. Cleavage from the solid support was performed by treating the peptidyl resin with TFA/ H_2O /thioanisole/ethanedithiol/PhOH (87.5:5:5:2.5:trace amount, 1.8 mL) for 2 h at rt. The cleavage mixture was cooled to 4°C , treated with ice-cold *t*-BuOMe, centrifuged at 3000 rpm for 10–15 min at 4°C , decanted, and the resulting pellet was treated three additional times with *t*-BuOMe and centrifuged ($3 \times$) as described above. The resulting pellet was dissolved in H_2O and lyophilized to a residue that was purified by RP-HPLC, employing a binary gradient formed from 0.1% TFA in H_2O (soln A) and 0.1% TFA in 75% MeCN in H_2O (soln B). The chromatographic run (flow rate of $8 \text{ mL} \cdot \text{min}^{-1}$) started with 20% of soln B in soln A, was kept constant for 10 min, and was followed by a gradient increase of soln B from 20% to 100% over an additional 55 min. Lyophilization of the collected fractions gave the title peptide; yield: not reported; purity 91% (HPLC); ESI-MS m/z : 953.6 $[\text{MH}]^+$.

21.11.2.5.2

Variation 2: Uronium/Guanidinium Salts

Three reagents of this type have become common tools for peptide synthesis: the HOBt-based reagent *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HBTU) (Scheme 23),^[266,275] its corresponding tetrafluoroborate (TBTU),^[277] and the HOAt-based reagent *N*-[(dimethylamino)(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU).^[242,276] Several variants of these reagents have also been developed possessing different amine components (i.e., dimethylamine and pyrrolidine) and different electron-withdrawing moieties such as *N*-hydroxy components and halogens (Table 10). These reagents were initially thought to exist as isouronium structures in which the oxygen atom of the benzotriazole moiety was attached to the central carbenium ion (Scheme 24). Subsequently, X-ray structural analysis of HBTU and HATU established that in the solid state these reagents existed as guanidinium salts in which one of the nitrogens of the benzotriazole was linked to the central carbon (Scheme 24).^[299]

Scheme 24 Structures of Uronium and Guanidinium Salts^[299]



Uronium/guanidinium salts, unlike phosphonium salts, may react with amino groups to form guanidino derivatives.^[300] Accordingly, the use of excess reagent should be avoided and the *N*-protected amino acid to be activated is commonly added to the reaction mixture prior to the coupling reagent. Preactivation can also be employed; however, because it may lead to racemization, activation is performed for a minimum time before the addition of a nucleophile.^[288,301] In the synthesis of cyclic peptides, the cyclization step, particularly when performed on-resin, is conducted using phosphonium salts, such as PyBOP, to avoid such side reactions.^[302,303] In uronium/guanidinium salt mediated couplings, di-

methylformamide is the most commonly used solvent; however, to reduce racemization, less polar solvent systems such as dichloromethane, chloroform, and dichloromethane/dimethylformamide (1:1) have been recommended for the synthesis of short peptides in solution,^[304–306] for fragment condensations,^[288] and for couplings with racemization-prone amino acids, respectively.^[301] Other solvents and solvent mixtures such as 1-methylpyrrolidin-2-one,^[4] dimethyl sulfoxide,^[308] dimethylformamide/dimethyl sulfoxide,^[309] dimethylformamide/1-methylpyrrolidin-2-one,^[310] and 1-methylpyrrolidin-2-one/dimethyl sulfoxide^[311] have also been advantageous in the SPPS of aggregation-prone peptide sequences. The bases of choice in couplings mediated by uronium/guanidinium salts have been generally *N,N*-diisopropylethylamine, 4-methylmorpholine,^[245,266,312] and 2,4,6-trimethylpyridine, the last of which has been favored when racemization-prone amino acids, such as Fmoc-Ser(*t*-Bu)-OH^[313] or Fmoc-Cys(Acm, Trt, Tmb or Xan)-OH,^[301] were coupled, and in the case of fragment condensations.^[245,314] In fragment condensations, the HOAt-derived reagent HATU has been commonly used to minimize epimerization.^[245,288,305,312,315,316] Additives, such as HOAt and HOBt, have been used to suppress racemization in both solution- and solid-phase peptide syntheses.^[4,317] However, these *N*-hydroxy compounds decrease the pH of the reaction, which may lower the yield.^[312] The HOAt-derived reagent HATU has been particularly effective in difficult coupling reactions such as those involving C α,α -disubstituted^[318–321] and *N*-alkylamino acids.^[322–326] Side-chain hydroxy groups should be protected in uronium/guanidinium mediated couplings to avoid O-acylation.^[327] Short peptides have, however, been synthesized successfully in solution without protection of serine side chains.^[328] The carboxamide group of asparagine and glutamine should also be protected to avoid dehydration and nitrile formation.^[164]

Boc-L-Tyr(Bzl)-Gly-Gly-OMe; Typical Procedure for Uronium/Guanidinium Salt Mediated Peptide Synthesis in Solution:^[266]

To a soln of Boc-L-Tyr(Bzl)-OH (925 mg, 2.5 mmol), H-Gly-Gly-OMe•HCl (473 mg, 2.6 mmol), and Et₃N (757 μ L, 5 mmol) in MeCN (20 mL), HBTU (983 mg, 2.6 mmol) was added and the mixture was stirred at rt for 15 min. Brine (70 mL) was added to the mixture, which was extracted with EtOAc (3 \times 50 mL). The combined organic phase was washed successively with 2 M HCl, H₂O, 5% NaHCO₃, and H₂O (5 mL each), dried (MgSO₄), filtered, and concentrated under reduced pressure to give the crystalline title compound; yield: 1.2 g (95%); mp 114 °C.

TBTU-Mediated SPPS of Ovine Corticotropin Releasing Factor (oCRF):^[329,330]

CRF was synthesized using Fmoc chemistry in an automated continuous flow reactor on 4-[(2,4-dimethoxyphenyl)aminomethyl]phenoxyacetamido resin (0.5 g, 0.22 mmol•g⁻¹). N^q-Fmoc-protected amino acid derivatives [0.3 M; Asn(Trt), Gln(Trt), His(Trt), Arg(Pmc), Asp(Ot-Bu), Glu(Ot-Bu), Lys(Boc), Thr(*t*-Bu), Ser(*t*-Bu)] were coupled using TBTU (0.3 M) in the presence of iPr₂NEt (2 equiv) in DMF. Single couplings were allowed to proceed for 20 min; N-terminal Fmoc deprotection was performed with 25% piperidine in DMF for 10 min, and all washes were made with DMF. Final cleavage from the resin and deprotection of side-chain functionalities was achieved by a mixture of 88% TFA/5% PhOH/5% H₂O/2% iPr₃SiH for 3 h. Purification of 100 mg samples was performed by preparative HPLC, employing a binary gradient formed from 0.1% TFA in H₂O (soln A) and 0.1% TFA in 50% MeCN in H₂O (soln B) and a linear gradient of 25–45% soln B in soln A over 70 min at a flow rate of 10 mL•min⁻¹, to give the title peptide; yield: 16.4 mg (13%); purity >98% (HPLC); MALDI-MS *m/z*: 4671 [M+H]⁺.

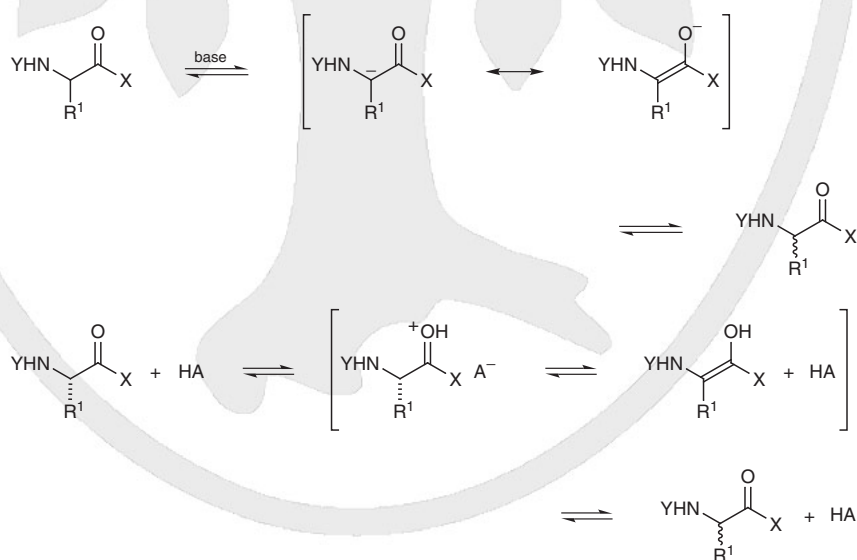
21.11.3 Racemization

The term “racemization” in organic chemistry is used to describe a process by which a mixture of enantiomers is created from an enantiomerically pure starting material. In

peptide chemistry, racemization is more generally ascribed to loss of configurational integrity. Because of the nature of peptide synthesis and the fact that peptides usually possess multiple chiral centers, racemization may describe epimerization at one chiral center irrespective of whether a mixture of enantiomers or diastereomers is formed during synthesis.^[331] Although amino acids are generally configurationally stable, their activation during peptide coupling renders them more configurationally labile contingent on the activated species and the experimental conditions. The enantiomeric and diastereomeric purity of the resulting peptide depends on the degree of epimerization during each coupling step as well as other reaction protocols such as saponification. For example, a 10-residue peptide would be only 90.4% diastereomerically pure if only 1% epimerization occurred at each amino acid coupling during synthesis. Because the biological properties of proteins and peptides depend critically on the configuration of the backbone carbons, maintaining configurational integrity is of utmost importance during peptide synthesis.^[331,332]

The relatively acidic hydrogen atom on the α -carbon of an amino acid renders this position susceptible to deprotonation, leading to racemization. Furthermore, activation of the carboxy group during the coupling step generally enhances the acidity of the α -proton. There are two predominant mechanisms for racemization or epimerization of the amino acid residues during peptide synthesis.^[331–334] Direct enolization may occur, promoted by base or acid media (Scheme 25).^[335,336] Alternatively, oxazolone formation may occur contingent on the amine protection and lead to racemization via an oxazole intermediate (Scheme 26).^[333,337] During peptide coupling with carbamate-protected amino acids, base-catalyzed enolization has been reported to play a significant role. The rate of racemization depends on the structure of the activated amino acid as well as the solvent, temperature, and nature of the base employed during coupling. This mode of epimerization is also observed during saponification of peptide esters. Acid-catalyzed enolization occurs generally under strongly acidic conditions, such as hydrogen bromide/acetic acid, particularly during treatment of *N*-acyl-*N*-alkylamino acid residues.^[331]

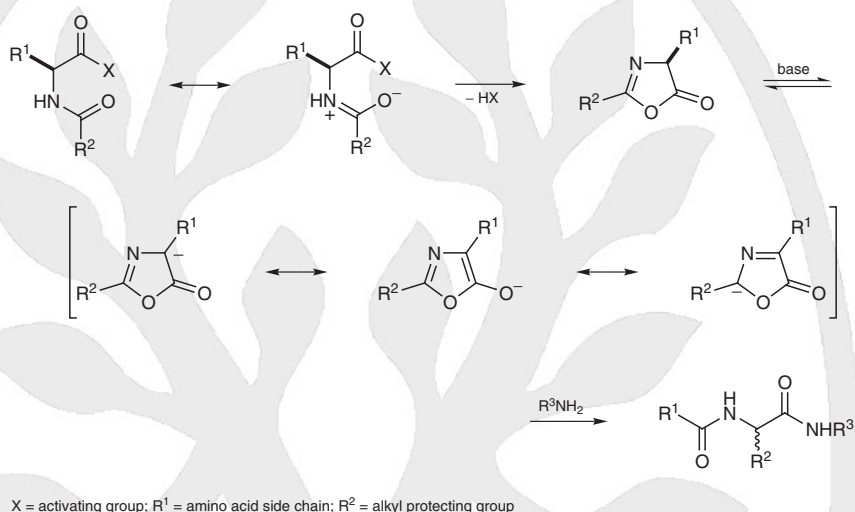
Scheme 25 Mechanism of Racemization via Base-Catalyzed and Acid-Catalyzed Enolization^[335,336]



X = activating group; Y = *N*^o-protecting group; HA = acid; R¹ = amino acid side chain

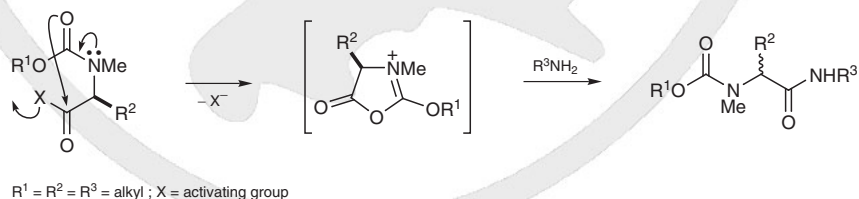
The other mechanism by which racemization occurs involves the formation of oxazol-5(4*H*)-one intermediates, which are generated by intramolecular attack of the N-terminal carbonyl on the activated carboxy group. *N*-Acyl moieties such as acetyl, benzoyl, or trifluoroacetyl favor oxazolone formation owing to the nucleophilic character of the amide carbonyl oxygen. The resulting oxazolones are reactive acylating agents that have been used for activation of α -amido carboxylates; however, they are prone to tautomerize to an achiral aromatically stabilized oxazole prior to coupling, which produces a racemic product (Scheme 26).

Scheme 26 Racemization via Oxazolone Formation^[333,337]



Carbamate-protected α -amino acids are less susceptible to oxazolone formation; however, oxazolones from *N*-Z- and *N*-Boc-protected amino acids have been isolated during their activation via acid chlorides or during coupling conditions in the presence of EDC. These 2-alkoxyoxazol-5(4*H*)-ones are, however, more configurationally stable than their amide-derived counterparts.^[341,342] Similarly, *N*-alkylated *N*-acylamino acids have been suggested to racemize by way of oxazolium ion intermediates even in the absence of base (Scheme 27).^[334,338–340] Although proline can be considered as an *N*-alkylated amino acid, constraint and steric interactions caused by its five-membered ring disfavor α -deprotonation and oxazolone formation.^[331] Proline is thus a choice C-terminal amino acid for minimizing racemization in segment condensations.

Scheme 27 Oxazolium Formation of *N*-Alkylated Amino Acids Leading to Racemization^[334,338–340]



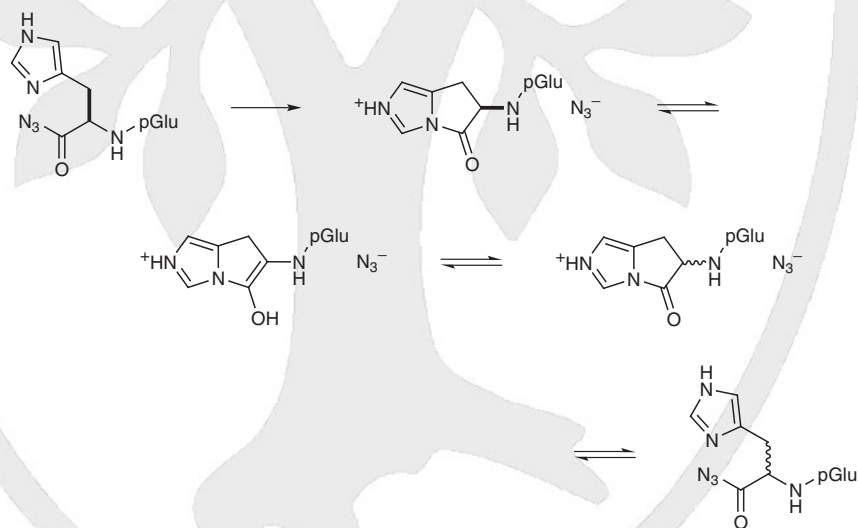
The configurational stability of amino acid residues is influenced by several factors, such as nitrogen protection, carboxylate activation, and coupling protocols, in which the reagent, solvent, and base all play important roles. Numerous experimental systems have been devised for studying racemization to evaluate the influence of such factors.^[230,343] Racemization-free coupling procedures must activate the carboxy group without facilitating

proton abstraction from the chiral α -carbon. Azides have been found to be less susceptible to racemization in fragment condensations, owing to both the relatively reduced acidity of the proton on the α -carbon which minimizes racemization by disfavoring enolization and to the greater stability of acyl azides which disfavors oxazol-5(4H)-one formation. Electrostatic stabilization of amido acyl azides by interaction of the amide oxygen with the central nitrogen of the azide has also been suggested to prevent oxazol-5(4H)-one formation.^[344]

Base plays an important role in racemization during amide bond synthesis.^[230,345] In the use of azides for amino acid activation and coupling, a slight excess of base can cause racemization.^[346,347] In azide couplings, the use of 1-(diethylamino)propan-2-ol and *N,N*-diisopropylethylamine is widely recommended instead of triethylamine.^[348] In symmetric anhydride coupling, the relatively weaker bases methylmaleimide and 4-methylmorpholine cause less racemization than triethylamine or *N,N*-diisopropylethylamine,^[346] albeit with slower reaction rates. In general, the use of 4-(dimethylamino)pyridine during activation and coupling leads to some racemization.^[349,350]

Two amino acids that are particularly susceptible to racemization are histidine and cysteine.^[331,332] In histidine, the proximity of the basic π -nitrogen of the imidazole side chain to the α -hydrogen is believed to facilitate epimerization of carboxy-activated histidine derivatives.^[351,352] The formation of imidazolidine during activation via azide has been shown to lead to loss of configurational integrity in the synthesis of thyroliberin analogues (pGlu = pyroglutamic acid; Scheme 28).^[352] However, the use of the *tert*-butoxymethyl (Bum) group for the protection of the π -nitrogen of the imidazole ring has been reported to give racemization-free couplings of *N*-Z/*N*-Fmoc-His(Bum)-OH with Phe-Ot-Bu using DCC/HOBt and long exposure to the basic reagent diethylamine.^[353]

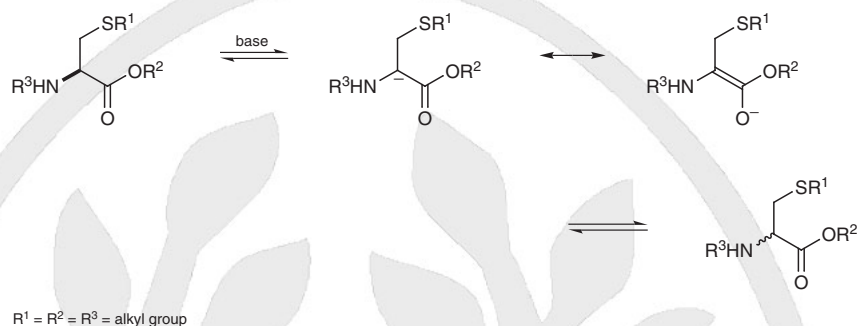
Scheme 28 Racemization of Histidine Residue via Imidazolidine Formation^[352]



Racemization in the case of *N,S*-protected cysteine active esters via α -proton abstraction in the presence of excess base has been commonly reported (Scheme 29).^[331,354,355] Couplings with *N*-Z-*S*-Acm/Trt/Tmb-cysteine using pentafluorophenyl esters,^[301,356] symmetric anhydrides,^[357] and TBTU/HOBt^[358] have all been performed with minimum racemization during peptide coupling. Cysteine residues may also epimerize when linked to the solid support via an ester bond, on repeated exposure to piperidine during the deprotection step in the Fmoc/*t*-Bu synthesis strategy.^[358] Epimerization has also been observed in the presence of bases other than piperidine, such as sodium–liquid ammonia, sodium hydroxide, etc.^[359,360] The thiol protecting group has a significant effect on the degree of epi-

merization, which decreases in the order: *S*-St-Bu > *S*-Trt > *S*-Tacm > *S*-Acem > *S*-Mob > *S*-t-Bu (where Mob = 4-methoxybenzyl, otherwise abbreviated as PMB).^[361]

Scheme 29 Racemization of N,S-Protected Cysteine Esters^[331,354,355]



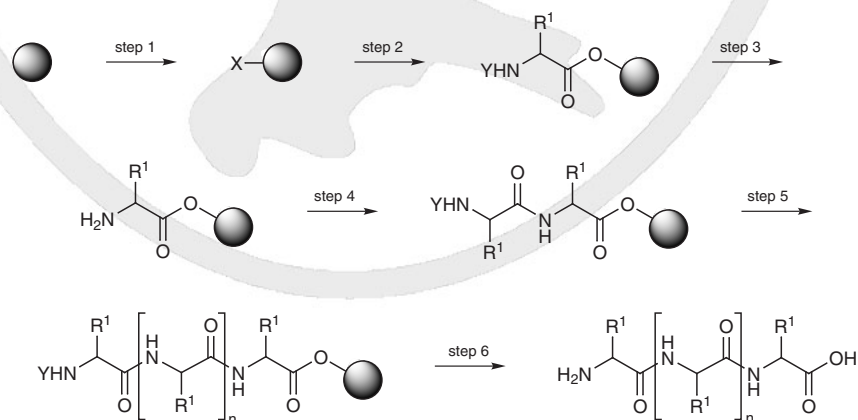
To reduce the rate of racemization during coupling, Lewis acids such as zinc(II) chloride^[362,363] and copper(II) chloride,^[364] as well as catalytic amounts of camphor-10-sulfonic acid^[363] or hydrogen cyanide,^[365] have been used as additives. Because these additives favor the rapid aminolysis of the oxazol-5(4*H*)-one species, they can significantly reduce the extent of racemization. Similarly, additives such as HOBt also retard the generation of oxazol-5(4*H*)-one species and thus minimize racemization.^[214,366]

21.11.4

Supports for Solid-Phase Peptide Synthesis

In the solid-phase peptide synthesis approach of Merrifield, as schematically described in Scheme 30,^[367] the C-terminal amino acid residue of the desired peptide is attached to an insoluble support via its carboxy group (steps 1 and 2). The side-chain functionalities of the amino acids are masked with protecting groups that are not affected by the reaction conditions employed during N-terminal amine deprotection and peptide chain assembly (step 3). The second amino acid with its N-terminal protection is then introduced by activation of its carboxy group for amide bond formation (step 4). After coupling, excess reagents are removed by washing and the protecting group is removed from the N-terminus of the dipeptide thus formed, prior to the addition of the third residue. This process is repeated until the synthesis of the desired peptide is complete (step 5). In the final steps, the peptide is released from the solid support and the side-chain protecting groups are removed (step 6).

Scheme 30 Representation of the Process of Solid-Phase Peptide Synthesis^[371]



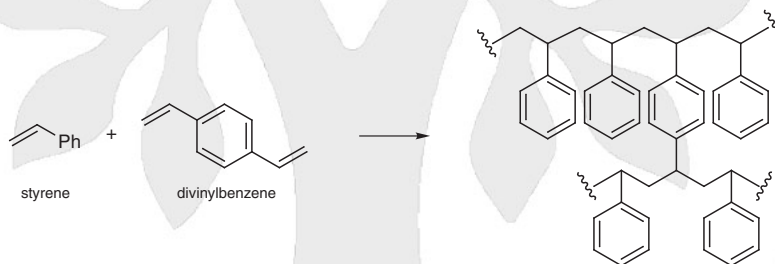
The polymer support has a significant influence on the outcome of the solid-phase chemistry. The shape, size, and mechanical stability of the support play crucial roles in the synthesis manipulations. Ideal polymer supports are chemically inert to all reagents and swell well in all solvents employed during the peptide synthesis, yet they must be sufficiently reactive for covalently linking and selectively cleaving the first amino acid residue in the peptide sequence. In order to achieve uniform reactivity throughout the resin, the swollen state of the support must be maintained.

Two procedures for resin washing have proven practical for solid-phase peptide synthesis: batchwise and continuous flow. In the batchwise process, the peptidyl resin is swollen and treated with reagents and solvents in portions that are removed by reduced pressure filtration. In continuous flow synthesis, the resin is packed in a column, swelled, reacted, and washed by pumping solvent through the resin bed. Different supports have proven effective in these two modes of synthesis.

21.11.4.1

**Method 1:
Polystyrene-Based Resins**

Cross-linked polystyrene (PS) beads are usually formed by the free-radical copolymerization of styrene with varying amounts of divinylbenzene (Scheme 31). The swelling of PS beads is contingent on the degree of cross-linking and inversely proportional to the amount of divinylbenzene used in the polymerization step. The standard matrix with 1–2% divinylbenzene cross-linked polystyrene exhibits a pronounced swelling capacity and high degree of mechanical stability during synthesis. The resin in the form of 200–400 Å mesh beads swells into a porous gel structure, possessing mobile polymeric chains, through which reagents effectively penetrate.

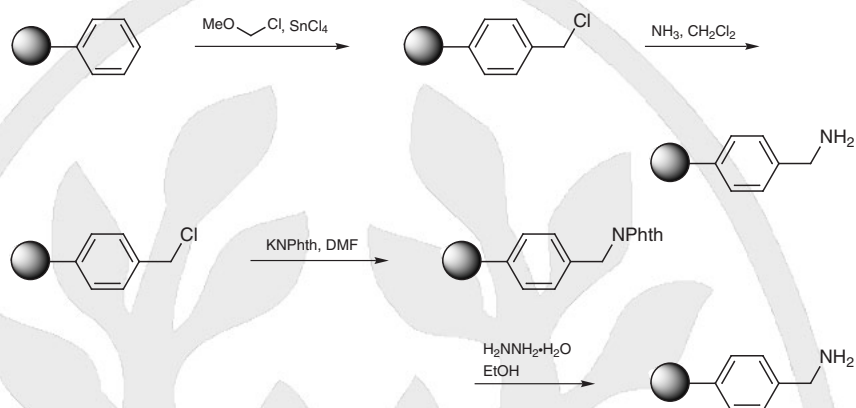
Scheme 31 Synthesis of Poly(styrene-co-divinylbenzene) Resin^[368]

PS-based resins are relatively inexpensive to make and can be readily functionalized using Friedel–Crafts alkylation and acylation reactions with various electrophiles such as chloromethyl methyl ether in presence of tin(IV) chloride, which is commonly used to make the chloromethylated PS (Scheme 32).^[7,369] Furthermore, displacement of the chloride of chloromethylated PS has been used to introduce a variety of functional groups and linkers. For example, amidoalkylation using potassium phthalimide followed by hydrazinolysis provides aminomethylated PS.^[370–373] Alternatively, chloromethylated PS reacts with liquid ammonia to provide directly aminomethylated PS (Scheme 32).^[374] Cross-linked PS beads of 20–80 mm in diameter are typically employed because of their good swelling in solvents such as dichloromethane (6–8 mL·g^{−1}) and dimethylformamide (3–5 mL·g^{−1}). Although suited for batchwise synthesis, PS-based resins are unsuitable for continuous-flow synthesis, because the swollen polymer can block the reactor pores, causing extreme pressures and collapse of the gel phase. Copacking of PS beads with glass beads and low flow rates have, however, provided effective continuous-flow synthesis systems. Moreover, PS resins are hydrophobic in nature, yet as the peptide chains grow they tend to become increasingly hydrophilic, which may account for difficulties in the synthesis of longer sequences on resin.^[375,376] Recognizing a need for supports having similar polarity

for references see p 799

as the peptide chain, Sheppard and co-workers pioneered the use of more hydrophilic supports (e.g., polyacrylamide) in the synthesis of a decapeptide fragment of acyl carrier protein in 1979.^[377–379]

Scheme 32 Chloromethylation and Aminomethylation of Polystyrene^[7,369,374]



21.11.4.2

Method 2: Polyacrylamide-Based Resins

Polyacrylamide polymer supports were introduced as alternatives to PS-based resins, with the intent of maintaining polymer hydrophilicity as the peptide chain grows. Polyacrylamide supports form gels that are well solvated by common solvents for peptide synthesis, such as dimethylformamide. Copolymerization of *N,N*-dimethylacrylamide, *N*-acryloylsarcosine methyl ester, and *N,N'*-ethylenebisacrylamide as cross-linking agents^[379] can produce polyacrylamide resin beads that exhibit superior swelling properties relative to PS-based resins in solvents such as water, dimethylformamide, and methanol.

Polyacrylamide supports were initially unsuitable for continuous-flow peptide synthesis owing to their mechanical degradation caused by high pressure. Polymerization of polydimethylacrylamide on kieselguhr, a porous inorganic solid, gave a matrix stable to high pressure and high flow rates. Such properties allowed columns to be prepared that are flow stable throughout the peptide synthesis.^[379] The porous kieselguhr structure allows rapid diffusion and penetration of solvents and reagents through the polyamide gel; however, uneven distribution of reagents through the resin bed may arise from irregular packing of the kieselguhr particles. In addition, polyacrylamide–kieselguhr matrices have been reported to degrade slowly over the course of long peptide assembly.

21.11.4.3

Method 3: Poly(ethylene glycol)-Based Resins

Poly(ethylene glycol) (PEG) is a polymer amphipathic in nature that solvates well in both polar and nonpolar solvents^[380] and exhibits high mobility and dynamic organization. Several PEG-grafted polystyrene (PEG-PS) and PEG-based supports have been effectively used in solid-phase peptide synthesis.

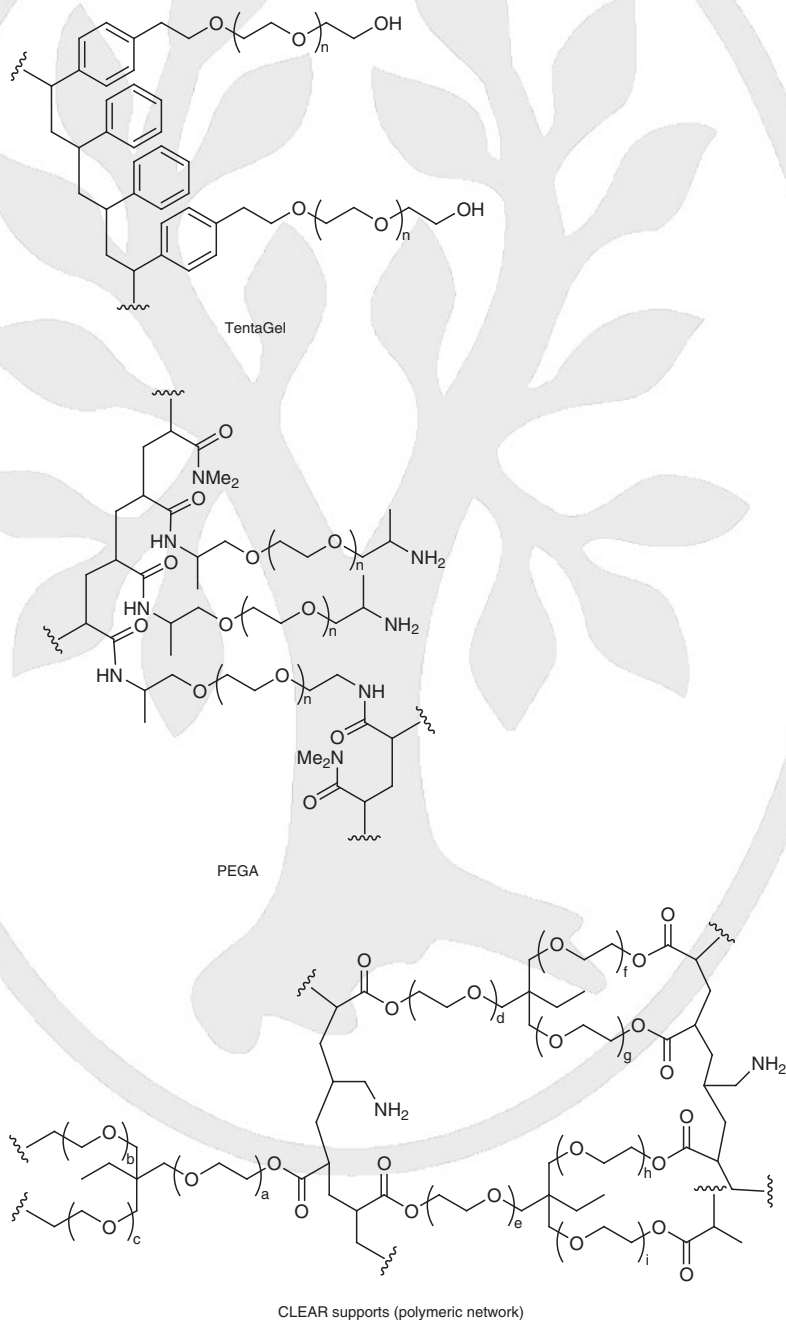
21.11.4.3.1

Variation 1: TentaGel

The grafting of PEG chains of varying degrees of polymerization onto polystyrene beads has produced copolymers bearing a hydrophobic core with hydrophilic tentacles, which are sold commercially as TentaGel resins (Scheme 33).^[381,382] The PEG chains are typically

introduced by anionic polymerization of ethylene oxide onto hydroxylated cross-linked PS beads. In this way, resins composed of 60–80% (w/w) PEG can be synthesized that possess remarkable swelling properties in a wide variety of solvents (H_2O , MeOH, MeCN, THF, CH_2Cl_2). Although their loading capacity ranges generally from 0.15 to 0.3 $\text{mmol}\cdot\text{g}^{-1}$, which is significantly lower than PS resins, such TentaGels are pressure resistant and can be used in both batch and continuous-flow reactors. For these reasons they have become very popular in solid-phase chemistry for the synthesis of peptides and small molecules.^[382,383]

Scheme 33 Poly(ethylene glycol)-Based Resins^[381,382,384,385]



21.11.4.3.2

Variation 2:**Poly(ethylene glycol)-Dimethylacrylamide Copolymer**

Copolymers of bisacrylamide PEG, monoacrylamide PEG, and *N,N*-dimethylacrylamide that are synthesized by radical polymerization, PEGA resins contain polyether and polyacrylamide backbones linked together by amide bonds (see Scheme 33).^[384] Inert and stable under peptide synthesis conditions, PEGA beads are flow stable, polar solid supports. Their effectiveness in solid-phase peptide chemistry has been demonstrated by the synthesis of the 65–74 amino acid fragment of acyl carrier protein,^[384] as well as in solid-phase chemical ligation.^[386,387] Furthermore, because PEGA beads show excellent swelling properties in both protic (water) and nonprotic solvents (CH_2Cl_2 , DMF), they have been used effectively in enzyme-catalyzed reactions such as enzymatic glycosylations of support-bound peptides.^[388] Although PEGA beads have typical loadings of 0.2–0.4 mmol·g⁻¹, beads with loadings up to 0.8 mmol·g⁻¹ have been synthesized^[389] by the addition of monomers, such as acrylates and acrylonitriles, in the resin synthesis.

21.11.4.3.3

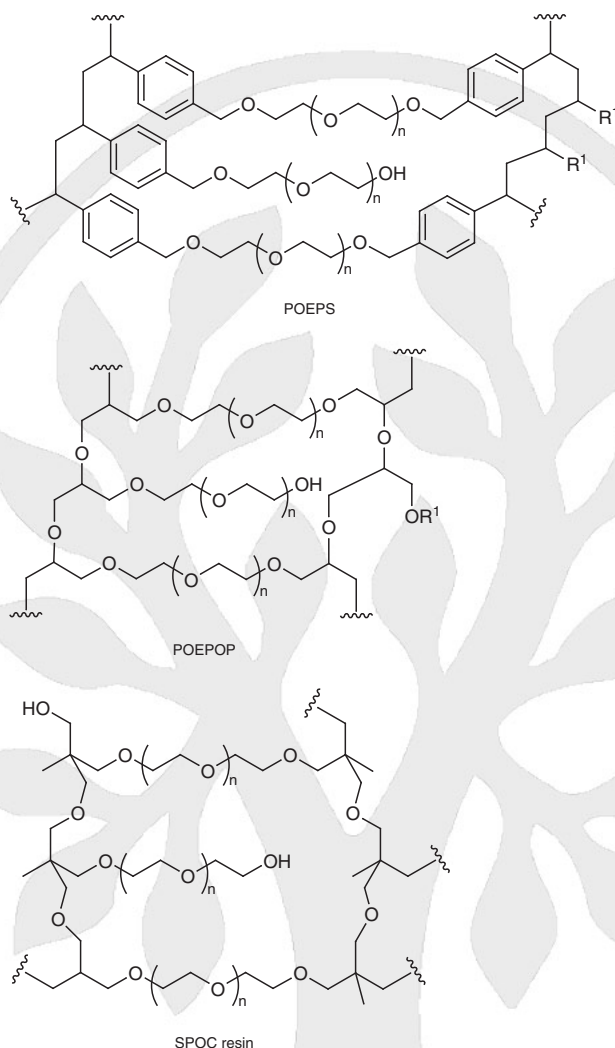
Variation 3:**Cross-Linked Ethoxylate Acrylate Resin**

Cross-linked ethoxylate acrylate resin (CLEAR)^[385] supports are highly cross-linked (ca. 95% by weight of cross linker) matrices that swell effectively and perform well in both batch-wise and continuous-flow syntheses. CLEAR supports are prepared by radical copolymerization of the branched cross-linker trimethylolpropane ethoxylate triacrylate with other monomers and cross-linkers, such as allylamine-CLEAR-I, 2-aminoethyl methacrylate-CLEAR-II, PEG₄₀₀ dimethacrylate-CLEAR-III, PEG ethyl ether methacrylate-CLEAR-IV, and with trimethylolpropane trimethacrylate-CLEAR-V.^[385] The CLEAR polymers have PEG-like character with oxoethylene chains and ester groups conferring a hydrophilic character (see Scheme 33). In peptide synthesis, the CLEAR supports, both powdered and beaded, exhibit chemical and mechanical stability and good swelling. Moreover, CLEAR supports also swell well in lipophilic solvents like toluene, ethyl acetate, and hexanes. Several challenging peptides have been synthesized on CLEAR supports, such as an acyl carrier protein (65–74 aa) fragment, a retro-acyl carrier protein (74–65 aa) fragment, and human gastrin-1 (17-mer).^[385]

21.11.4.3.4

Variation 4:**Polyethylene–Polystyrene and Polyethylene–Polyoxopropylene Resins**

Ester- and amide-containing PEG-cross-linked supports such as PEGA and CLEAR have been used successfully in the synthesis of difficult peptide sequences. They have also proved useful in reactions of support-bound substrates with enzymes. In solid-phase organic chemistry, however, many organic reactions are not compatible with ester and amide groups. For example, such resins can react with strong bases and nucleophiles. Consequently, PEG-cross-linked resins were developed containing polyethylene–polystyrene (POEPS) and polyethylene–polyoxopropylene (POEPOP)^[390] copolymers, replacing the amide and ester linkages by more stable ether bonds (Scheme 34). POEPS and POEPOP were respectively prepared by reacting mono- or disodium derivatives of PEG₁₅₀₀ with vinylbenzyl chloride and epichlorohydrin [2-(chloromethyl)oxirane] to prepare macromonomers that were polymerized respectively under radical and anionic conditions. These resins swell well in a variety of solvents, including dichloromethane, dimethylformamide, and water.

Scheme 34 PEG-Based Resins^[390]

Anionic polymerization of oxirane-derivatized PEG monomer in the synthesis of POEPOP results in a mixture of secondary and primary alcohol groups on the resin. This heterogeneity may result in unequal reactivity on the surface of the resin. Furthermore, the presence of secondary ether bonds formed during the polymerization process makes POEPOP chemically labile in strong acid and alkaline conditions.

21.11.4.3.5

**Variation 5:
Super Permeable Organic Combinatorial Chemistry Resin**

Super permeable organic combinatorial chemistry (SPOC) resin^[391] was later developed as an alternative support containing stable primary ether bonds, quaternary carbon junction points, and primary alcohol functionality (see Scheme 34). SPOC resins were synthesized from different lengths of PEG chains substituted with oxetanes by cationic ring-opening polymerization. Contingent on PEG chain length, SPOC resins can have loadings between 0.4–0.6 mmol·g⁻¹ (PEG₁₅₀₀) to 1.1–1.2 mmol·g⁻¹ (PEG₄₀₀). SPOC resin beads of controlled and uniform size (300–500 μm) are also obtained by suspension polymerization in silicon oil.^[391] SPOC resins are inert to a range of extreme conditions required in organic

chemistry. The feasibility of enzyme reactions and synthesis of glycopeptides and peptide isosteres on SPOC₁₅₀₀ resin have demonstrated its potential use as a polar support for chemical and enzymatic solid-phase methodologies. Although SPOC₁₅₀₀ could be effectively used in peptide synthesis as well as other chemical transformations, its high swelling properties and low loading may restrict its use in concentration sensitive chemistry. To overcome this limitation, a much higher loading polymer matrix (SPOC₁₉₄)^[392] was developed based on homogeneous tetraethylene glycol (TEG₁₉₄) macromonomers. SPOC₁₉₄ resins show high loading of 0.9–1.2 mmol·g⁻¹ and are inert to a range of extreme conditions, including 12 M hydrochloric acid, trifluoroacetic acid, butyllithium in tetrahydrofuran, and sodium in liquid ammonia. Among contemporary resins, SPOC resins exhibit remarkable properties for solid-phase synthesis, including the potential for a high loading/swelling ratio, compatibility in organic and aqueous media, and inertness under electrophilic conditions.

21.11.5 Handles and Linkers for Solid-Phase Peptide Synthesis

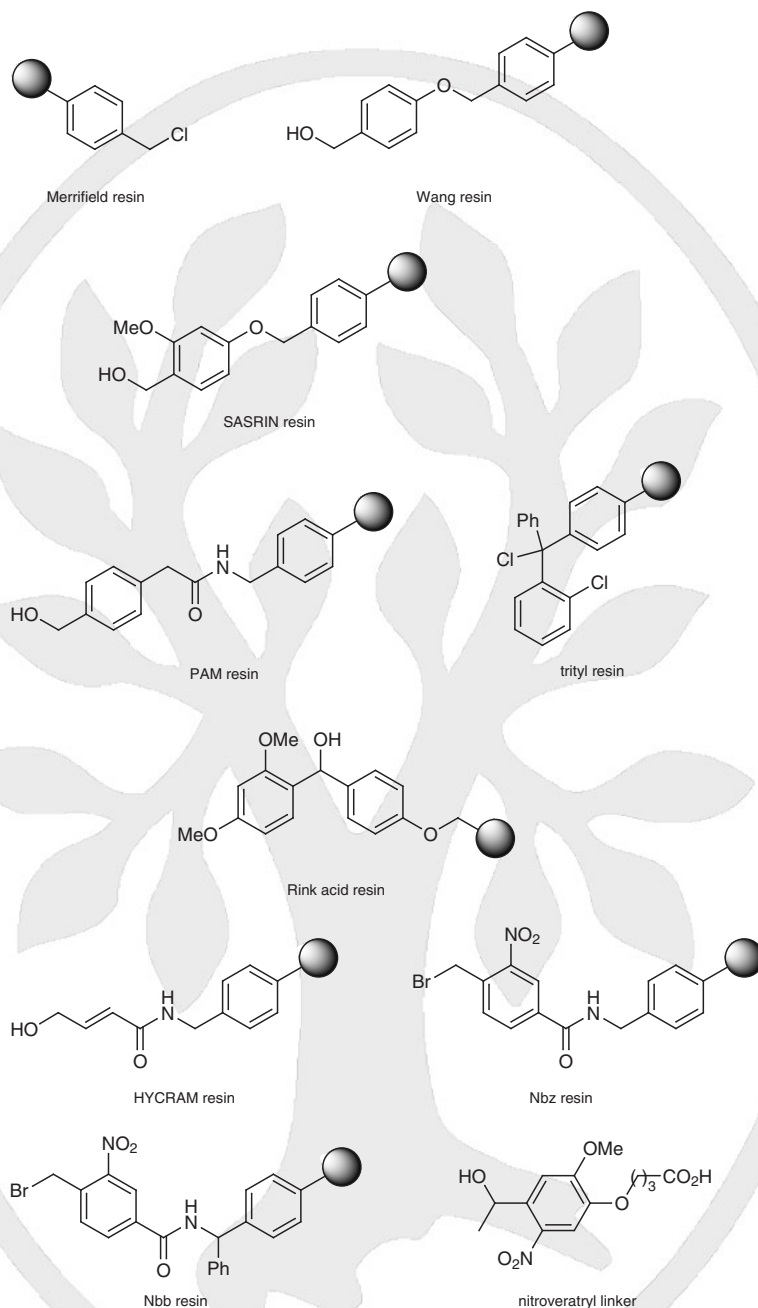
Solid-phase peptide synthesis normally proceeds from the carboxylate to the amino terminus (C→N), with the C-terminus anchored to the solid support. This anchorage is achieved through a spacer (a handle or a linker), which provides a cleavable linkage between the peptide chain and the solid support. The growing peptide chain is usually linked to the handle by an ester or amide moiety which may be cleaved or released under appropriate conditions to provide the final peptide as a C-terminal carboxylic acid or amide. A portion of the handle usually remains permanently attached to the functionalized resin after peptide cleavage.

The choice of linker is based primarily on two factors: (1) the chemistry necessary for synthesizing the desired peptide on the solid phase and (2) the desired C-terminal functionality of the final peptide, which is commonly a C-terminal acid, but may be an amide, aldehyde, or alcohol. Handles may also be used to control the level of resin substitution (resin loading), as well as to modify the physical and spectroscopic properties of the resin matrix. Finally, handles may also serve as internal references for monitoring reaction steps and for estimating the yield of reactions on the resin-bound substrate.^[377,393] One such example is the use of resin-bound indicators such as bromophenol blue, which are attached to the solid support to facilitate *in situ* monitoring of peptide synthesis.^[394]

A wide range of linkers have been reported in the literature over the years and reviewed.^[395–397] This section discusses the more commonly used linkers, which are classified according to the C-terminal functionality they produce. Certain linkers are discussed because of their unique properties.

21.11.5.1 Method 1: Generation of C-Terminal Peptide Carboxylic Acids

The solid-phase synthesis of peptides possessing a C-terminal carboxylic acid is generally accomplished by linking the first amino acid residue as an ester to the solid support. Among handles for the linkage and selective release of C-terminal carboxylic acids, the most common are cleaved with acid or by palladium-catalyzed reactions under neutral conditions (Scheme 35).

Scheme 35 Resins for Synthesis of C-Terminal Carboxylic Acids

21.11.5.1.1

**Variation 1:
Merrifield Resin (Chloromethyl Cross-Linked Polystyrene Resin)**

In the solid-phase peptide synthesis strategy developed by Merrifield, the polystyrene–divinylbenzene copolymer is first chloromethylated by Friedel–Crafts alkylation using an alkoxy-substituted chloromethane (i.e., MeOCH_2Cl) in the presence of a Lewis acid such as tin(IV) chloride.^[398] The first amino acid residue is typically linked to the resin by nucle-

ophilic displacement of the chloride using the cesium carboxylate salt of the N-protected amino acid in the presence of a catalytic amount of potassium iodide in an inert solvent (e.g., DMF, EtOH, THF, dioxane) at reflux.^[399] Instead of the cesium salt, trialkylammonium salts,^[400] sodium salts in tetrahydrofuran,^[401] and zinc salts in ethanol^[402] have also been employed to provide the resin-bound benzyl-type peptidyl ester. After completion of peptide chain assembly, the ester is cleaved under strongly acidic conditions, such as anhydrous hydrogen fluoride,^[403,404] trifluoromethanesulfonic acid,^[106] trimethylsilyl trifluoromethanesulfonate–bromotrimethylsilane^[125,405] or hydrogen bromide/trifluoroacetic acid.^[406]

Anhydrous hydrogen fluoride is one of the most commonly used reagents for cleaving peptide from the polystyrene resins, with concomitant removal of side-chain protecting groups. Hydrogen fluoride cleavage is generally performed at 0–5 °C for a period of 30–60 minutes. However, cleavage of the side chains of certain amino acids such as Arg(Ts), Cys(Mob), and Lys[Z(2-Cl)] may require longer reaction times (i.e., 2 h) at 5 °C. Owing to the potential for high concentrations of alkylating species generated during the deprotection reaction, scavengers such as anisole, *p*-thiocresol (4-methylbenzenethiol), and dimethyl sulfide are recommended to avoid side reactions. Two procedures are commonly used for hydrogen fluoride cleavage: standard “high” cleavage and “low–high” cleavage.

An alternative to hydrogen fluoride that can be used in regular laboratory glassware,^[106] trifluoromethanesulfonic acid is not volatile and cannot be removed by standard evaporation techniques; nevertheless, the cleaved peptide may be precipitated from the cleavage medium. The cleaved peptide may be prone to salt and scavenger association, and is usually neutralized before purification. Similar to hydrogen fluoride, this approach has been performed by two modes of cleavage contingent on the concentration of trifluoromethanesulfonic acid: standard “high” trifluoromethanesulfonic acid cleavage and “low–high” trifluoromethanesulfonic acid cleavage.

Bromotrimethylsilane/tetrahydrofuran is yet another cleavage cocktail used for cleaving peptides from solid supports, which is particularly effective for deprotecting side-chains such as Arg(Mtr). An effective two-step protocol has been developed for the cleavage of peptides from the solid support which employs a combination of bromotrimethylsilane/thioanisole/tetrahydrofuran in the first step followed by trimethylsilyl trifluoromethanesulfonate/thioanisole/trifluoroacetic acid treatment.^[405]

An alternative to hydrogen fluoride and trifluoromethanesulfonic acid for cleaving peptides from the solid support, trimethylsilyl trifluoromethanesulfonate also removes most of the side-chain protecting groups used in Boc synthesis; however, some cysteine protecting groups such as benzyl or acetamidomethyl (Acm) are stable to this reagent.^[405]

Hydrogen bromide/tetrahydrofuran or acetic acid mixtures have been used to cleave peptide–resin linkages since the discovery of solid-phase peptide synthesis.^[403,406] The procedure is also suitable for cleaving peptide C-terminal amides from MeBHA resin (see Section 21.11.5.2.1) and it uses 30% hydrogen bromide in acetic acid along with pentamethylbenzene, which is reported to accelerate the cleavage and acidolytic removal of protecting groups.

Albeit in low yield, cleavage has also been accomplished by hydrogenolysis^[407] and by hydrolysis using aqueous lithium hydroxide in methanol.^[408] This ester handle is usually employed in the Boc strategy for peptide synthesis in which the amino acid side chains are protected using benzyl-derived blocking groups that may be removed during the final cleavage step. In the case of longer peptides, the acidolysis step for Boc group removal has been reported to lead to 1–1.5% loss of the peptide chain from the support during elongation.^[370]

Attachment of *N*-Boc-Amino Acids to Merrifield Resin via Cesium Salts; General Procedure:^[399]

The appropriate *N*-Boc-amino acid (10 mmol) was dissolved in EtOH (15 mL) and treated with H₂O (5 mL) followed by 20% aq Cs₂CO₃ to adjust the pH to 7.0. The soln was diluted with dioxane and concentrated to dryness. The resulting cesium salt (1.2 equiv) was then added to the swollen resin in DMF (6–8 mL·g⁻¹ of resin) and the mixture was heated to 50 °C overnight. In some cases, KI (0.1 equiv) was added to the mixture to accelerate completion. After 12 h, the resin was filtered and washed with DMF (3 ×) and MeOH (3 ×), and dried under reduced pressure; yield: 72–100%.

Hydrogen Fluoride Cleavage from Merrifield Resin; General Procedure:^[403,404]

CAUTION: Anhydrous HF is colorless and extremely hazardous; exposure to trace amounts of HF can easily result in death or permanent injury. Anhydrous HF should only be handled with the utmost caution by appropriately trained personnel with HF-specific reaction equipment such as a Teflon vacuum line.^[215]

Method A: Standard “high” HF cleavage: The peptide resin was placed in a Teflon HF reactor equipped with a Teflon-coated stirring bar. Scavenger mixtures [DMS/anisole (1:1) for peptides without Cys residues and DMS/anisole/*p*-thiocresol (1:1:0.2) for peptides containing Cys] were added and the reactor was capped and cooled to 0 to –5 °C for about 10 min. HF was then distilled into the reaction vessel, with the temperature kept between 0 and –5 °C. The mixture was stirred for about 45 min. The HF and DMS were removed using a stream of N₂. The resin was washed with TFA (3 ×) to remove the cleaved deprotected peptide. The TFA washings were concentrated and the peptide was precipitated using cold Et₂O; yield: 90%

Method B: “Low–high” HF cleavage: The experimental details were similar to the standard HF cleavage discussed above.^[404] The difference was in the concentration of HF in proportion to the scavenger used. Side reactions involving sensitive amino acids such as Tyr and Trp may be avoided using this method, which proceeded slowly and required large amounts of scavenger such as DMS (1:3 v/v of HF); yield: 92%.

Trifluoromethanesulfonic Acid Cleavage of Peptide Carboxylates from Merrifield Resin; General Procedure:^[106,125]

CAUTION: Trifluoromethanesulfonic acid is an extremely strong acid; always use an efficient hood. Vapors are very harmful if inhaled.

Method A: Standard “high” TfOH cleavage: The peptide resin (0.25 g) was placed in a round-bottomed flask, treated with the scavenger mixture of thioanisole/ethanedithiol (1:1, 0.75 mL), and stirred at 0 °C in an ice bath for 5 min. TFA (5 mL) was added to the mixture, which was stirred for 10 min, then treated dropwise with TfOH (0.5 mL), with vigorous stirring to dissipate the heat generated. The reaction was allowed to warm to rt and stirred for about 2 h. The resin was filtered and washed with TFA (2 ×). The combined filtrate and TFA washings were treated with a cold 8-to-10-fold volume of Et₂O to precipitate the deprotected peptide; yield: 52–83%.

Method B: “Low–high cleavage”: A lower concentration of TfOH and a larger volume of scavenger, e.g. DMS, were employed in the cleavage reaction, which usually proceeded slowly. To the peptide-resin (250 mg), *m*-cresol (0.25 mL) and DMS (0.75 mL) were added as scavengers, followed by TFA (1.25 mL) and finally TfOH (0.25 mL). The reaction was typically stirred for 3 h as the temperature was maintained at 0–5 °C; yield: 52–83%.

Trimethylsilyl Trifluoromethanesulfonate Mediated Cleavage of Peptides from Resin;**General Procedure:**^[405]

The peptide resin (1 g) was placed in a round-bottomed flask and treated with a cleavage mixture comprised of TMSOTf (1.95 mL), TFA (6.9 mL), and *m*-cresol (1.2 mL) at 0 °C, stirred at 0 °C for 2 h, and filtered. The deprotected peptide was then precipitated from the filtrate by dilution with cold Et₂O; yield: 37–52%.

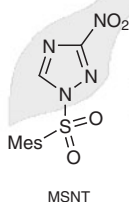
Hydrogen Bromide Cleavage Protocol; General Procedure:^[403]

The peptide resin (0.25 g) was treated with pentamethylbenzene (0.5 mL), thioanisole (0.6 mL), and TFA (10 mL), followed by a 30% HBr/AcOH soln (0.4 mL, 5 M), stirred for 3 h, and filtered. Subsequent evaporation of the filtrate and trituration of the residue with dry Et₂O provided the peptide, which was dried under reduced pressure; yield: 89%.

21.11.5.1.2

Variation 2:**Wang Resin (4-Benzyloxybenzyl Alcohol Cross-Linked Polystyrene)**

One of the most widely used linkers for generating peptide carboxylic acids, Wang resin^[409] (see Scheme 35) possesses a 4-benzyloxybenzyl alcohol anchor that imparts increased acid-lability to the linker, which is typically attached to the Merrifield resin by displacement of chloride using the sodium alkoxide of 4-hydroxybenzyl alcohol.^[409] Attachment of the first amino acid to Wang resin is achieved by 4-(dimethylamino)pyridine-catalyzed esterification with an appropriate symmetric anhydride,^[410] by acylation with a mixed anhydride derived from treating the N-protected amino acid with 2,6-dichlorobenzoyl chloride and pyridine in dimethylformamide,^[411] as well as by acylation using an N-protected amino acid, 1-(mesitylsulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT, Scheme 36), and 1-methyl-1*H*-imidazole in dichloromethane.^[412]

Scheme 36 1-(Mesitylsulfonyl)-3-nitro-1*H*-1,2,4-triazole^[412]

The first of the above methods is commonly used for attaching N-protected amino acids onto a hydroxy-functionalized resin via an ester bond and has been performed in dimethylformamide, using 5 equivalents of anhydride and a catalytic amount of 4-(dimethylamino)pyridine.^[410] Although the reaction proceeds rapidly, the risk of racemization is relatively high owing to favorable enolization of the 1-acyl-4-(dimethylamino)pyridinium intermediate. This method is thus unsuitable for attaching histidine or cysteine residues.

The second method involves formation of a mixed anhydride between the appropriate N-Fmoc-amino acid derivative and 2,6-dichlorobenzoyl chloride in dimethylformamide/pyridine. Although this reaction proceeds relatively slowly (ca. 24 h), the resulting esters have been reported to be obtained enantiomerically pure.^[411]

The third method, using MSNT in the presence of 1-methyl-1*H*-imidazole, has been particularly effective for attaching N-Fmoc-amino acids onto relatively unreactive hydroxy groups. The activation of the protected amino acid and resin esterification with MSNT in dichloromethane involve both reagents and intermediates that are moisture sensitive.^[412]

After the attachment of the appropriate N-protected amino acid onto the hydroxy-functionalized resin, the unreacted hydroxy groups are generally capped to avoid their

acylation during subsequent couplings with activated amino acids, which may later result in deletion sequences. For capping, reactive carboxylic acid derivatives are commonly used, such as acetic anhydride,^[116] benzoyl chloride,^[409] or pivaloyl chloride,^[413] in the presence of pyridine.

Cleavage of product linked to Wang resin is typically achieved using 90% trifluoroacetic acid in dichloromethane to yield the peptide carboxylic acid, with concurrent removal of *tert*-butyl side-chain protecting groups. This linker is commonly used in the Fmoc strategy for the synthesis of peptides having C-terminal carboxylates. Wang resin is incompatible with the Boc strategy for peptide synthesis.

Release of peptides anchored to alkoxybenzyl alcohol handles is generally achieved by treating the peptidyl-resin with 95% trifluoroacetic acid for 1–3 hours. Usually, cleavage is performed with trifluoroacetic acid/triisopropylsilane/water (95:2.5:2.5).^[184] Because methionine, cysteine, tryptophan, and tyrosine are susceptible to alkylation reactions by cations produced during the acidolytic cleavage, scavengers are usually added to the cleavage cocktail. The most common scavenger, ethanedithiol, is often used to trap *tert*-butyl and trityl cations formed in the deprotection of cysteine residues.^[148,414,415] Suppression of acid-catalyzed methionine oxidation has also been reported using ethanedithiol or thioanisole. Phenol has been used to prevent side reactions on tyrosine and tryptophan.^[416]

Attachment of *N*-Boc/*N*-Fmoc-Amino Acids to Hydroxy-Functionalized Resins via Symmetric Anhydrides; General Procedure in the Presence of 4-(Dimethylamino)pyridine:^[410]

CAUTION: Carbodiimides are severe eye, skin, and respiratory tract irritants, and skin sensitizers. They should only be handled with gloves in a fumehood.

The *N*-Fmoc-amino acid (10 equiv) was dissolved in CH_2Cl_2 (3 mL·mmol⁻¹), cooled to 0 °C, treated with DIC (5 equiv), and stirred at 0 °C for about 15 min. The symmetric anhydride soln and DMAP (0.1 equiv) were then added to a suspension of swollen Wang resin in CH_2Cl_2 . After stirring for 1 h, the resin was filtered and washed with DMF; yield: $\leq 90\%$.

Attachment of *N*-Fmoc-Amino Acids to Hydroxy-Functionalized Resin; General Procedure Using 2,6-Dichlorobenzoyl Chloride:^[411]

The hydroxymethyl resin was swollen in DMF (5 mL·g⁻¹), treated with the appropriate *N*-Fmoc-amino acid (2 equiv) and pyridine (3 equiv), agitated at rt for ca. 10 min, and treated with 2,6-dichlorobenzoyl chloride (2 equiv). The suspension was shaken for 18 h. The resin was filtered and washed with DMF; yield (for Fmoc-Phe-OH): 71%. The remaining hydroxy groups were capped as described below.

Attachment of *N*-Fmoc-Amino Acids to Hydroxy-Functionalized Resin; General Procedure Using MSNT in the Presence of 1-Methyl-1*H*-imidazole:^[412]

The appropriate *N*-Fmoc-amino acid (2 equiv) was dissolved in dry CH_2Cl_2 (3 mL·mmol⁻¹) containing a few drops of THF to give a 0.1 M soln. 1-Methyl-1*H*-imidazole (1.5 equiv) followed by MSNT (2 equiv) were added to the amino acid soln under an inert atmosphere and the mixture was stirred until the MSNT had dissolved. The resulting soln was transferred by syringe to the pre-swollen resin in CH_2Cl_2 and the mixture was allowed to stand at rt for 1 h, with gentle shaking. After 1 h, the resin was filtered and washed with CH_2Cl_2 (3 ×), DMF (3 ×), and CH_2Cl_2 (3 ×), and dried under reduced pressure; yield: 55–90%.

Capping of Unreacted Hydroxy Groups; General Procedure:^[116,409,413]

After esterification with the *N*-protected amino acid as described above, the resin was treated with either a soln of Ac_2O /pyridine/ CH_2Cl_2 (1:2:2, 10 mL·g⁻¹ resin) or 0.3 M BzCl /

0.4 M pyridine in CH_2Cl_2 and left at rt for 30 min. The resin was filtered and washed with CH_2Cl_2 (3 \times), DMF (3 \times), and CH_2Cl_2 (3 \times), and dried under reduced pressure; yield: 70–95%.

Cleavage of Peptide Acids from Wang Resin Using Trifluoroacetic Acid; General Procedure:^[409]

The peptide resin was suspended in a TFA soln (10–25 $\text{mL}\cdot\text{g}^{-1}$ resin) containing the appropriate scavengers [(1) TFA/ $\text{iPr}_3\text{SiH}/\text{H}_2\text{O}$ (95:2.5:2.5) for peptides containing all amino acids except Arg(Mtr), Cys(Trt), Met, and unprotected Trp; (2) TFA/ $\text{iPr}_3\text{SiH}/\text{H}_2\text{O}$ /ethanedithiol (94:1:2.5:2.5) for peptides containing all amino acids except Arg(Mtr) and/or unprotected Trp; (3) TFA/thioanisole/ H_2O /PhOH/ethanedithiol (82.5:5.5:5.5:2.5:4 for all peptides)] and allowed to stand at rt with occasional swirling for 1.5–18 h, depending on the sequence. The resin was filtered and the filtrate was concentrated under reduced pressure and treated with cold anhyd Et_2O to facilitate precipitation of the deprotected peptide; yield: 42–68%.

21.11.5.1.3

Variation 3: Super Acid Sensitive Resin

Introduction of a second electron-donating *ortho*-methoxy group onto the benzyl alcohol moiety of Wang resin increases the linker's sensitivity to acid in super acid sensitive resin (SASRIN; 2,4-dialkoxybenzyl alcohol) (see Scheme 35).^[417,418] This resin has been synthesized by a two-step sequence involving displacement of the chloride of chloromethyl Merrifield resin using the alkoxide of 4-hydroxy-2-methoxybenzaldehyde followed by reduction of the aldehyde with sodium borohydride to provide the benzylic alcohol.

Attachment of the first amino acid residue to SASRIN resin has been achieved by similar procedures as those described above for Wang resin. Cleavage of the final carboxylate product can be accomplished using 0.5–1% trifluoroacetic acid in dichloromethane as well as by treatment with acidic alcohols, such as 1,1,1,3,3,3-hexafluoropropan-2-ol in dichloromethane. The acid-sensitive SASRIN resin is thus well suited for the synthesis of fully side-chain-protected peptide acids.

Cleavage of Protected Peptides from Highly Acid Labile Resins Using Dilute Trifluoroacetic Acid; General Procedure:^[59,419,414]

The peptide resin (1 g) was swollen in CH_2Cl_2 (10 $\text{mL}\cdot\text{g}^{-1}$ resin) prior to cleavage. To the swollen resin, a soln of 1% TFA/ CH_2Cl_2 (10 mL) was added and the mixture was shaken for 2 min. The resin was filtered into a flask containing 10% pyridine in MeOH. The addition of 1% TFA soln to the resin was repeated (3 \times) and the filtrates were again collected in 10% pyridine/MeOH soln. The combined filtrates were concentrated to 5% of the volume under reduced pressure. H_2O (40 mL) was then added to the concentrated residue and the contents were cooled with ice to aid precipitation of the protected peptide; yield: 90–95%.

21.11.5.1.4

Variation 4: PAM Resin

Widely used in solid-phase peptide synthesis with the Boc strategy, the PAM [4-(hydroxymethyl)phenylacetylaminomethyl] anchor^[370,372] (see Scheme 35) is relatively stable to acid because of the presence of the electron-withdrawing acetylaminomethyl group. After acylation of (aminomethyl)polystyrene with 4-(hydroxymethyl)phenylacetic acid, the first amino acid can be introduced by DCC-mediated coupling or via active ester chemistry for forming resin-bound esters.^[420] Alternatively, PAM resin can be prepared using a preformed handle strategy in which the Boc-protected amino acid is first attached to the protected linker in solution and then coupled to the aminomethyl resin, followed by capping of unreacted aminomethyl groups.^[372] This approach can produce a well-defined res-

in by preventing the formation of side products. The PAM resin is fully compatible with the Boc/Bzl protection scheme and has been cleaved using strong acids such as anhydrous hydrogen fluoride, trifluoromethanesulfonic acid, and hydrogen bromide/trifluoroacetic acid to release peptides with C-terminal carboxylic acids.

21.11.5.1.5 **Variation 5: Trityl Resin**

Trityl resins (e.g., 2-chlorotrityl chloride resin) have had extensive use in solid-phase synthesis because of their steric bulk and acid lability. For example, 2-chlorotrityl resin (Barlos resin) (see Scheme 35) has been commonly used in the Fmoc/*t*-Bu strategy for solid-phase peptide synthesis.^[421,422] The attachment of the first amino acid to the 2-chlorotrityl resin is usually achieved by the nucleophilic substitution of the halogen group with an appropriate N-protected aminocarboxylate trialkylammonium salt such as ethyldiisopropylammonium or triethylammonium. The steric bulk of the 2-chlorotrityl group impedes intramolecular cyclization and loss of material by formation of piperazine-2,5-dione (diketopiperazine) at the dipeptide stage, such that *N*-alkyl and prolyl residues can be used as the first amino acid in the peptide sequence. Cleavage of the peptide is accomplished with 0.5% trifluoroacetic acid in dichloromethane and with 1,1,1,3,3,3-hexafluoropropan-2-ol in dichloromethane.^[419]

Attachment of N-Fmoc-Amino Acids to Trityl Chloride Resin; General Procedure:^[421]

The appropriate N-Fmoc-amino acid (0.3–0.8 mmol) in CH₂Cl₂ (10 mL·g^{−1} of resin) was treated with iPr₂NEt (3 mmol) and the mixture was added to the trityl resin (1.4–1.6 mmol Cl[−] g^{−1}) in CH₂Cl₂ and agitated for about 10 min. Additional iPr₂NEt (1.5 equiv, with respect to the N-Fmoc-amino acid) was added to the mixture, which was agitated vigorously for 1 h. The resin mixture was then treated with HPLC grade MeOH (3 mL) to convert the remaining trityl groups into methyl ethers. The resin was filtered, washed with CH₂Cl₂ (3 ×), MeOH (3 ×), and CH₂Cl₂ (3 ×), and dried under reduced pressure. The substitution of the resin was estimated from the increase in weight; yield: 70–75%.

21.11.5.1.6 **Variation 6: Rink Acid Resin**

This type of linker (see Scheme 35) is an acid-labile support well suited for the synthesis of protected peptide fragments by the Fmoc strategy. Peptide carboxylic acids can be released from this support using as little as 10% acetic acid in dichloromethane. The first amino acid is attached to the resin via the symmetric anhydride method using DIC and a catalytic amount of 4-(dimethylamino)pyridine. Because of the acid sensitivity of this resin, coupling reactions with N-Fmoc-amino acids are usually performed under basic conditions to prevent premature cleavage from the resin.^[423]

Cleavage of Peptide Acids from Rink Acid Resin; General Procedure:^[423]

The peptide resin was suspended in AcOH/CH₂Cl₂ (1:9, 10 mL·g^{−1} resin). The contents were allowed to stand at rt for 4 h. The resin was filtered and washed with dry pyridine to remove any remaining peptide. The combined filtrate and pyridine washings were concentrated under reduced pressure to afford the protected peptide acid; yield: 23%.

21.11.5.1.7 **Variation 7: HYCRAM Resin**

Allyl-based linker systems have proven to be compatible with both the Fmoc and Boc strategies because of the reasonable stability of allyl esters to the acids and bases em-

ployed during peptide synthesis. The HYCRAM [(hydroxycrotonyl)aminomethyl] resin (see Scheme 35) is typically prepared by the acylation of (aminomethyl)polystyrene with 4-bromobut-2-enoic acid or 4-hydroxybut-2-enoic acid in the presence of DCC and HOBT. Either *N*-Boc- or *N*-Fmoc-amino acid cesium salts can be linked onto the allyl linker via displacement of the corresponding allylic halide or allylic alcohol.^[424] Alternatively, the allylic alcohol may be acylated using the corresponding amino acid and conditions described for the acylation of Wang resin. With the aim of constructing acid- and base-sensitive glycopeptides by solid-phase synthesis, cleavage conditions for the removal of the final product from the HYCRAM linker have been developed which employ neutral conditions, such as tetrakis(triphenylphosphine)palladium(0) and a several-fold excess of a suitable weakly basic nucleophile (i.e., morpholine or *N*-methylaniline). The cleavage reaction involves a palladium(0)-catalyzed allyl group transfer to the nucleophile. HYCRAM resin has thus been used for the successful syntheses of *N*- and *O*-linked glycopeptides possessing sensitive glycosyl bonds.^[424–427]

Cleavage of Peptides from HYCRAM Resin; General Procedure:^[428]

The peptide resin (100 mg, ca. 0.075 mmol) was suspended in a degassed mixture of DMSO/THF/0.5 M HCl (2:2:1, 5 mL), shaken vigorously under argon, treated with Pd(PPh₃)₄ (30 mg, 0.026 mmol), shaken until the catalyst was dissolved, treated with *N*-methylaniline (0.385 mL, 3.5 mmol), and shaken under argon at rt for 12 h. The resin was filtered and washed with DMF (3 ×) and CH₂Cl₂ (3 ×). The combined filtrate and washings were concentrated under reduced pressure to give the crude peptide; yield: 70–86%.

21.11.5.1.8

Variation 8: Photolabile Linkers

Photolytic cleavage of a peptide after solid-phase peptide synthesis is a mild, noninvasive technique,^[429] compatible with both Fmoc/*t*-Bu and Boc/Bzl approaches for preparing side-chain protected and unprotected peptides.^[430] For example, nitrobenzyl-based photolabile linkers have been prepared by linking 4-(bromomethyl)-3-nitrobenzoic acid to (aminomethyl)polystyrene (Nbz; see Scheme 35)^[431] or benzylhydramine resin (Nbb).^[432,433] The first amino acid is incorporated as its cesium carboxylate by nucleophilic displacement of the benzyl bromide. Cleavage of the peptide from the photolinker is achieved by irradiation at 360 nm in a mixture of dichloromethane and 2,2,2-trifluoroethanol. During photolytic cleavage, 2-nitrosobenzaldehyde is produced as a side product, which may further decompose to azo and azoxy compounds. The azo and azoxy compounds are typically red in color and may act as internal filters that reduce the efficiency of photolysis, contingent on the amount of peptide resin photolyzed.^[434] Loss of peptide from the Nbz and Nbb resins has been reported to occur on treatment with piperidine, dependent on the steric hindrance of the C-terminal amino acid.^[435] Synthesis of longer peptide sequences is thus not recommended with Nbz and Nbb resins. However, a nitroveratryl-based handle (see Scheme 35) has been developed that possess two additional alkoxy groups and a methyl group on the benzylic carbon. This handle is more efficient for the synthesis and photolytic cleavage of longer peptide sequences and small molecule libraries.^[436] Products are efficiently released from the nitroveratryl resin in high yields by irradiation at 360 nm in 2,2,2-trifluoroethanol/dichloromethane (1:4).

Cleavage of Peptides from Photolabile Resins; General Procedure:^[437]

The peptide resin (0.5 g) was suspended in a mixture of 2,2,2-trifluoroethanol/CH₂Cl₂ (1:4, 100 mL) in a presilylated glass reaction vessel that was prepared by rinsing the glass vessel with 10% TMSCl in toluene followed by washing with abs EtOH and drying. The peptide resin suspension was degassed prior to photolysis by evacuating with a water-pump vacuum and purging with argon (3 ×). The resin suspension was then photolyzed at 360 nm in

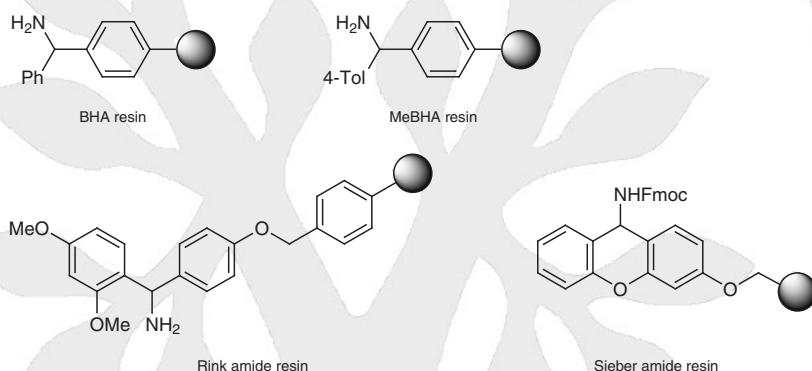
a Rayonnet apparatus with vigorous stirring at rt. The mixture was filtered and the resin was washed with 2,2,2-trifluoroethanol/ CH_2Cl_2 (1:4, 3 \times), CH_2Cl_2 (3 \times), and MeOH (3 \times). The filtrate and washings were combined and the solvent removed under reduced pressure; yield: 85–95%.

21.11.5.2

Method 2: Generation of C-Terminal Peptide Amides

Many natural peptide hormones, such as oxytocin, apamin, and calcitonin, exhibit biological activity as C-terminal amides. Although such amides may be made by ammonolytic cleavage of resin-bound esters, the limited swelling of most resins under such cleavage conditions, as well as the potential for epimerization and mediocre yields, have all stimulated the development of linkers to facilitate the solid-phase synthesis of peptide amides. Such handles include active ester linkages for ammonolysis and amine handles onto which the peptide can be anchored and released as a C-terminal amide.^[397] Common supports for generating peptide amides are described in this section (Scheme 37).

Scheme 37 Common Supports for Generating Peptide Amides^[397]



21.11.5.2.1

Variation 1: Benzhydrylamine and 4-Methylbenzhydrylamine Resins

Widely used for the synthesis of peptide amides, the benzhydrylamine linkers are usually synthesized by a two-step process involving Friedel–Crafts acylation of polystyrene beads with benzoyl chloride for benzhydrylamine (BHA) resin or with 4-methylbenzoyl chloride for 4-methylbenzhydrylamine (MeBHA) resin, in the presence of aluminum trichloride in nitrobenzene, followed by a reductive amination on the intermediate ketone to provide the amine.^[438,439] These linkers are labile to treatment with hydrogen fluoride. The extra methyl group of the MeBHA linkage facilitates cleavage with acid relative to the benzhydrylamine linkage of the BHA resin.

Amino acids are attached to such amine resins by common coupling methods, such as those which employ carbodiimides, preformed active esters, and reagents such as TBTU and HBTU. Effective cleavage of the peptide amide has typically been achieved by employing anhydrous hydrogen fluoride or trifluoromethanesulfonic acid in the presence of scavengers, such as *m*-cresol and ethanedithiol.

21.11.5.2.2

Variation 2: Rink Amide Resin

In Rink amide resin (2,4-dimethoxybenzhydrylamine), the presence of additional *para*- and *ortho*-alkoxy groups on the aromatic rings of the benzhydryl linker renders the acyl-

ated amine more labile to acidolysis. In the two types of Rink amide resins, the benzhydrylamine linker is attached either directly to the support through a benzylic ether bond (see Scheme 37), or by way of an electron-withdrawing acetylamino spacer. Lacking the amide group, the former resin is more acid sensitive than the latter. In both cases, the first N-protected N-Fmoc-amino acid is usually attached using DIC/HOBt.^[423] The deprotected peptide product can be cleaved from the Rink resin in a single step using 95% trifluoroacetic acid and a trialkylsilane as scavenger to yield the corresponding C-terminal peptide amide with good purity. Rink amide resin has found extensive application in the Fmoc strategy for solid-phase peptide synthesis, as well as in the solid-phase synthesis of heterocycles such as isoxazoles and dihydroisoxazoles.^[440]

21.11.5.2.3

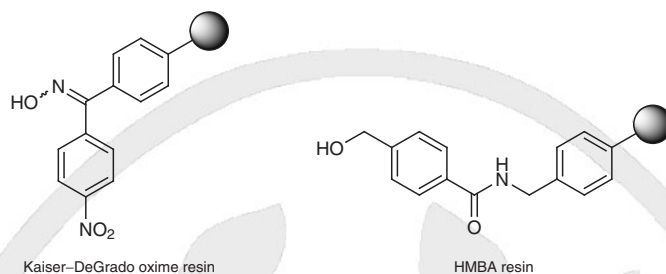
**Variation 3:
Sieber Amide Resin**

Sieber amide handles (see Scheme 37) are preferred supports for the preparation of side-chain protected peptide amides and acid-labile carboxamides, because the product can be cleaved under mild acid conditions (i.e., 1% TFA in CH₂Cl₂).^[411] The first amino acid is attached via standard coupling conditions, such as DIC/HOBt. Because the amino group is less hindered than that of the Rink resin, the Sieber amide resin is better suited for sterically demanding reactions. The resin has also been reductively alkylated to afford supports suitable for the synthesis of N'-alkylcarboxamides.^[326]

21.11.5.2.4

**Variation 4:
Oxime-Based (Kaiser–DeGrado) Resin**

Kaiser–DeGrado resin (Scheme 38) has been used in the synthesis of Boc/Bzl-protected peptide fragments with various C-terminal modifications.^[441,442] Synthesis of the resin is accomplished by Friedel–Crafts acylation of polystyrene–1% divinylbenzene with 4-nitrobenzoyl chloride, followed by reaction of the resulting ketone with hydroxylamine in ethanol.^[443] Attachment of the first amino acid to the linker is generally performed using DCC-mediated coupling, often in the presence of ethyl 2-cyano-2-(hydroxyimino)acetate in dichloromethane.^[443,444] Peptide fragments can be cleaved from the resin using various nucleophiles. For example, hydroxylamine has been used to produce hydroxamates^[444] and hydrazine has been used to produce peptide hydrazides. Acetate salts of amino acids or peptide esters react to provide peptide C-terminal acids and esters, respectively,^[445,446] which have also been made by reactions with water and alcohols in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene.^[447] In addition, primary amines and ammonia have been used to produce protected peptide amides.^[448] Cyclative cleavage on oxime resin has also been used for the synthesis of many cyclic peptide analogues.^[449–452] Transesterification of the peptide resin with 1-hydroxypiperidine (HOPip) has also been used to prepare peptide piperidino esters, which on treatment with zinc/acetic acid afford the corresponding peptide carboxylic acids.^[453] Owing to its sensitivity to nucleophiles, neutralization of oxime resin with base after removal of Boc groups with acid has been observed to cause some loss of peptide from the resin.

Scheme 38 Kaiser–DeGrado Oxime Resin and HMBA Resin^[441,442,454,455]
Attachment of *N*-Boc-Amino Acids to Oxime Resin via DCC/Ethyl 2-Cyano-2-(hydroxyimino)acetate; General Procedure:^[444,453]

CAUTION: *N,N'*-Dicyclohexylcarbodiimide is a severe eye, skin, and respiratory tract irritant, and a skin sensitizer. Since it has a low melting point (34–35 °C), it can also be handled as a liquid after gentle warming in a water bath.

The oxime resin (1 g) swollen in CH_2Cl_2 (10 mL) was treated at -10°C with the *N*-Boc-amino acid (1 mmol) and DCC (1 mmol), followed by ethyl 2-cyano-2-(hydroxyimino)acetate (2 mmol), stirred at -10°C for 30 min, then at rt for 24 h, filtered, washed with CH_2Cl_2 and $\text{CH}_2\text{Cl}_2/\text{EtOH}$ (2:1), and dried under reduced pressure. The loading of the *N*-Boc-amino ester was determined by weighing the displaced amide from treating an aliquot of resin with iBuNH_2 ; yield: not reported.

Cleavage of Peptide Hydroxamates from Oxime Resin; General Procedure Using Hydroxylamine:^[444,453]

A 0.175 M stock solution of NH_2OH in $\text{MeOH}/\text{CHCl}_3$ (1:10) was prepared by initially dissolving $\text{NH}_2\text{OH}\cdot\text{HCl}$ (0.7 g, 10 mmol) in anhyd MeOH (5 mL), cooling to 0°C , and treating with NaOMe in MeOH (25% w/w, 8.75 mmol). The precipitated NaCl was removed by filtration and the filtrate was diluted with CHCl_3 (50 mL). The *N*-Boc-amino acid oxime resin (0.06 mmol), swollen in CHCl_3 (0.5 mL), was treated with the NH_2OH stock soln (0.175 mmol), agitated at rt for 12 h, and filtered. The resin was washed with CHCl_3 (3×1 mL) and $\text{CHCl}_3/\text{MeOH}$ (1:1, 3×1 mL). The combined filtrate and washings were concentrated to yield crude hydroxamate, which was further analyzed by RP-HPLC on a C18 column using 10–100% $\text{MeCN}/\text{H}_2\text{O}/0.1\%$ TFA; yield: 72–99% (purity 77–90%).

Cleavage of Protected Peptide Acids from Oxime Resin; General Procedure Using 1-Hydroxypiperidine:^[453]

The peptide-oxime resin was suspended in CH_2Cl_2 [$1\text{ g}\cdot(10\text{ mL})^{-1}$], shaken with HOPip (3 equiv) at rt for 3–16 h, filtered, and washed with CH_2Cl_2 , DMF, and MeOH . The combined filtrate and washings were concentrated under reduced pressure and the crude residue was triturated with Et_2O to afford the crude peptide-piperidino ester. This crude ester was dissolved in 90% AcOH ($15\text{ mL}\cdot\text{g}^{-1}$), treated with Zn dust (30 equiv), and stirred at rt for 30 min. The Zn was filtered and washed with 90% AcOH (3×5 mL). The combined filtrate and washings were concentrated under reduced pressure to yield crude peptide carboxylic acid, which was dissolved in a mixture of $\text{CHCl}_3/\text{MeOH}/\text{AcOH}$ and filtered through a pad of silica gel to remove residual Zn and side products originating from HOPip . After evaporation of the filtrate, the residue was purified by gel filtration [Sephadex LH-20, $\text{MeOH}/\text{CHCl}_3$ (9:1) or DMF] and fractions were monitored by UV at 270 nm and by TLC. The pure fractions were concentrated and triturated with Et_2O to yield pure peptide carboxylic acid; yield: not reported.

Cleavage of Boc-Gly-Ile-OH from Oxime Resin; Typical Procedure Using 1-Hydroxypiperidine:^[453]

Boc-Gly-Ile-oxime resin (1.0 g, 0.302 mmol) was suspended in CH_2Cl_2 (10 mL), shaken with HOPIp (91 mg, 0.9 mmol) at rt for 18 h, filtered, and washed with CH_2Cl_2 , DMF, and MeOH. The combined filtrate and washings were concentrated under reduced pressure and the crude residue was triturated with Et_2O to afford crude peptide-piperidino ester. This crude ester was dissolved in 90% AcOH (5 mL), treated with Zn dust (0.6 g), and stirred at rt for 30 min. The Zn was filtered and washed with 90% AcOH (3×5 mL). The combined filtrate and washings were concentrated under reduced pressure to yield crude peptide carboxylic acid, which was further dissolved in a mixture of $\text{CHCl}_3/\text{MeOH}/\text{AcOH}$ and filtered through a pad of silica gel to remove residual Zn and side products originating from HOPIp. After evaporation of the filtrate, the residue was purified by gel filtration [Sephadex LH-20, $\text{MeOH}/\text{CHCl}_3$ (9:1) or DMF] and fractions were monitored by UV at 270 nm and by TLC. The pure fractions were concentrated and triturated with Et_2O to yield pure peptide carboxylic acid; yield: 80%.

**21.11.5.2.5 Variation 5:
4-Hydroxymethylbenzoic Acid Resin**

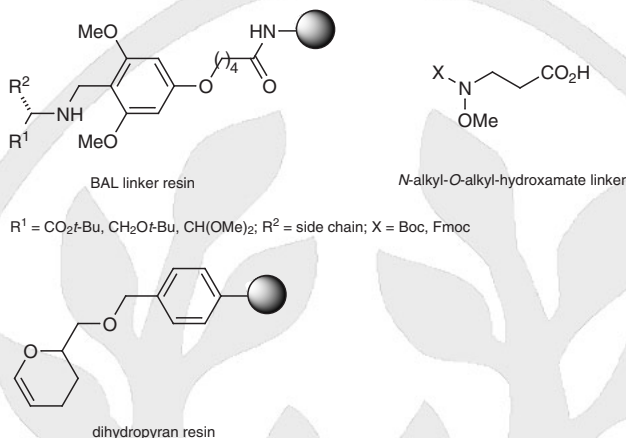
4-Hydroxymethylbenzoic acid (HMBA) resin (see Scheme 38) can similarly be treated with amines to release peptide amides.^[455] Similar to the phenylacetamide moiety of PAM resin, the benzamide of HMBA resin renders the support-bound ester reactive towards nucleophilic attack and inert to strong acid. The linker is usually attached to (aminomethyl)-polystyrene through activation as a trichlorophenyl ester^[456] or using DIC and HOBT. The first amino acid is attached either by 4-(dimethylamino)pyridine-catalyzed esterification with the appropriate symmetrical anhydride, by using 2,6-dichlorobenzoyl chloride and pyridine, or by MSNT and 4-methylmorpholine. Esters linked to HMBA resin have been cleaved by a variety of nucleophiles, including ammonia,^[403,456] hydroxide ions, alkoxides,^[403,457] hydrazine,^[403,458] and lithium borohydride^[403] to release C-terminal amides, acids, esters, hydrazides, and alcohols, respectively.

**21.11.5.3 Method 3:
Generation of Peptides with Other C-Terminal Modifications**

Peptides with other C-terminal functionalities, such as aldehydes, alcohols, hydrazides, and hydroxamic acids, exhibit a variety of biological activities and have, for example, been used as enzyme inhibitors.^[397,459] As described in Section 21.11.5.2, certain C-terminal functions may be prepared by nucleophilic cleavage of resin-bound esters from an appropriate support. Alternatively, linking a peptide to the resin by way of its backbone amides provides an effective strategy for modifying the C-terminal carboxylates (Scheme 39). For example, C-terminal peptide aldehydes have been synthesized on a solid support using the backbone amide linker (BAL) strategy, which involves the attachment of a backbone amide nitrogen to a trialkoxybenzylamide system.^[460] The BAL anchor is achieved by reductive amination with an appropriate amino acid residue. The strategy involves the coupling of BALdehyde^[461] onto the support using a solution of HATU/*N,N*-diisopropylethylamine/dimethylformamide, followed by reductive amination with an appropriate amino acid analogue to afford the desired BAL anchor in good yield.^[460] Moreover, a series of C-terminal linkers has been developed to produce specific functionality, for example *N*-alkyl-*O*-alkylhydroxamate linkers (see Scheme 39) have been employed in the synthesis of peptide aldehydes by both Boc and Fmoc strategies featuring reductive cleavage with lithium aluminum hydride.^[462] A hemisuccinate linker has also been used to prepare peptide C-terminal alcohols.^[463] A dihydropyran-based linker has been employed to link alcohols to the resin (Scheme 39), which are cleaved using trifluoroacetic acid.^[464,465] Other

handles and techniques for making peptide C-terminal hydroxamic acids, hydrazides, thioacids, and thioesters have been reviewed.^[396,397]

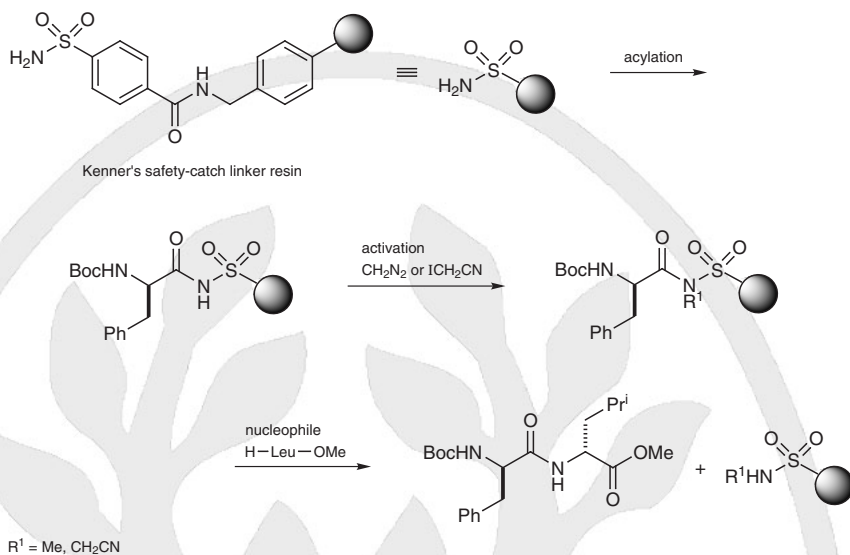
Scheme 39 Further Linker Resins^[460,462,464,465]



21.11.5.4

Method 4: Safety-Catch Linker Resins

This strategy involves the synthesis of a growing peptide chain on a relatively stable linker moiety which is capable of becoming labile to cleavage after a site-specific chemical modification.^[466–468] Such linkers are typically designed to be stable to the acidic and basic conditions used during peptide synthesis; however, on activation with an alkylating agent, the linker becomes susceptible to cleavage by nucleophilic attack. For example, Kenner's sulfonamide safety-catch linker has been used to tether carboxylic acids onto (aminomethyl)polystyrene or MeBHA resin during standard coupling procedures (Scheme 40).^[466] After activation by treatment with diazomethane, the *N*-acyl-*N*-alkylsulfonamide becomes reactive to a variety of chemical modifications, such as aminolysis and hydrolysis to provide peptide amides and acids. This linker strategy has, however, certain limitations, such as a typically low loading capacity, potential for racemization during loading onto the relatively unreactive sulfonamide resin, and the potential for an explosion using diazomethane. The use of iodoacetone nitrile as the alkylating agent has, however, enhanced the utility of Kenner's resin, particularly because the *N*-acyl-*N*-(cyanomethyl)sulfonamide is more reactive in nucleophilic displacement reactions than the *N*-acyl-*N*-methylsulfonamide.^[467,468] Safety-catch linkers which can be activated by oxidative reactions have also been employed in the synthesis of cyclic peptides.^[469,470]

Scheme 40 Safety-Catch Linker Resin^[466–468]

21.11.5.5

Method 5: Analytical Procedures for Determining Loading on the Solid Support

21.11.5.5.1

Variation 1: Fmoc Monitoring

The strong UV absorbance of the Fmoc group aids in monitoring the acylation reaction on the resin. The deprotection of Fmoc by piperidine results in the formation of a dibenzofulvene–piperidine adduct which shows strong absorption at 301 nm (ϵ 7800 M⁻¹·cm⁻¹). The UV absorbance of this adduct upon release from the resin allows calculation of the substitution levels on the resin.^[471]

Fmoc Monitoring; General Procedure:^[471]

The *N*-Fmoc-amino acid (5–7 mg) was suspended in piperidine/DMF (1:4, 0.5 mL) and allowed to stand for 30 min, with occasional shaking. After 30 min, EtOH (6.5 mL) was added and the resin was allowed to settle. For a reference, the piperidine/DMF soln (1:4, 0.5 mL) was diluted with EtOH (6.5 mL). The UV absorbance of the solns containing the resulting fulvene–piperidine adducts and the reference were measured at 301 nm and compared with the soln from treatment of a *N*-Fmoc-amino acid of known concentration under identical conditions. The substitution level was calculated as follows, where y = path length:

$$\text{Loading in mmol} \cdot \text{g}^{-1} = \frac{(A_{301} \times [\text{amino acid}] \times 7 \text{ mL})}{(7800 \text{ M}^{-1} \cdot \text{cm}^{-1} \times y \text{ cm} \times \text{mg of resin})}$$

21.11.5.5.2

Variation 2: Picric Acid Test

The amine content on the solid support can also be determined by treating the resin with picric acid solution in dichloromethane, followed by elution of the retained acid with base. The UV absorbance of the resulting picrate reflects the amine content of the resin.^[472]

Picric Acid Test; General Procedure:^[472]

The resin was swollen in CH_2Cl_2 , neutralized with a mixture of $\text{iPr}_2\text{NEt}/\text{CH}_2\text{Cl}_2$ (1:19) twice, and washed with CH_2Cl_2 (5 \times) for 1 min per washing. The washed resin was treated with 0.1 M picric acid in CH_2Cl_2 (2 \times) for 1 min per treatment. The resin was washed with CH_2Cl_2 (5 \times) for 1 min per washing. The retained picrate was eluted twice with $\text{iPr}_2\text{NEt}/\text{CH}_2\text{Cl}_2$ (1:19, 1 mL) for 1 min per elution and the eluent was collected and diluted with 95% EtOH (50 mL). The UV absorbance of the resulting EtOH soln was measured at 350 nm (ϵ 14,500 $\text{M}^{-1}\cdot\text{cm}^{-1}$). The substitution level is calculated as follows, where y = path length:

$$\text{Loading in mmol} \cdot \text{g}^{-1} = \frac{(A_{358} \times [\text{amino acid}] \times 50 \text{ mL})}{(14,500 \text{ M}^{-1} \cdot \text{cm}^{-1} \times y \text{ cm} \times \text{mg of resin})}$$

21.11.5.6

Method 6:**Qualitative Tests for Determination of Free Amino Groups on the Solid Support**

21.11.5.6.1

Variation 1:**Ninhydrin (Kaiser) Test**

Among the most widely used qualitative tests for the presence of free amino groups, this analysis typically gives a dark purple color indicative of the presence of the primary amine of amino acid residues; however, proline does not yield a positive reaction.^[216]

Ninhydrin Test; General Procedure:^[216]

CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic.

Three reagents were prepared: (1) 0.01 M aq KCN, from which 2 mL were diluted with pyridine (100 mL); (2) 5% ninhydrin soln in EtOH (100 mL); (3) 80% PhOH in *t*-BuOH. A sample of resin was washed several times with EtOH, treated with 2 drops of each of the three solns, and heated to 120 °C for 2 min. The presence of resin-bound free amine was indicated by blue-purple beads.

21.11.5.6.2

Variation 2:**2,4,6-Trinitrobenzenesulfonic Acid Test**

This test is more sensitive than the Kaiser test for detecting primary amines. Here the beads turn an orange-red color.^[473]

2,4,6-Trinitrobenzenesulfonic Acid Test; General Procedure:^[473]

A small resin sample was washed several times with EtOH, treated with a drop of a soln composed of $\text{iPr}_2\text{NEt}/\text{DMF}$ (1:9) and 1% (w/v) 2,4,6-trinitrobenzenesulfonic acid in DMF. The suspension was allowed to stand at rt for 10 min. The red-orange color of the beads was indicative of free amino groups.

21.11.5.6.3

Variation 3:**Chloranil Test**

This test has been developed to detect secondary amino groups reliably, but it can also detect primary amines. It is particularly recommended for proline-containing peptides. Blue-stained resin beads are indicative of the presence of free secondary amines.^[474]

Chloranil Test; General Procedure:^[474]

A small sample of resin was treated with a drop of 2% acetaldehyde soln in DMF and with 2% *p*-chloranil in DMF. The mixture was allowed to stand at rt for 10 min. A blue staining of the beads was indicative of free amino groups on the solid support.

21.11.6 Interpeptide Amide Bond Formation

Previously published information on this product class is covered in *Houben–Weyl*, Vol. E 22a, pp 604–641.

Solid-phase peptide synthesis protocols are generally effective for synthesizing peptides of up to 60 amino acids in length. The synthesis of longer peptides, as well as peptides possessing normally incompatible protecting groups, may require the need to form an amide bond between two synthetic peptide segments. The general problems faced when joining together peptide segments are similar to those faced in stepwise peptide synthesis. Coupling reactions must be efficient, selective, and maintain configurational integrity. The peptide product must also be purified effectively after the coupling reaction. Two general approaches have been developed to fulfill these requirements. The first, segment condensation, couples fully protected peptides in solution^[475] or on the solid phase.^[476] The second, chemoselective ligation, involves an orthogonal coupling reaction between unprotected peptides in aqueous solution^[477] and has been accomplished on an aqueous-compatible solid phase.^[387,478]

**21.11.6.1 Method 1:
Protected Segment Condensation**

The first general approach for segment condensation to be developed was solution-phase coupling of larger peptide subunits. The segment condensation strategy employs standard coupling reagents in solution to form an amide between the unprotected N- and C-termini of two fully protected peptide segments of 6–10 amino acids in length. Purification is performed after each coupling step. A very successful method uses a combination of Boc/Bzl/OPac protection,^[475] as illustrated in the herculean synthesis of green fluorescent protein (238 amino acids) from 24 segments.^[4] On the other hand, protected segment condensation suffers from two major issues for which there is presently no satisfactory solution. The first is racemization and/or poor coupling at the activated C-terminal ester, which prevents a significant number of residues (Cys, His, Tyr, Ile, Val, Trp, Phe, Thr, Arg) from being employed at the C-terminus, and similarly makes coupling to an N-terminal Pro impractical. The number of potential coupling sites within a protein is thus diminished by nearly half (209 remaining out of a theoretical 400). Moreover, even at ideal sites (Gly/Gly or Pro/Gly) within soluble peptide segments, coupling rarely exceeds 90%. The added need for routine purifications reduces the efficiency of chain assembly. The second issue is the insolubility of many fully protected peptide chains, which compromises their characterization by common methods of analysis, such as ESI-MS. Solubility and coupling can be improved by using hydrophobic solvents like 1,1,1,3,3,3-hexafluoropropan-2-ol and mixtures such as chloroform/2,2,2-trifluoroethanol;^[479] however, the manipulation of fully protected segments above 60 amino acids is very difficult. The assembly of protected peptide segments on the solid phase (so-called “convergent protein synthesis” or CPS)^[476] can facilitate purification; however, the issues associated with the coupling reaction are magnified. As a result, only a few proteins have been made with CPS with efficiency comparable to that of a stepwise total synthesis.

If possible, the synthesis of the desired sequence is broken into segments around 10 amino acids in length. Junctions between fully protected segments (Boc-peptide-CO₂H + H₂N-peptide-OPac) are chosen such that the carboxy residue is either Gly or Pro, to eliminate the possibility of racemization. Protected segments are dissolved in dimethylform-

amide if possible; otherwise, chloroform/2,2,2-trifluoroethanol (3:1) or chloroform/phenol (9:1 to 5:1) may be used as solvents for the coupling reaction. The C-terminal phenacyl ester (Pac) can be removed by treatment with zinc powder in acetic acid at 40–50 °C (see Section 21.11.1.2.4); this selective deprotection gives options for the direction of segment assembly if handling problems occur.

Condensation of Protected Segments by Boc/Bzl/OPac Strategy; General Procedure:^[480]

CAUTION: *HOBt is commercially available with or without water of crystallization; the hydrated form can be used for peptide coupling by the DCC/HOBt method. However, when water-free material is required, drying should be carried out carefully, as HOBt (and HOAt) decompose in a rapid exothermal reaction above 180 °C. Water-free HOBt can also be obtained by recrystallization from EtOH or EtOH/Et₂O.*

CAUTION: *Carbodiimides are severe eye, skin, and respiratory tract irritants, and skin sensitizers. They should only be handled with gloves in a fumehood.*

In a minimum volume of solvent, e.g. CHCl₃/2,2,2-trifluoroethanol (3:1, 50 mL), the Boc-peptide acid (1 mmol) and H₂N-peptide-OPac (1 mmol) were dissolved together and cooled to 0 °C. HOBt (0.2 g, 1.2 mmol) and EDC (0.22 mL, 1.2 mmol) were added to the soln, which was stirred for 1 h, warmed to rt, and stirred overnight. The solvent was removed by rotary evaporation and the residue was triturated with an excess of chilled 1% aq NaHCO₃. The resulting precipitates were filtered and washed with 1 M HCl and H₂O. The product was then dissolved in the same reaction solvent (e.g., CHCl₃/2,2,2-trifluoroethanol 3:1) and concentrated again. To the residue, MeCN was added and the precipitates were collected and washed with MeOH, EtOAc, and hexane, successively; yield: 85–93%.

21.11.6.2 Method 2: Chemoselective Ligation

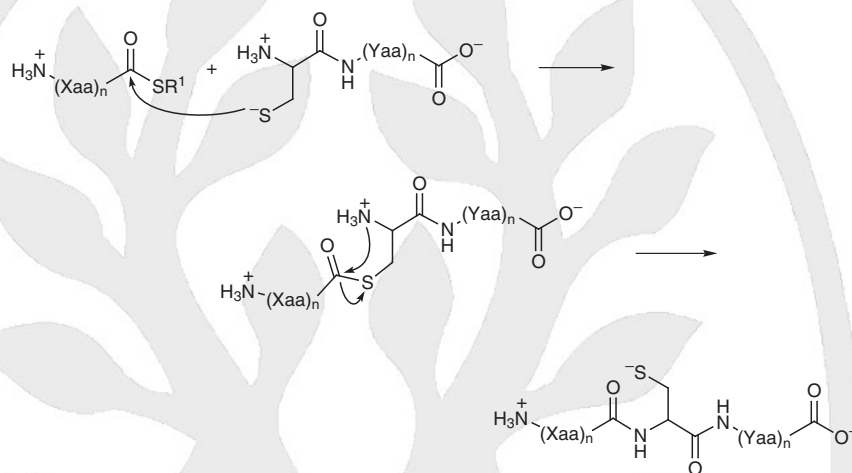
The second general approach for fragment coupling, called chemoselective ligation,^[481] employs a selective reaction to join specific chemical functional groups at the N- and C-termini of two unprotected peptide fragments of short to moderate length (up to 60 amino acids). In this process, the larger size of the individual components reduces the number of steps to the final product, and the lack of side-chain protection markedly improves overall handling and analysis. Additional solubility can be conferred in solution by the addition of chaotropic salts (e.g., guanidine hydrochloride) to the ligation mixture. A number of chemoselective reactions have been developed that result in the formation of thioester,^[481] sulfide,^[482] oxime,^[483] and pseudoproline/thiazolidine/oxazolidine^[484–486] bonds. These chemoselective ligations (with the exception of the thioester-forming reaction) form generally poor isosteres of the amide bond, which may not be a problem if the ligation site is in an unstructured region of the protein or peptide of interest. In spite of thioester bonds and some pseudoprolines being chemically reactive at neutral and basic pH, a number of stable and bioactive protein analogues, such as HIV protease,^[487–489] cMyc-Max,^[490] and integrin $\alpha_{\text{IIb}}/\beta_{\text{III}}$,^[491] have been constructed by chemoselective ligation.

21.11.6.2.1 Variation 1: Native Chemical Ligation

The full potential of chemoselective ligation became apparent with the development of methods that could form native amide bonds. The first (and most versatile) of these ligation methods is native chemical ligation,^[8] in which a peptide with a C-terminal thioester reacts with a peptide with an N-terminal cysteine residue. This process was first recog-

nized in the synthesis of an *N*-acylcysteine dipeptide in which a valine thioester exchanged onto the side-chain thiol of cysteine and subsequently underwent an S→N acyl migration.^[492] The modern ligation process normally features the coupling of larger peptide fragments for which an additional alkyl thioester activation step is performed in situ by treatment with an arenethiol (e.g., Bzl-SH or PhSH), resulting in the formation of a significantly more active α -aryl thioester,^[8,9] thioester exchange with the cysteine side-chain thiol, and an S→N acyl shift, which provides the amide and regenerates the initial cysteine side chain (Scheme 41).

Scheme 41 Native Chemical Ligation^[477]



The process is fast and efficient, noncompetitive with internal cysteine residues, and generally compatible with all X-Cys ligation sites (with the exception of Pro-Cys). The ability to store the thioester peptides as alkyl thioesters until ligation also offers a number of additional advantages with handling and preparation. The primary drawback to this technique is that a cysteine residue is required in a synthetically desirable location. Inserting a cysteine into a desirable location can be effectively accomplished by peptide synthesis; however, a number of potential consequences may occur, such as oxidative cross-linking of proteins and disruption of protein folding, which may perturb functional assays of the final product. Cysteine is a uniquely reactive amino acid and can be easily alkylated after ligation with alkyl halides (i.e., iodoacetamide) or desulfurized by treatment with Raney nickel (to provide an Ala residue).^[493] Such approaches must be used judiciously, because they will also likely effect other cysteine and methionine residues in the protein.

Peptide Thioesters Generated from TAMPAL Resin Compatible with the Boc/Bzl Solid-Phase Approach; General Procedure:^[494]

CAUTION: Hydrogen fluoride fumes are severely irritating and extremely destructive to the respiratory system.

Boc-Leu-OH (924 mg, 4 mmol) was activated with a soln containing HBTU (1.37 g, 3.6 mmol) and *i*Pr₂NEt (730 μ L, 6 mmol) in DMF (4 mL) and coupled for 16 min to MeBHA resin (2 mmol) swollen in DMF; coupling yield: 99.9%. [Preloaded Boc-Leu-*p*-amidomethyl (PAM) resin has also been used as the starting solid support.] The resin was filtered, washed with DMF for 30 s, treated with TFA for 1 min, and washed with DMF (2 \times 30 s). *S*-Trityl propanethioate (1.04 g, 3 mmol) was activated with a soln containing HBTU (2.7 mmol) and *i*Pr₂NEt (6 mmol) in DMF (3 mL) and coupled for 16 min to the Leu-MeBHA resin; coupling yield: 99.9%. The resin was filtered and flow-washed with DMF (2 \times 30 s). The result-

ing trityl-associated propanethioic S-acid-leucyl (TAMPAL) resin was then used as a starting resin for polypeptide-chain assembly after removal of the Trt protecting group with two 1-min treatments with a soln of 2.5% $i\text{Pr}_3\text{SiH}$ and 2.5% H_2O in TFA. Care was taken to avoid pulling air through the resin after Trt deprotection to avoid the formation of disulfides on the resin. The thioester bond can generally be formed with any desired amino acid by using standard *in situ* neutralization amino acid coupling protocols^[162] for 1 h. After terminal Boc deprotection, peptide synthesis can be carried out. Treatment of the final peptide on resin with anhyd HF yields the C-terminal activated propanethioic S-acid-leucine (MPAL) thioester peptides that are ready to be used for native chemical ligation. Synthetic yields of human secretory phospholipase A_2 (hsPLA₂) fragments synthesized on TAMPAL resin were between 73% and 85%.^[494]

Peptide Thioesters Generated from Sulfamylbutanyl Resin Compatible with the Fmoc/*t*-Bu Solid-Phase Approach; General Procedure:^[495]

3-Carboxypropanesulfonamide Resin:^[495]

CAUTION: Carbodiimides are severe eye, skin, and respiratory tract irritants, and skin sensitizers. They should only be handled with gloves in a fumehood.

CAUTION: HOBt is commercially available with or without water of crystallization; the hydrated form can be used for peptide coupling by the DCC/HOBt method. However, when water-free material is required, drying should be carried out carefully, as HOBt (and HOAt) decompose in a rapid exothermal reaction above 180 °C. Water-free HOBt can also be obtained by recrystallization from EtOH or EtOH/Et₂O.

PEG-PS•HCl resin (1 g, 0.19 mmol·g⁻¹) or TentaGel (0.8 g, 0.24 mmol·g⁻¹) was weighed in a 35-mL polypropene syringe equipped with a 20-μm polyethene filter. The resin was washed with $i\text{Pr}_2\text{NEt}$ (2 × 5 min) and DMF (5 × 2 min) until the resin was fully swollen. 3-Carboxypropanesulfonamide (159 mg, 0.95 mmol), DIC (148 μL, 0.95 mmol), and HOBt (128 mg, 0.95 mmol) were then added in the minimum amount of DMF suitable for keeping the swollen resin covered with solvent. After agitation on a rotary shaker for 24 h, and verification of completion of coupling by a ninhydrin test on a sample of the resin, the resin was filtered, washed extensively with DMF, and used for the assembly of the peptide thioester or washed further with CH_2Cl_2 and dried under reduced pressure until further use; yield: quant.

Attachment of the First Amino Acid and Peptide Synthesis:^[496]

In a typical experiment, 3-carboxypropanesulfonamide resin (0.2 mmol), CH_2Cl_2 or CHCl_3 (5 mL), $i\text{Pr}_2\text{NEt}$ (342 μL, 2 mmol), and the *N*-Fmoc-amino acid (1 mmol) were added to a 50-mL round-bottomed flask, stirred for 20 min, cooled to -20 °C, then treated with solid PyBOP (520 mg, 1 mmol). The mixture was stirred at -20 °C for 8 h, filtered, and washed with CH_2Cl_2 or CHCl_3 (5 × 5 mL). The extent of incorporation was quantified by the Fmoc release UV assay.^[497] Coupling was repeated when loading was ≤70%. After initial coupling, standard Fmoc coupling protocols were used to extend the peptide chain on the resin.

Alkylation of the Peptide-Acylsulfonamide Resin with TMS-CHN_2 :^[495]

In a typical experiment, *N*-acylsulfonamide resin (20 mg, 0.4 mmol·g⁻¹ or 42 mg, 0.19 mmol·g⁻¹) was weighed in a 3-mL polypropene syringe equipped with a 20-μm polyethene filter. The resin was washed with THF until fully swollen, treated with a soln of 1 M TMSCHN_2 (2.4 mL) in hexane/THF (1:1), and agitated on a rotary plate for 2 h. After filtration, the resin was washed with THF (5 × 3 mL) and DMF (5 × 3 mL) and used in the dis-

placement reaction (see below) or further washed with CH_2Cl_2 (5×2 mL) and dried under reduced pressure until further use; yield: not reported.

Displacement with Ethyl 3-Sulfanylpropanoate:^[495]

The activated *N*-acylsulfonamide resin (8 μM) was swollen in DMF, drained, and treated with a soln of DMF or CH_2Cl_2 (350 μL) and ethyl 3-sulfanylpropanoate (52 μL , 400 μM , 50 equiv). The mixture was agitated on a rotary plate for 24 h, after which time the resin was filtered and washed with DMF (3×1 mL). The combined filtrate and washes were collected in a 25-mL round-bottomed flask and rotary evaporated. Before cleavage of side-chain protecting groups, the residue was triturated with cold Et_2O (5×4 mL) to remove traces of DMF and ethyl 3-sulfanylpropanoate which may interfere with the action of TFA; yield: not reported.

Removal of N-Terminal and Side-Chain Protecting Groups:^[495,498]

In a typical experiment, the cleaved, protected peptide (12 mg) was treated with a soln of 88% TFA, 5% PhOH, 2% iPr_3SiH , 5% H_2O (3 mL) for 2 h at 21 °C. The TFA soln was added dropwise to screw-cap centrifuge tubes containing TFA/*t*-BuOMe (1:10). After centrifugation at 3200 g (30 min), the *t*-BuOMe was removed and the peptide precipitate was resuspended in *t*-BuOMe (50 mL). The centrifugation and suspension were repeated twice. The final precipitated peptide thioester was dissolved in 50% aq MeCN and lyophilized.

Native Chemical Ligation; General Procedure:^[8,9,494]

Lyophilized peptide thioester (1 equiv, typically 2.5 mg, 1–3 mmol) and the N-terminal cysteine-containing peptide (1 equiv, typically 2.5 mg, 1–3 mmol) were dissolved in an Eppendorf tube (1.5 mL) containing a soln of degassed 6 M guanidine hydrochloride and 0.1 M Na_3PO_4 (1 mL, pH 8.5) with 2%/2% PhSH/Bzl-SH (resulting in a final pH of ~7 owing to thiols and residual salts accompanying lyophilized peptides). The tube was closed and vortexed periodically. The ligation reaction was accelerated by placing the tube in a heating block at 37 °C. The progress of the reaction was followed by analytical HPLC using a C4 column and ESI-MS; reactions were typically completed in 5–16 h, depending on the C-terminal amino acid thioester; yield: ca. 90%. Prior to purification, oxidized thiols were separated by centrifugation in a microcentrifuge. The oxidized thiols appeared white and floated to the surface of the soln. Purification was accomplished by semipreparative HPLC. In cases when the retention times of the peptide overlapped with those of the remaining thiol additives (Bzl-SH, PhSH), the thiols could be removed before further purification by washing the aqueous mixture with ice-cold anhyd Et_2O .

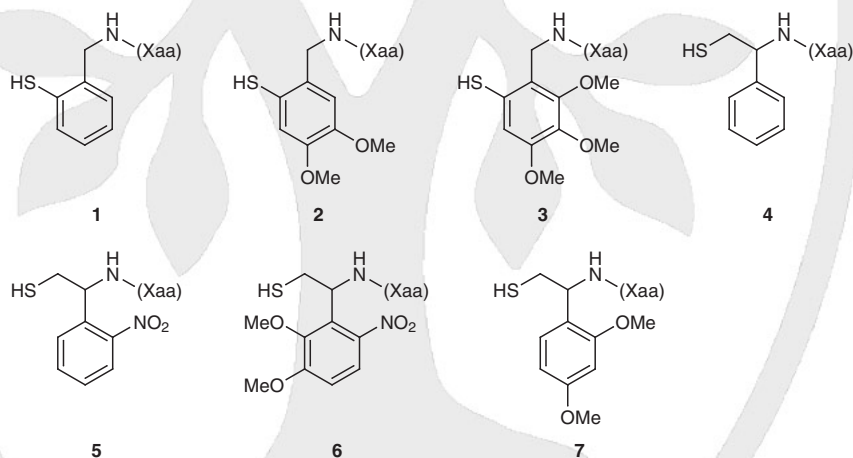
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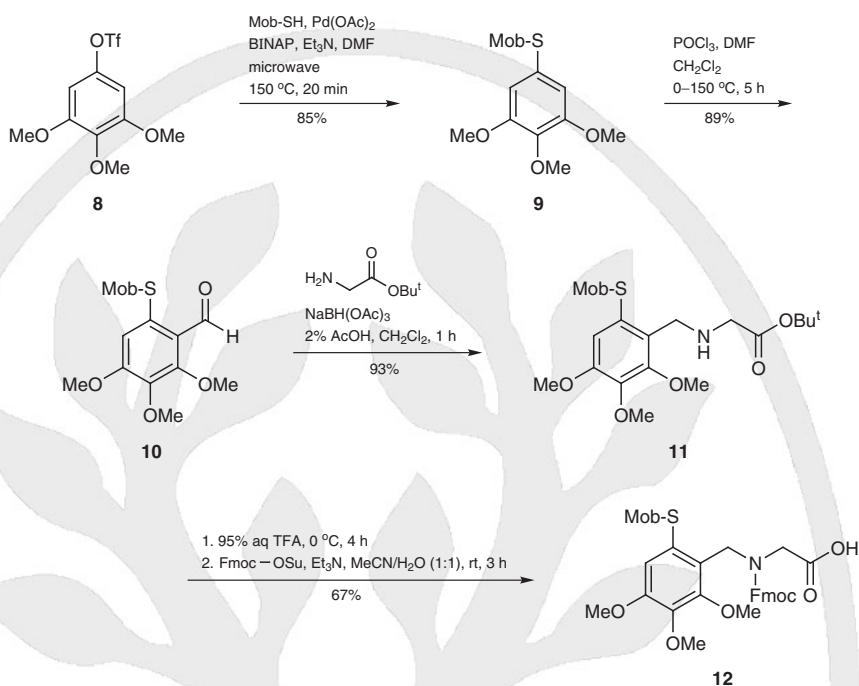
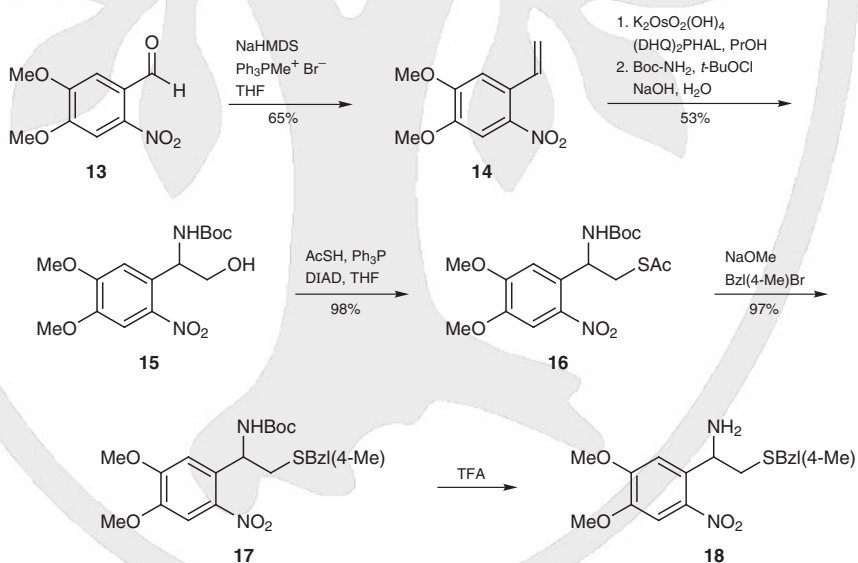
Variation 2: Auxiliary-Mediated Chemical Ligation

To extend the utility of chemoselective ligation for making amide bonds, research has focused on auxiliary-mediated native chemical ligation,^[307,499–503] aiming to remove the requirement of an N-terminal cysteine residue by moving the thiol functionality to an N-linked auxiliary. Pioneering research using the “thiol capture” strategy had shown that auxiliary-mediated ligation was possible using a C-linked 4,6-disubstituted dibenzofuran^[504–506] and a peptide with an N-terminal cysteine residue. The N-linked auxiliary approach mimics native chemical ligation: the thioester exchanges onto the thiol of the auxiliary, then migrates from the sulfur to the nitrogen of the amine terminus. However, unlike native chemical ligation, the auxiliary must then be removed by selective deprotection to generate the native amide bond. Rates of acyl transfer are usually contingent on ring size of the auxiliary; most auxiliaries transfer the acylating fragment via a six-membered transition state, which usually proceeds at a relatively slower rate of acyl transfer than the five-membered counterpart in native chemical ligation. Additionally,

acylating a secondary amine is generally more difficult than a primary amine. Success using this strategy has necessitated strict requirements on the size of the auxiliary and the use of preactivated thioesters. Two general classes of auxiliaries have been developed. The first class developed from the 2-sulfanylbenzyl auxiliary **1**,^[502] and includes the 4,5-dimethoxy-2-sulfanylbenzyl **2** [Dmb(2-SH)] and 4,5,6-trimethoxy-2-sulfanylbenzyl **3** [Tmb(2-SH)] auxiliaries (Scheme 42),^[499,500,507] which offer reasonable reaction rates, and have extended the range of potential ligation junctions to Xaa-Gly and Gly-Xaa (where Xaa is a proteinogenic amino acid other than proline). Dmb(2-SH) **2** can be removed by treatment with anhydrous hydrogen fluoride after ligation, and Tmb(2-SH) **3** can be cleaved by trifluoroacetic acid after ligation.^[499] The second class of auxiliaries, developed from the 1-amino-1-phenyl-2-sulfanylethyl group **4**,^[501] offer similar reactivity as the first class; moreover, analogues have been developed that can undergo photochemical deprotection (e.g., **5**^[501,508,509] and **6**^[509]) or deprotection by trifluoroacetic acid (e.g., **7**).^[307,510] One limitation of this class of racemic auxiliaries (**4–7**) are the lengthy syntheses, which produce mixtures of enantiomers such that peptide coupling produces diastereomeric products, which may complicate purification and analysis. The configuration of the auxiliary, however, has been reported to cause no effect on the rate of ligation.^[509] Preactivation of the thioester is necessary for ligation of sterically demanding residues (other than Gly-Gly, His-Gly, Cys/nbhy;Gly) using these auxiliaries, because free thiols can inhibit ligation;^[499] for less sterically demanding ligations, TAMPAL thioesters have been used successfully. The syntheses of *N*-(9-fluorenylmethoxycarbonyl)-*N*-(2,3,4-trimethoxy-6-[(4-methoxybenzyl)sulfanylbenzyl]glycine^[509] and 1-(4,5-dimethoxy-2-nitrophenyl)-2-[(4-methylbenzyl)sulfanylethylamine^[509] are shown in Schemes 43 and 44, respectively.

Scheme 42 Scaffolds for Auxiliary-Mediated Chemical Ligation^[307,499–502,507–510]



Scheme 43 Synthesis of *N*-(9-Fluorenylmethoxycarbonyl)-*N*-[2,3,4-trimethoxy-6-[(4-methoxybenzyl)sulfanyl]benzyl]glycine^[509]**Scheme 44** Synthesis of 1-(4,5-Dimethoxy-2-nitrophenyl)-2-[(4-methylbenzyl)sulfanyl]ethylamine^[509]**Peptide α -Phenyl Thioesters; General Procedure:**^[8,477,499]

Thioacid peptides were synthesized on the appropriate Boc-aminoacyl-S-resins.^[511] Alternatively, thioester peptides were synthesized on TAMPAL resin^[494] (see also Section 21.11.6.2.1) and converted into thioacids by dissolving the crude peptide in 6 M guanidine hydrochloride containing 0.2 M Na₃PO₄ (pH 7.2) and 0.2 M (NH₄)₂S. [(NH₄)₂S was intro-

duced into the guanidine buffer by addition of 0.5 M (NH₄)₂S; the soln was adjusted to the final pH after this addition.] Conversion was monitored by analytical HPLC. Peptide α -phenyl thioesters were prepared after dissolving the peptide thioacid (100 mg, typically 0.02 mmol) and 5,5-dithiobis(2-nitrobenzoic acid) (10 equiv, typically 72 mg, 0.2 mmol) in a soln of 6 M guanidine hydrochloride (10 mL) containing 0.1 M Na₂HPO₄ at pH 6.0. The mixture was agitated with a vortex shaker briefly and let stand for 20 min before treatment with 2% PhSH. The exchange reaction was monitored by analytical HPLC and purified using semipreparative HPLC. After lyophilization, the peptide α -phenyl thioesters were used immediately or stored under reduced pressure; yield: not reported.

N-(2,3,4-Trimethoxy-6-sulfanylbenzyl)glycine and Incorporation into Peptides:^[510]

3,4,5-Trimethoxyphenyl Trifluoromethanesulfonate (8):

3,4,5-Trimethoxyphenol (2 g, 11 mmol) was dissolved in toluene (15 mL) and 30% K₃PO₄ soln (15 mL) was added. The mixture was cooled to 0 °C and TFAA (2.2 mL, 13 mmol) was added slowly dropwise with stirring to maintain the temperature below 10 °C. The mixture was allowed to warm to rt and stirred further for 1 h, then extracted with toluene (2 × 10 mL). The combined organic extracts were washed with H₂O (30 mL), dried (MgSO₄), and concentrated to give the trifluoromethanesulfonate as a pale yellow solid which was used without further purification; yield: 3.23 g (92%); ¹⁹F NMR (235.3 MHz, CDCl₃, δ): -73.8.

1,2,3-Trimethoxy-5-[(4-methoxybenzyl)sulfanyl]benzene (9):

Trifluoromethanesulfonate **8** (100 mg, 0.32 mmol) was placed in a microwave tube and 6 mol% Pd(OAc)₂ and 8 mol% (+)-(R)-BINAP were added. The tube was sealed with a metal cap with septum, then DMF (5 mL), Mob-SH (66 μ L, 0.47 mmol), and Et₃N (90 μ L, 0.64 mmol) were added under argon. The tube was placed in a CEM Discover microwave operated with ChemDriver software and heated at 150 °C at a microwave power of 200 W for 20 min. The mixture was diluted with EtOAc (40 mL) and washed with brine (20 mL), then dried (MgSO₄), filtered, and the solvent removed under reduced pressure. The crude residue was purified by column chromatography [silica gel, EtOAc/petroleum ether (bp 40–60 °C) 1:4] to give the product as a yellow gummy solid; yield: 87 mg (85%).

2,3,4-Trimethoxy-6-[(4-methoxybenzyl)sulfanyl]benzaldehyde (10):

Sulfide **9** (870 mg, 2.72 mmol) was dissolved in anhyd CH₂Cl₂ (5.0 mL) and added to a flame-dried flask fitted with a condenser under argon, treated with anhyd DMF (0.21 mL, 2.7 mmol), cooled to 0 °C, and treated dropwise with POCl₃ (0.29 mL, 3.1 mmol) over 10 min. The reaction was allowed to warm to rt, heated to 150 °C for 5 h, allowed to cool, treated dropwise with sat. NaHCO₃ (20 mL), and stirred at rt for 3 h. The mixture was then extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄), and concentrated under reduced pressure to give a brown solid, which was purified by column chromatography [silica gel, EtOAc/petroleum ether (bp 40–60 °C) 1:4] to give the product as a white solid; yield: 841 mg (89%).

tert-Butyl N-(2,3,4-Trimethoxy-6-[(4-methoxybenzyl)sulfanyl]benzyl)glycinate (11) by Reductive Amination onto an Amino Acid:

The aldehyde **10** (100 mg, 0.29 mmol) was dissolved in CH₂Cl₂ (10 mL) and 2% AcOH (0.2 mL). The amino acid *tert*-butyl ester (0.34 mmol) was added, followed by NaBH(OAc)₃ (120 mg, 0.57 mmol). The mixture was stirred at rt for 1 h, then neutralized with sat. NaHCO₃ (20 mL). The mixture was extracted with CH₂Cl₂ (3 × 20 mL), washed with brine (30 mL), then dried (MgSO₄), filtered, and concentrated to a yellow oil. The crude products were purified by column chromatography [silica gel, EtOAc/petroleum ether (bp 40–60 °C) 1:10] to afford the pure product, typically as a white foam; yield: 93%.

N-(9-Fluorenylmethoxycarbonyl)-N-{2,3,4-trimethoxy-6-[(4-methoxybenzyl)sulfanyl]benzyl}glycine (12):

The ester **11** was treated with TFA/H₂O (19:1) at 0 °C. The mixture was stirred at 0 °C for 4 h, concentrated under reduced pressure, and azeotroped with toluene. The crude N-{2,3,4-trimethoxy-6-[(4-methoxybenzyl)sulfanyl]benzyl}glycine was used directly in the next step.

The benzylglycine (120 mg, 0.26 mmol [assumed]) was dissolved in H₂O (5 mL), treated with Et₃N (36 μ L, 0.26 mmol), followed by a soln of Fmoc-OSu (84 mg, 0.25 mmol) in MeCN (5 mL) and stirred at rt for 3 h, maintaining a pH of 8.5–9.0 by the addition of more Et₃N as necessary. The mixture was neutralized with 1.5 M HCl and extracted with CH₂Cl₂ (3 \times 20 mL). The combined organic extracts were washed with 1.5 M HCl (30 mL) and brine (30 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure to give a yellow gum, which was purified by column chromatography [silica gel, EtOAc/petroleum ether (bp 40–60 °C) 9:1] to give a white foam as the product; yield: 110 mg (67% over 2 steps).

S-Mob Deprotection of N-Terminal N-{2,3,4-Trimethoxy-6-[(4-methoxybenzyl)sulfanyl]benzyl}glycine after Peptide Synthesis and Purification:

The S-Mob-protected peptide (1.0 mg) was dissolved in 10% AcOH (0.5 mL) at 0 °C, treated with Hg(OAc)₂ (1.0 mg), followed shortly afterwards by solid dithiothreitol to a final concentration of 5% w/v. The mixture was shaken (250 rpm) at rt under argon. After 1 h, LC-MS analysis indicated that the reaction was complete as no starting material was observed. The thick white precipitate was removed by centrifugation at 13,000 rpm for 5 min. The remaining soln was purified directly by semipreparative HPLC and the collected fractions were lyophilized to afford the thiol as a fluffy white solid; yield: not reported.

2,3,4-Trimethoxy-6-sulfanylbenzyl-Mediated Chemical Ligation and Deprotection; General Procedure:^[510]

Ligation: The auxiliary-linked peptide was dissolved in ligation buffer [6 M guanidine hydrochloride/200 mM Na₃PO₄, pH 8.0/2% sodium 2-sulfanylethanesulfonate/20 mM tris(2-carboxyethyl)phosphine] (0.25–0.5 mL) to a final concentration of 3 mM (typically 4 mg·mL⁻¹). This soln was then transferred to an Eppendorf tube containing the lyophilized peptide thioester (1:1 equiv to auxiliary thioester). The mixture was then shaken at rt (250 rpm) under argon and the reaction was monitored using LC-MS. Ligation products were purified using HPLC, and lyophilized to give the peptides; yield: not reported.

Auxiliary removal: The purified ligation products were dissolved in 95% TFA and allowed to stand with occasional agitation at rt for 3 h. After this time the bulk of the TFA was removed under a stream of argon (this step appeared crucial for efficient product recovery) and the ligated product was precipitated with ice-cold Et₂O. The precipitated product was collected by centrifugation and purified by semipreparative HPLC; yield: not reported.

2-(4,5-Dimethoxy-2-nitrophenyl)ethanethiol Auxiliary and Incorporation into Peptides:^[509]**2-Nitro-4,5-dimethoxystyrene (14):**

To a suspension of Ph₃P⁺MeBr⁻ (22.1 g, 61.6 mmol) in THF (100 mL), 2 M NaHMDS in THF (31 mL, 62 mmol) was added dropwise over 30 min at 0 °C and stirred for 1 h. A soln of 4,5-dimethoxy-2-nitrobenzaldehyde (**13**; 10 g, 47.4 mmol) in THF (120 mL) was then added dropwise to the mixture, which was then stirred at rt for an additional 12 h and concentrated. The residue was partitioned between CHCl₃ (300 mL) and sat. aq NH₄Cl (300 mL). The layers were separated and the organic layer was washed with sat. aq NH₄Cl (2 \times 300 mL) and brine (2 \times 300 mL), dried (Na₂SO₄), and concentrated under reduced pressure.

Column chromatography of the residue (silica gel, EtOAc/petroleum ether 1:9) afforded the product; yield: 6.2 g (65%); R_f 0.42 (silica gel, EtOAc/petroleum ether 3:7).

2-(*tert*-Butoxycarbonylamino)-2-(4,5-dimethoxy-2-nitrophenyl)ethanol (15):

To a stirred soln of *tert*-butyl carbamate (843 mg, 7.2 mmol) in PrOH (10 mL), 0.5 M aq NaOH (9.6 mL) and freshly prepared *t*-BuOCl^[512] (0.5 mL) were sequentially added and the resulting mixture was stirred for 5 min. The flask was placed into an ice slurry and the mixture was treated sequentially with (DHQ)₂PHAL (hydroquinine phthalazine-1,4-diyl diether; 112 mg, 0.14 mmol) in PrOH (10 mL), styrene **14** (500 mg, 2.4 mmol) in PrOH (40 mL), and K₂OsO₂(OH)₄ (35 mg, 0.1 mmol), stirred at 4°C for 45 h, and quenched with sat. aq Na₂S (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (2 × 500 mL), dried (Na₂SO₄), and concentrated. Column chromatography of the residue (silica gel, EtOAc/petroleum ether 3:7) afforded the product; yield: 434 mg (53%); R_f 0.45 (EtOAc/petroleum ether 1:1); as well as the unreacted styrene **14** (190 mg, 38%).

S-[2-(*tert*-Butoxycarbonylamino)-2-(4,5-dimethoxy-2-nitrophenyl)ethyl] Ethanethioate (16):

To an ice-cold, stirred soln of Ph₃P (680 mg, 2.6 mmol) in THF (20 mL), diisopropyl azodicarboxylate (DIAD; 0.56 mL, 2.6 mmol) was added. The mixture was stirred for 30 min, during which time a white precipitate was formed. A soln of alcohol **15** (410 mg, 1.2 mmol) in THF (25 mL) and thioacetic S-acid (0.19 mL, 2.6 mmol) were sequentially added dropwise and the mixture was stirred at rt for an additional 10 h. The solvent was removed and the residue was dissolved in toluene (150 mL) and left standing at 0°C for 10 h. The precipitate was filtered and the solvent was removed. Column chromatography of the residue (silica gel, EtOAc/petroleum ether 2:3) afforded the product; yield: 490 mg (98%); R_f 0.43 (EtOAc/petroleum ether 1:1).

N-(*tert*-Butoxycarbonyl)-1-(4,5-dimethoxy-2-nitrophenyl)-2-[(4-methylbenzyl)sulfanyl]ethylamine [17, R¹ = Bzl(4-Me)]:

To a stirred soln of **16** in abs EtOH (100 mL), 1 M NaOMe in MeOH (1.32 mL, 1.3 mmol) was added and the resulting mixture was stirred for 5 min. Bzl(4-Me)Br (245 mg, 1.3 mmol) was added and the mixture was stirred for an additional 20 min. The pH was adjusted to 4 by adding Dowex H⁺. The resin was filtered and the solvent was removed. Flash column chromatography of the residue (silica gel, EtOAc/petroleum ether 1:19) afforded the product; yield: 500 mg (97%); R_f 0.8 (EtOAc/petroleum ether 2:3).

1-(4,5-Dimethoxy-2-nitrophenyl)-2-[(4-methylbenzyl)sulfanyl]ethylamine (18):

Boc-amine **17** was dissolved in neat TFA, stirred for 5 min, and the solvent was removed under reduced pressure; yield: not reported. The crude product was used without further purification in the following reaction with the bromoacetyl peptide.

Bromoacetylation of Peptide Resin; Coupling of Auxiliary to Peptide Resin:

CAUTION: Carbodiimides are severe eye, skin, and respiratory tract irritants, and skin sensitizers. They should only be handled with gloves in a fumehood.

After removal of the penultimate N^α-Boc or Fmoc group, the peptide resin was neutralized with iPr₂NEt and washed with DMF and CH₂Cl₂. A soln of the α-bromo symmetric anhydride in CH₂Cl₂ (20 equiv relative to resin loading) was prepared by treating a 0°C soln of bromoacetic acid in CH₂Cl₂ with DIC (10 equiv), the ice/salt bath was removed, and the mixture stirred for 1 h. The resulting anhydride mixture was added to the peptide resin, agitated for 1 h, and washed with DMF. The resulting resin mixture was treated with a

soln of **18** (3 equiv) in a DMF/*i*Pr₂NEt soln (2:1, 6 equiv *i*Pr₂NEt for each equiv of auxiliary), and left standing for 12 h. The peptide resin was washed with DMF, CH₂Cl₂, and dried under reduced pressure. The peptide was obtained after HPLC purification and lyophilization; yield: ≥60%.

2-(4,5-Dimethoxy-2-nitrophenyl)ethanethiol-Mediated Chemical Ligation and Deprotection; General Procedure:^[509]

Ligation: Peptides were dissolved in a 1:1 ratio in 200 mM Na₃PO₄ buffer (pH 8.5), in the presence of 35 mM tris(2-carboxyethyl)phosphine, to a final peptide concentration of 5–8 mM (typically 10–15 mg·mL⁻¹). The final pH of the soln after addition of the peptides was 7.5. The reaction was monitored by analytical HPLC. Typical chromatographic yields for ligations were >90%. At the end of the reaction the mixture was diluted with HPLC buffer (H₂O/TFA 999:1) and the product was isolated by semipreparative HPLC; yield: not reported.

Photolytic removal of auxiliary 18: Ligated peptides were dissolved in a mixture of MeCN/H₂O (1:4) to a final peptide concentration of about 0.3 mg·mL⁻¹ and the soln was put in a quartz tube and degassed by argon bubbling for 15 min. The tube was irradiated in a Rayonet 310 nm photoreactor and the reaction was monitored by analytical HPLC. At the end of the reaction the soln was diluted with HPLC buffer (H₂O/TFA 999:1) and the product was purified by semipreparative HPLC; yield: not reported.

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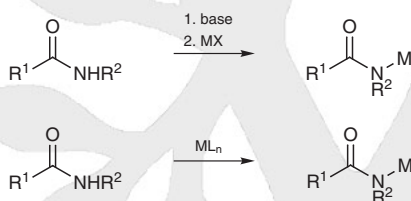
Product Class 12: Metal Amides and Imides

T. R. Bailey

General Introduction

This product class was previously described in *Houben-Weyl*, Vol. E 5/2, pp 1213–1216. Metal amides and imides, in particular those made from group 1 elements and silicon, have shown extensive utility in organic synthesis as intermediates for the generation of N-substituted amides and imides,^[1] imines as in the aza-Peterson alkenation,^[2] sulfur-substituted amides,^[3] and transmetalated amides and imides.^[4] For most other metals, amides and imides have been described. There are examples in the patent literature specifically claiming the synthesis of metal amides or imides as part of a synthetic process. In general, metalation of amides or imides proceeds straightforwardly through deprotonation of the amide hydrogen with a metal–base complex, or a ligand-exchange process (Scheme 1). Detailed descriptions of these processes are outlined in this section.

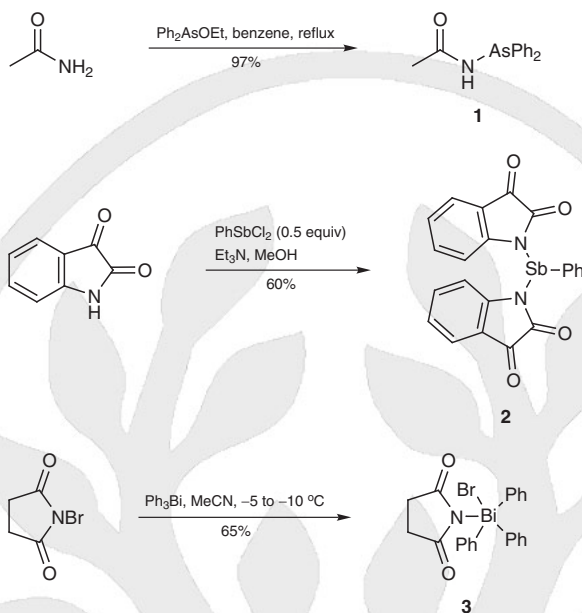
Scheme 1 General Processes for Metal Amide Formation^[1]



A relatively small number of transition metal amides are present in the literature, and little is known about their reactivity or toxic properties. While no multidentate transition-metal amide complexes will be discussed, transition-metal amides with synthetic applications will be described. The focus for this section will be on metal amides that possess demonstrated synthetic use or potential. In general, it is prudent to exercise due caution when synthesizing or handling all metal amides since hazards and toxicology have not been evaluated.

Product Subclass 1: Group 15 (Arsenic, Antimony, and Bismuth) Amides and Imides

Relatively few examples of group 15 metal amides or imides have been described in the literature. In the reaction of N-unsubstituted amides with group 15 metals, it is common to form acylimino metal species known as iminopnictoranes where the metal has a double bond to the amide nitrogen.^[5] Due to their metal-complex nature, these pnictoranes are outside the scope of this review,^[6] and therefore, only systems with single-bonded attachments of the metal to nitrogen will be discussed. Despite the facile formation of iminopnictoranes, there are some reports of single-bonded attachments of N-unsubstituted amides to group 15 metals.^[7,8] Far more common in the chemical literature is the formation of arsenic amides **1**, or antimony or bismuth imides, **2** and **3**, respectively (Scheme 2).

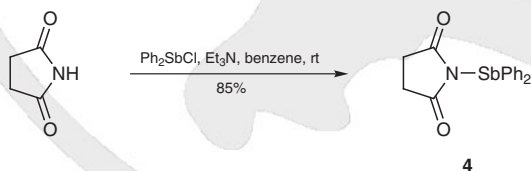
Scheme 2 Examples of Arsenic, Antimony, and Bismuth Amides and Imides^[7,9,10]

These arsenic, antimony, and bismuth amides and imides appear to be stable at room temperature, but decompose thermally.^[9]

21.12.1.1 Synthesis of Product Subclass 1

21.12.1.1.1 Method 1: Synthesis from Arsenic, Antimony, and Bismuth Halides

Group 15 amides and imides can be prepared at ambient temperature by treating the amides or imides with the desired halogenated metal species in the presence of a base such as triethylamine, in benzene or methanol (Scheme 3).^[10,11] Only a few examples have been described in the literature. Synthetic utility has been described in the case of (diphenylstibino)carboxamides such as **4**.^[11] The Sb—N bond is sufficiently labile to undergo reaction with bromine. The carbonyl functionality apparently attenuates reactivity enough to prevent reaction with carbon disulfide. The antimony carboximides are solids that have stability in water, methanol, and carbon disulfide.^[11]

Scheme 3 Preparation of an Imide from a Group 15 Halide^[11]

Diphenyl-*N*-succinimidostibine (**4**):^[11]

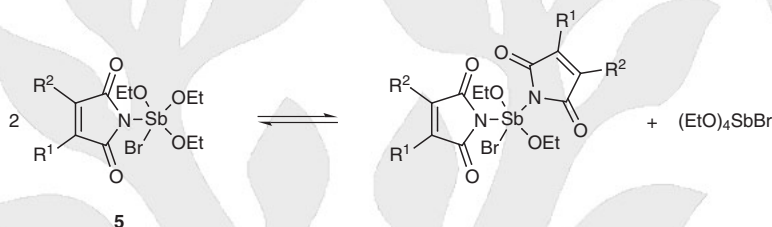
Under an O₂-free atmosphere, a soln of Ph₂SbCl (0.3112 g, 1 mmol) in anhyd benzene (30 mL) (**CAUTION: carcinogen**) was added to a soln of succinimide (0.099 g, 1 mmol) and Et₃N (0.11 g, 1.1 mmol) in anhyd benzene (30 mL). The mixture was then stirred at rt for 3 h. The Et₃N•HCl precipitate was removed by filtration, and the filtrate was concentrated

under reduced pressure. The white crystalline solid was recrystallized [petroleum ether (bp 40–60 °C)] affording the product as a white solid; yield: 0.318 g (85%); mp 156 °C.

21.12.1.1.2 Method 2: Generation by Ligand Displacement

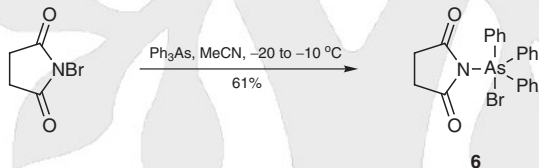
Oxidative addition of haloimides to group 15 trisubstituted organometallic compounds is facile in polar aprotic solvents (Scheme 5).^[9] The pentavalent arsine compound **6** is formed in this way. When triethoxystibine rather than trialkyl- or triarylstibine is used, NMR studies have shown dissociation of compound **5**, demonstrating the equilibrium between bis- and monoimides (Scheme 4). This dissociation has not been observed otherwise.

Scheme 4 Solution Equilibrium of Triethoxybromostibine Imides^[9]



No synthetic applications for these pentavalent antimony derivatives (Scheme 4) have been described, and their stability appears limited.

Scheme 5 Preparation of Pentavalent Arsine from Triphenylarsine^[9]

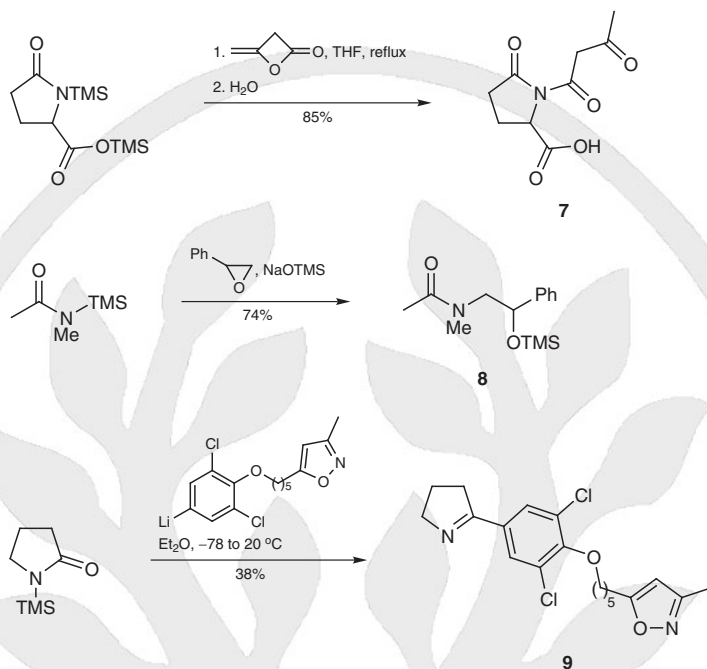


Triphenylsuccinimidylarsine Bromide (**6**); Typical Procedure:^[9]

To a magnetically stirred soln of Ph_3As (3.06 g, 0.01 mol) in abs MeCN (30 mL), maintained between -20 and -10 °C, was added, over 5 min, a soln of NBS (1.79 g, 0.01 mol) in abs MeCN (15 mL). The reaction was placed under medium-high vacuum, and the soln volume was reduced by two-thirds while the mixture was kept between 0 – 5 °C. The soln was then cooled in a dry ice/acetone bath to crystallize the product. The colorless crystals were dried under medium-high vacuum for 10 min at rt to provide the product arsine imide **6**; yield: 3.0 g (61%); mp 132 – 134 °C. The arsine imide may be stored at 0 °C for weeks without substantial decomposition.

21.12.2 Product Subclass 2: Silicon Amides and Imides

Silicon amides and imides are important synthons in organic synthesis (Scheme 6). As reactants, they have been used to generate substituted amides, e.g. **7**, from lactones,^[12] or amides, e.g. **8**, from epoxides or ketones.^[13] Additionally, silicon amides may be employed in the aza-Peterson alkenation reaction giving products such as **9**.^[14] The versatile nature of these reagents has led to numerous methods of synthesis.

Scheme 6 Examples of Synthetic Uses of Silicon Amides and Imides^[12–14]

In general, silicon amides are very stable when kept anhydrous. Most silicon amides and imides are colorless liquids or low melting solids. There have been reports of silicon carboxamides with fungicidal,^[15,16] local anesthetic,^[17] and herbicidal^[18] activity.

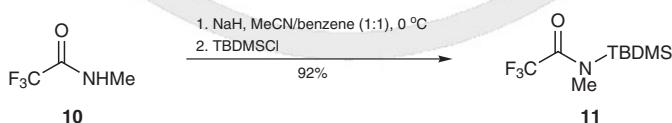
21.12.2.1 Synthesis of Product Subclass 2

21.12.2.1.1 Method 1: Synthesis from Trialkylhalosilanes

Transfer of the organosilicon functionality to the nitrogen of an amide or imide can be effected via an S_N2 displacement of trialkylhalosilanes or trifluoromethylsulfonylsilanes under the appropriate conditions (Scheme 7). The primary modes of synthesis are described in the following sections.

21.12.2.1.1.1 Variation 1: Anion Formation on Amide

Deprotonation of amides, such as **10**, or imides with group 1 hydrides, followed by treatment with a trialkyl halide in a polar, aprotic solvent, has been a method of choice for generating silicon amides **11** or imides^[19] (Scheme 7). Formation of the requisite lithium, sodium, and potassium amide or imide reagents is discussed in detail in Section 21.12.7.

Scheme 7 Preparation of a Silicon Amide from Chlorotrimethylsilane^[19]

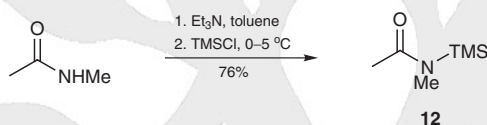
2,2,2-Trifluoro-*N*-methyl-*N*-(*tert*-butyldimethylsilyl)acetamide (11); Typical Procedure:^[19]

To a dry soln of benzene (**CAUTION: carcinogen**) (400 mL) and MeCN (400 mL) was added 2,2,2-trifluoro-*N*-methylacetamide (127.0 g, 1.0 mol), and the mixture was maintained at 0 °C under N₂ with stirring. To this soln was slowly added NaH (23.5 g, 0.98 mol). Upon completion of the addition, the mixture was stirred at 4 °C for 2 h then TBDMSCl (173.3 g, 1.15 mol) was added in equal aliquots over 80 min. Upon completion of the addition, the soln was stirred at 4 °C for an additional 2 h. The NaCl precipitate was removed by filtration under dry N₂, and the filter cake was washed with benzene (2 × 100 mL). The solns were combined, and concentrated under reduced pressure to provide the crude product as a yellow liquid. Fractional distillation (168–170 °C/760 Torr) afforded the product as a colorless liquid; yield: 181.9 g (92%).

**21.12.2.1.1.2 Variation 2:
Using Nitrogenous Bases**

Using a nitrogen base in an anhydrous solvent, carboxamides and imides may be efficiently *N*-silylated with trialkylhalosilanes (Scheme 8). Among the commonly used bases are triethylamine,^[20] (e.g., in the formation of the acetamide **12**), *N,N*-diisopropylethylamine,^[21] and imidazole.^[22] Typically, these reactions are performed at temperatures between 0–5 °C.

Scheme 8 Preparation of an *N*-Silyl Amide Using Triethylamine^[20]

***N*-Methyl-*N*-trimethylsilylacetamide (12); Typical Procedure:**^[20]

To a soln of *N*-methylacetamide (7.3 g, 0.1 mol) and Et₃N (30.3 g, 0.3 mol) in anhyd benzene (75 mL) (**CAUTION: carcinogen**) (anhyd toluene or MeCN may be substituted) at 0–5 °C, was added dropwise TMSCl (16.3 g, 0.15 mol). A precipitate of Et₃N•HCl formed over several hours. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant crude oil was then distilled (48–49 °C/11 Torr) to give a clear oil; yield: 11.0 g (76%).

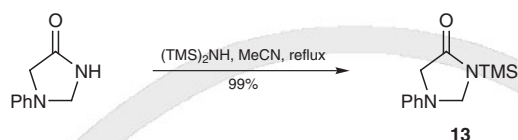
**21.12.2.1.2 Method 2:
Exchange with Silylated Nitrogen Compounds**

A common method for the synthesis of *N*-silyl amides and imides is through exchange with silylated nitrogen species such as hexamethyldisilazane,^[20] tetramethyldisilazane,^[21] and *N*-silylcarboxamides.^[19] Catalysts such as saccharin have been employed to enhance reaction yields.^[22]

**21.12.2.1.2.1 Variation 1:
With Hexamethyldisilazane**

A common method for generating *N*-silyl amides and imides is through exchange with the low boiling hexamethyldisilazane. An example of this is the preparation of the *N*-silyl amide **13**. This is a very clean reaction, ammonia is the major byproduct, and excess hexamethyldisilazane may be readily removed under vacuum, providing clear, colorless products (Scheme 9).

Scheme 9 Preparation of an *N*-Silyl Amide by Silicon Exchange with Hexamethyldisilazane^[23]



1-Phenyl-3-(trimethylsilyl)imidazolidin-4-one (13**); Typical Procedure:**^[23]

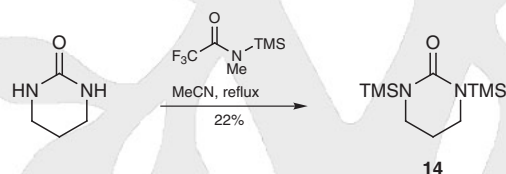
A mixture of 1-phenylimidazolidin-4-one (4.9 g, 30 mmol) in MeCN (30 mL) with $(\text{TMS})_2\text{NH}$ (14.5 g, 90 mmol) was refluxed for 60 min. The solvent was removed under reduced pressure to provide the crystalline product quantitatively; yield: 7.0 g (99%); mp 90–92 °C; bp 140 °C /0.75 Torr.

21.12.2.1.2.2

**Variation 2:
With *N*-Silylated Amides**

The least commonly used of the *N*-silyl exchange reagents, (trimethylsilyl)carboxamides have been shown to undergo silyl transfer with other amides (Scheme 10), as in the preparation of the silylated imide **14**. Normally, the silylcarboxamides are activated by electron withdrawing functionality, as in 2,2,2-trifluoro-*N*-methyl-*N*-(trimethylsilyl)acetamide.^[24]

Scheme 10 Silicon Exchange with an *N*-Silylcarboxamide^[24]



1,3-Bis(trimethylsilyl)tetrahydropyrimidin-2(1H)-one (14**):**^[24]

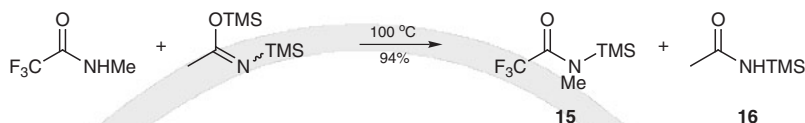
A soln of tetrahydropyrimidin-2(1H)-one (5.80 g, 50 mmol) and 2,2,2-trifluoro-*N*-methyl-*N*-(trimethylsilyl)acetamide (24.9 g, 125 mmol) was refluxed for 18 h under a dry N_2 atmosphere. Upon cooling, the solvent was removed under reduced pressure. Bulb-to-bulb distillation (110–120 °C/0.8 Torr) provided the product as a white solid; yield: 3.0 g (22%); mp 78–79 °C.

21.12.2.1.3

**Method 3:
Exchange with *N,O*-Bis(trimethylsilyl)acetamide**

Another means employed for the formation of silylcarboxamides or imides is transfer of silicon from *N,O*-bis(trimethylsilyl)acetamide or 2,2,2-trifluoro-*N,O*-bis(trimethylsilyl)acetamide. Normally, more than 1 equivalent of *N,O*-bis(trimethylsilyl)acetamide is utilized, despite the presence of two exchangeable trimethylsilyl groups. Presumably, the *O*-trimethylsilyl group transfers, providing **15** and *N*-(trimethylsilyl)acetamide (**16**) as a byproduct.^[25] Reactions can be performed under relatively mild conditions, and isolation of the product is readily accomplished by vacuum distillation (Scheme 11).

Scheme 11 Preparation of an *N*-Silyl Amide by Silicon Transfer from *N,O*-Bis(trimethylsilyl)acetamide^[26]



2,2,2-Trifluoro-*N*-methyl-*N*-(trimethylsilyl)acetamide (15**):^[26]**

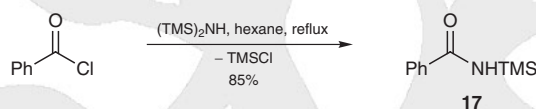
A stirred soln of 2,2,2-trifluoro-*N*-methylacetamide (127 g, 1.00 mol) and BSA (244 g, 1.20 mol) was heated at 100 °C for 4 h. Upon cooling, the mixture was distilled affording the product as a colorless oil; yield: 188 g (94%); bp 130–132 °C.

21.12.2.1.4

Method 4:
Synthesis from Acid Chlorides and Hexamethyldisilazane

In a variation not starting from an amide, acid chlorides have been shown to react with hexamethyldisilazane to form *N*-silyl amides such as *N*-(trimethylsilyl)benzamide (**17**) (Scheme 12).^[27] While aromatic silyl amides such as *N*-(trimethylsilyl)benzamide are readily prepared as crystalline solids, aliphatic silyl amides are less easily isolated due to their volatility.

Scheme 12 Preparation of a Silyl Amide with an Acid Chloride and Hexamethyldisilazane^[27]



***N*-(Trimethylsilyl)benzamide (**17**); Typical Procedure:^[27]**

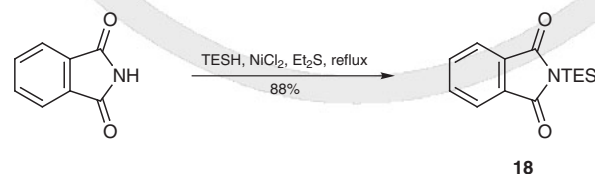
To a stirred soln of (TMS)₂NH (40.3 g, 250 mmol) in hexanes (90 mL) was added dropwise a soln of BzCl (34.7 g, 247 mmol) in hexanes (50 mL). A white precipitate was formed, and the mixture was refluxed for 2 h under N₂. Upon cooling, the solid was recovered by filtration, and the crude product recrystallized [hot CCl₄ (**CAUTION: toxic**)] to provide the product as a white, crystalline solid; yield: 40.6 g (85%); mp 62–65 °C.

21.12.2.1.5

Method 5:
Oxidative Addition of Trialkylsilanes

Oxidative silylation of amides and imides utilizing a transition-metal catalyst and triethylsilane proceeds efficiently under reflux.^[28] The *N*-(triethylsilyl)phthalimide (**18**) is prepared in this way. After experimentation with a number of different catalysts, the nickel(II) chloride–diethyl sulfide complex was found to be the best. Triethylsilylation of amides and imides proceeds in good yields using this methodology (Scheme 13).

Scheme 13 Preparation of a Silyl Amide via Oxidative Addition of Triethylsilane^[28]



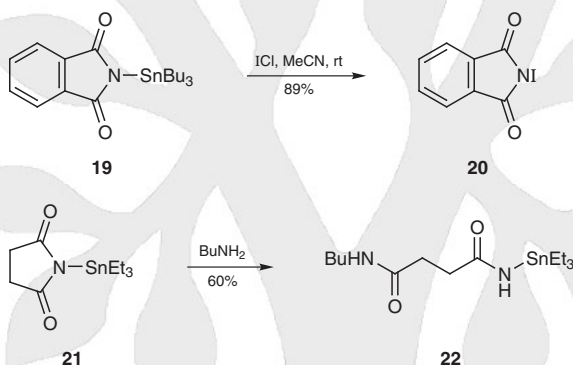
N-(Triethylsilyl)phthalimide (18); Typical Procedure:^[28]

A suspension of anhyd NiCl_2 (2.0 g, 16 mmol), Et_2S (0.4 g, 4.4 mmol), and TESH (23.2 g, 200 mmol) was refluxed for 20 h to prepare the $\text{Ni}/\text{Et}_2\text{S}$ catalyst. Phthalimide (29.4 g, 200 mmol) was then added to the flask, which was equipped with a reflux condenser, CaCl_2 drying tube, and balloon to monitor H_2 evolution. The mixture was refluxed further under an argon atmosphere until H_2 evolution ceased, as monitored by the balloon (20 h). The catalyst was removed by decantation, and the product **18** crystallized upon cooling, as a white solid; yield: 46.0 g (88%); mp 180 °C.

21.12.3

Product Subclass 3:**Group 14 (Germanium, Tin, and Lead) Amides and Imides**

Amides of the group 14 metals, germanium, tin, and lead, can be prepared in a straightforward manner from trialkylmetal halides^[29] or through the use of metal oxides.^[30] Synthetic use of these group 14 amides or imides has been limited to the tin variants where the metal intermediate **19** is either oxidatively cleaved with elemental halogens to form haloimide **20**,^[31] or in which tin succinimide **21** is opened by a nitrogen nucleophile to provide the ring-opened tin amide **22** (Scheme 14).^[32]

Scheme 14 Synthetic Uses of Tin Imides^[31,32]

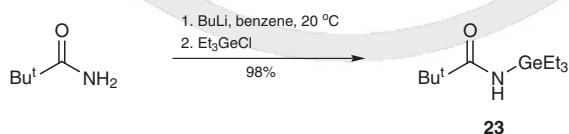
21.12.3.1

Synthesis of Product Subclass 3

21.12.3.1.1

Method 1:**Synthesis from Trialkylmetal Halides**

The synthesis of group 14 amides and imides is nearly identical to the procedure described in Section 21.12.2.1.1.1. Generally a high yielding process, this method of synthesis has been used to produce germanium amides such as **23** (Scheme 15),^[33] tin imides,^[34] and lead amides.^[35] The tin imides have utility as insecticides.^[34] Group 14 amides and imides are stable, but due caution should be used in their handling since toxicity from dermal absorption of organostannanes has been observed.

Scheme 15 Synthesis of a Germyl Amide via Metalation^[33]

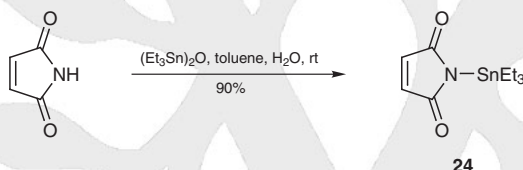
2,2-Dimethyl-N-(triethylgermyl)propanamide (23); Typical Procedure:^[33]

To a soln of *t*-BuCONH₂ (1.04 g, 10.3 mmol) in anhyd benzene (3 mL) (**CAUTION: carcinogen**) was added a 1.5 M soln of BuLi in hexane (6.83 mL, 10.25 mmol) under argon at rt. After stirring the mixture at 20 °C for 3 h, a soln of Et₃GeCl (2.01 g, 10.25 mmol) in anhyd benzene (3 mL) was added, resulting in an exothermic reaction. After stirring for an additional 3 h, the mixture was filtered through Celite, and the solvent was removed under reduced pressure to give the product as a white solid; yield: 2.71 g (98%); mp 46 °C.

21.12.3.1.2

**Method 2:
Synthesis from Metal Oxides**

No examples of the synthesis of group 14 amides from metal oxides exist in the literature. For group 14 imides, only the synthesis of trialkyltin variants via trialkyltin oxides has been described in the literature. Two methods for generating (trialkylstannyl)imides were reported in 1983. In the first of these, the tin imide was synthesized by azeotropically removing water from the reaction.^[31] The tin imide product was never fully characterized, but used directly to generate an *N*-halo imide product. The second synthetic method is a biphasic process (Scheme 16) in which the succinimide is suspended in water, and a benzene solution of tin oxide is vigorously mixed for 15–20 minutes^[30] to give the tin imide **24**. Toluene can be used in place of benzene in this reaction.

Scheme 16 Synthesis via Exchange with Bis(triethylstannyl) Oxide^[30]**N-(Triethylstannyl)maleimide (24):**^[30]

A suspension of maleimide (0.90 g, 9.3 mmol) in H₂O (20 mL) was added to a soln of (Et₃Sn)₂O (2.00 g, 4.8 mmol) in toluene (20 mL). The biphasic mixture was very rapidly stirred for 15–20 min and then the organic layer was separated. The aqueous layer was washed with toluene (10 mL), and the organic layers were combined. After drying the organic phase (MgSO₄), the toluene was removed under reduced pressure, and the product was isolated as a viscous liquid, which was crystallized (hexane) to afford the product **24** as fine, long needles; yield: 2.53 g (90%).

21.12.4

**Product Subclass 4:
Boron Amides and Imides**

Boron carboxamides and carboximides do not appear frequently in the chemical literature. Generation of boron carboxamides from *N*-unsubstituted carboxamides with disubstituted boron halides can result in polymers, oligomers,^[35] or dimers.^[37] A complicating quality of boron carboxamides is the O/N borotropic propensity whereby the ability of boron to form tetrahedral complexes can cause these amides to resemble boron imidates.^[35,36] More commonly, boron amides can exist as boratacycles where intramolecular stabilization of boron by the carbonyl oxygen results in a five-membered ring. The O/N borotropes may be influenced synthetically by the choice of substituent on boron or nitrogen to yield boron carboxamides.^[36,37] Other than the synthesis and structural investigation of boron amides, no other applications appear in the literature. Care should be taken when using boron amides and imides as their toxicity has not been evaluated.

21.12.4.1 Synthesis of Product Subclass 4

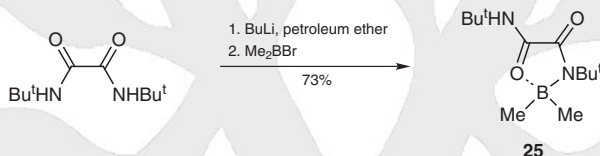
21.12.4.1.1 Method 1:
Synthesis from Boron Halides

Illustrative of the O/N borotropic nature of boron amides, the use of disubstituted boron halides can lead to an equilibrium mixture of the cyclic and acyclic boron amides.^[38] X-ray crystallography of the cyclic boron amides confirms their structure. Functional groups on the amide nitrogen can influence the ratio of the open and closed forms with smaller R¹ groups favoring the cyclic boron amides. While equilibrium mixtures of open and closed forms can be obtained, the individual boron amide forms can be separated. Interestingly, these forms may, in some cases, be generated exclusively through selection of the synthetic route. The generation of the specific boron amide forms is the focus of this section.

21.12.4.1.1.1 Variation 1:
Via Transmetalation

Although infrequently used, boron amides may be synthesized directly via reaction of the lithium amide with a monohaloborane (Scheme 17).^[38] As seen in this example, O/N borotropy leads to the boratacycle **25** in good yield.

Scheme 17 Synthesis of a Boron Amide via Lithium Exchange with a Boron Halide^[38]

**3-*tert*-Butyl-5-(*tert*-butylamino)-2,2-dimethyl-1-oxonia-3-aza-2-boratacyclopentan-4-one (25):**^[38]

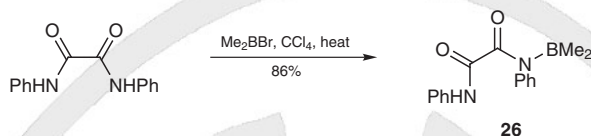
To a soln of *N,N'*-di-*tert*-butylethanedi-1,2-diamide (20.0 g, 0.1 mol) in petroleum ether (400 mL) was added a 6.5 M soln of BuLi in hexane (65 mL, 0.1 mol). The reaction was refluxed for 4 h as butane was generated during lithium diamide formation. To this soln was added Me_2BBr (12.1 g, 0.1 mol) in hexanes (70 mL), and the mixture was heated for 4 h. Upon cooling, the reaction solvent was removed under reduced pressure using a water aspirator. The remaining residue was heated at 200 °C under high vacuum, and the crude product was isolated in a cold trap. The residual solvent was removed under high vacuum at 20 °C, and the product purified through sublimation (75 °C/ 1.5×10^{-3} Torr) affording a white solid; yield: 17.5 g (73%); mp 111–113 °C.

21.12.4.1.1.2 Variation 2:
By Addition of Dialkylbromoboranes

Boron amides (either cyclic or open-chained form) may be formed directly from amides by refluxing with a dialkylbromoborane in a solvent. When using diamides, the cyclic dicycloboratoamides are formed in yields of 5–20%.^[38] With lower boiling or sublimation temperatures, these byproducts are reported to be easily separated from the monocyclic amides. Carbon tetrachloride appears to be the preferred solvent for these reactions; due caution should be exercised to avoid contact with this solvent. While the azaborocyclic amides are generally the observed product, the open-chain amide **26** can be isolated when the secondary amide carries a phenyl substituent (Scheme 18). When the diamide is substituted with a phenyl group, the cyclic product can be converted into the open-chain

boron amide by dissolution in dichloromethane. Presumably, steric and electronic considerations influence the conformation of the boron amides.

Scheme 18 Synthesis of a Boron Amide via Direct Addition of Bromodimethylborane^[38]



***N*-(Dimethylboryl)-*N,N'*-diphenylethanedi- amide (26):^[38]**

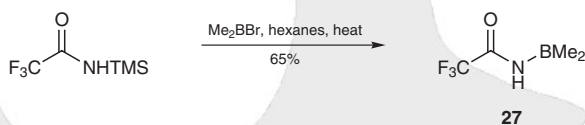
To a soln of *N,N'*-diphenylethanedi- amide (24.0 g, 0.1 mol) in CCl_4 (250 mL) (**CAUTION: toxic**) was added dropwise a soln of Me_2BBr (12.1 g, 0.1 mol) in CCl_4 (100 mL). The soln was then refluxed for 24 h with the condenser cooled to -20°C to minimize sublimation loss. Upon cooling, the solvent was carefully removed using a rotary evaporator, and the crude product was purified by sublimation ($160^\circ\text{C}/1.5 \times 10^{-3}$ Torr) affording a colorless solid; yield: 24.2 g (86%); mp $242\text{--}244^\circ\text{C}$ (dec).

21.12.4.1.2

**Method 2:
Exchange with *N*-Silylated Amides**

A preferred method for generating boron amides is through exchange of boron halides with *N*-silylcarboxamides (Scheme 19).^[37] This reaction has been examined using mono-, di-, and trihaloboranes, but only the substituted monohaloboranes will be described here. Unlike the diamide example cited in Section 21.12.4.1.1.1 where an internal carbonyl oxygen allows for formation of an azaboratacycle, the monoamides can exist as an equilibrium mixture of monomer or dimer of the boron amide. Whether the product exists as a monomer or an equilibrium mixture of monomer and dimer is dependent upon the nature of the amide and borane substituents, but monohaloboranes generally produce monomeric products such as **27**.^[35] Rules governing the equilibrium ratios have not been formulated, but published work suggests di- and trihaloboranes lead to increasing amounts of dimeric products.^[35,37] Ratios may be determined from ^{11}B NMR spectra where low field resonance (δ 7–12) indicates a dimer and higher field resonance (δ 21–59) corresponds to a monomeric product.^[35]

Scheme 19 Synthesis of a Boron Amide by Exchange with an *N*-Silylcarboxamide^[37]



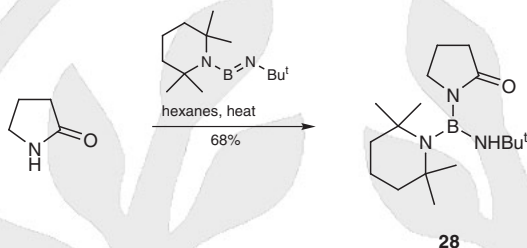
***N*-(Dimethylboryl)-2,2,2-trifluoroacetamide (27):^[37]**

Me_2BBr (12.1 g, 0.1 mol) was added dropwise to a soln of 2,2,2-trifluoro-*N*-(trimethylsilyl)acetamide (18.5 g, 0.1 mol) in hexane (250 mL). The mixture was refluxed for 4 h. Upon cooling, the solvent was removed using a rotary evaporator, and the crude product purified by sublimation ($60^\circ\text{C}/1.5 \times 10^{-3}$ Torr) providing the colorless product as a monomer; yield: 9.9 g (65%); mp 95°C ; ^{11}B NMR (δ): 32.8.

21.12.4.1.3

**Method 3:
Synthesis from Boron Imidates**

Preparation of boron amides from boron imidates is an infrequently used method.^[39] The imidates are combined with an N-substituted amide, such as pyrrolidin-2-one, and refluxed. Distillation provides products such as **28** as monomers in good yield (Scheme 20).

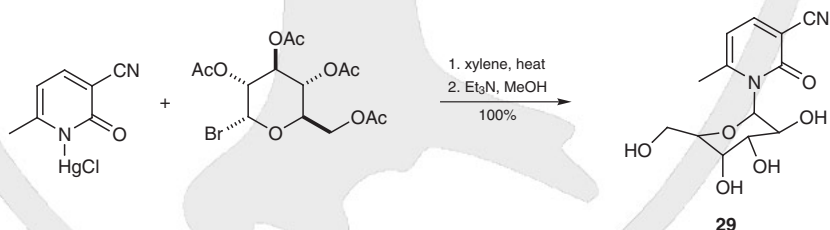
Scheme 20 Synthesis of a Boron Amide from a Boron Imidate^[39]**(tert-Butylamino)(2-oxopyrrolidino)(2,2,6,6-tetramethylpiperidino)borane (28):**^[39]

A 0.6 M soln of (tert-butylimino)(2,2,6,6-tetramethylpiperidino)borane^[40] in hexane (12.7 mL) was added dropwise with stirring to pyrrolidin-2-one (700 mg, 8.2 mmol). After the addition was complete, the mixture was refluxed for 7 h. Distillation of the mixture (109°C/1.5 × 10⁻³ Torr) provided the product as a thick yellow liquid; yield: 1.7 g (68%).

21.12.5

**Product Subclass 5:
Groups 3–13 Transition Metal Amides**

Of the many group 3–13 transition metal–amide complexes described in the literature,^[41,42] only mercury has demonstrated synthetic utility, particularly with regard to the formation of glycosides of pyridin-2-ones, e.g. **29** (Scheme 21).^[43] Discussion in this section will be restricted to these mercury amides. Because heavy metal toxicity is a serious health problem, all heavy metal amides should be handled with extreme caution using proper personal protective equipment.

Scheme 21 Synthesis of a Glycoside from Chloro(3-cyano-6-methyl-2-oxo-1,2-dihydro-1-pyridyl)mercury(II)^[45]

21.12.5.1

Synthesis of Product Subclass 5

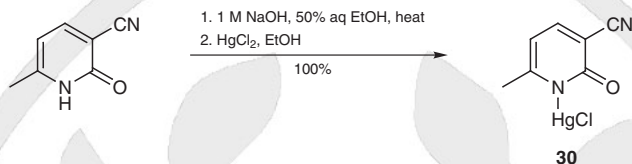
21.12.5.1.1

**Method 1:
Synthesis from Metal Halides**

The use of mercury(II) chloride as a reagent to generate nucleosides from purines and ribofuranosyl chlorides is a well established procedure.^[44] This process has been used to synthesize mercury(II) amides such as **30** from pyridin-2-ones in a very straightforward

fashion (Scheme 22).^[45] Additionally, mercury(II) chloride has been used synthetically to generate the penam ring speculatively via a transient mercury(II) chloride amide intramolecularly cyclizing on an aldehyde.^[46] Care should be exercised whenever handling these toxic mercury(II) amides.

Scheme 22 Synthesis of an Amide Using Mercury(II) Chloride^[43]



Chloro(3-cyano-6-methyl-2-oxo-1,2-dihydro-1-pyridyl)mercury(II) (30); Typical Procedure:^[43,45]

CAUTION: Mercury(II) chloride is a poison by ingestion and is toxic by skin contact. When heated to decomposition it emits toxic fumes of mercury.

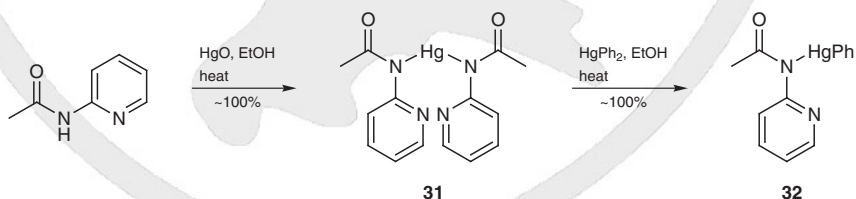
3-Cyano-6-methylpyrimidin-2(1H)-one (1.61 g, 12.0 mmol) was added to boiling 50% aq EtOH (60 mL) with vigorous stirring. A 1 M NaOH soln was slowly added providing a clear soln. To this sodium amide was added dropwise a soln of HgCl₂ (3.34g, 12.0 mmol) in a minimum volume of hot, 95% EtOH. After the entire soln of HgCl₂ was added, the soln (now cloudy with white precipitate) was stirred for a few minutes while hot before adding H₂O (20 mL). Upon cooling, the suspension was vacuum filtered, and the solid washed successively with H₂O and abs EtOH; yield: ~100%.

21.12.5.1.2

**Method 2:
Synthesis from Diphenylmercury**

Alkylmercury(II) amides have been described in the literature,^[47] and their use is currently restricted to probes for DNA affinity experiments.^[48] These substances are stable, covalent species as observed in X-ray crystallographic studies.^[48] They can be prepared in a two step process via the bis[mercury(II)] amide **31** to yield **32** through disproportionation with dialkyl/diarylmercury (Scheme 23), or through ligand exchange of an amide with alkylmercury(II) hydroxide. Little is known about the toxic profile of these alkylmercury(II) amides, but the toxicity of dialkylmercury(II) reagents is well-known.^[49] Extreme caution should be exercised when using these reagents.

Scheme 23 Synthesis by Exchange with Diphenylmercury(II)^[47]



[Acetyl(2-pyridyl)amino](phenyl)mercury(II) (32); Typical Procedure:^[47]

CAUTION: Mercury vapor is readily absorbed by inhalation and is neurotoxic.

CAUTION: Organic mercury compounds are toxic by skin contact, inhalation, or ingestion. When heated to decomposition they emit highly toxic fumes of Hg. Appropriate safety precautions and procedures should be taken during all stages of their handling and disposal.

Equimolar amounts of HgO and N-(2-pyridyl)acetamide were refluxed in EtOH. Upon cooling to rt, filtration afforded the bis-mercury(II) intermediate **31**; mp 234 °C. An equimolar amount of bis(N-2-pyridylacetamido)mercury(II) and diphenylmercury(II) was briefly refluxed in EtOH. Upon cooling, the solid was filtered, and subsequently washed with EtOH affording the product **32** as colorless crystals; yield: ~100%; mp 120 °C.

21.12.6

Product Subclass 6:**Group 2 (Beryllium, Magnesium, Calcium, and Barium) Amides and Imides**

The use of group 2 metal amides in organic synthesis is restricted to the elements magnesium, calcium, and barium. While not used as widely as the group 1 metal amides, magnesium^[50,51] and barium amides^[52] have been employed to make alkylated amides or phthalimides. These group 2 amides are hydrolytically unstable, and are never isolated.

21.12.6.1

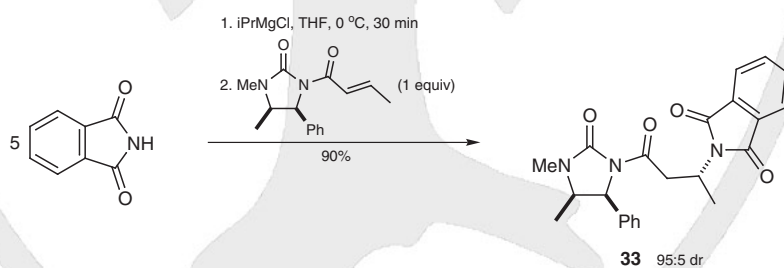
Synthesis of Product Subclass 6

21.12.6.1.1

Method 1:**Metalation with Grignard Reagents**

The only examples of magnesium(II) amides are those produced by Grignard chemistry. Used in examples where the amide proton is most acidic, both methylmagnesium chloride^[50] and isopropylmagnesium chloride^[51] have been employed under anhydrous conditions to prepare compounds such as **33**. Both N-substituted amides^[50] and phthalimides^[51] have been metalated in this manner (Scheme 24).

Scheme 24 Imide Metalation with Isopropylmagnesium Chloride^[51]

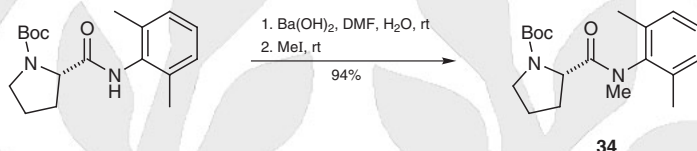
**1,5-Dimethyl-4-phenyl-3-(3-phthalimidobutanoyl)imidazolidin-2-one (33):**^[51]

To a soln of phthalimide (0.56g, 3.8 mmol) in dry THF was added 2 M iPrMgCl (1.9 mL, 3.8 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C, and 1,5-dimethylbut-3-enoyl-4-phenylimidazolidin-2-one (0.20 g, 0.76 mmol) in dry THF was added slowly to the phthalimidylmagnesium chloride soln. The mixture was stirred for 24 h at 25 °C. After quenching with 1 M aq NaHCO₃, the crude mixture was extracted with CH₂Cl₂. The organic phase was washed with H₂O and brine soln before drying (MgSO₄). Chromatography (SPHERI-5 RP-18, MeCN/H₂O gradient) followed by recrystallization (EtOH) provided the product as separated diastereomers in 95:5 ratio; yield: 90%.

21.12.6.1.2

**Method 2:
Metalation with Metal Carbonates and Metal Hydroxides**

Of the group 2 metal hydroxides, barium hydroxide is the only reagent described for metalating carboxamides.^[52] The procedure is mild, and is performed at room temperature with excess barium hydroxide as in the preparation of **34** (Scheme 25). Carbonates of the group 2 metals are not well known in the literature as metalating agents. There is a suggestion that calcium carbonate can be used to metalate a carboxamide.^[53]

Scheme 25 Amide Metalation with Barium Hydroxide^[52]**1-(tert-Butoxycarbonyl)-N-(2,6-dimethylphenyl)-N-methylpyrrolidine-2-carboxamide (**34**);
Typical Procedure:^[52]**

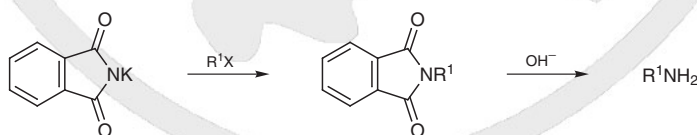
CAUTION: Inhalation, ingestion, or skin absorption of iodomethane can be fatal.

To a mixture of 1-(tert-butoxycarbonyl)-N-(2,6-dimethylphenyl)pyrrolidine-2-carboxamide (0.7 g, 2.2 mmol) in a soln of DMF (30 mL) and H₂O (10 mL), was added Ba(OH)₂ (2.3 g, 13.2 mmol), at rt. After addition of MeI (11.2 g, 79.2 mmol) to the suspension, the mixture was stirred for 12 h. Filtration, followed by extraction with petroleum ether, provided the product **34**; yield: 94%.

21.12.7

**Product Subclass 7:
Group 1 (Lithium, Sodium, Potassium, Rubidium, and Cesium) Amides and Imides**

Use of group 1 metal amides and imides is ubiquitous in organic synthesis. One of the earliest examples is the Gabriel synthesis,^[54] where a potassium phthalimide is alkylated and subsequent hydrolysis affords a primary amine as shown in Scheme 26. In general, when N-alkylations of carboxamides are performed, they are accomplished by means of group 1 metal amides. It is the purpose of this section to provide a comprehensive overview of group 1 metalation methods. Because group 1 metal amides are generated in situ, descriptions of their preparation will include their alkylation, an indication of metalation. These metal amides are extremely labile in water. Care should be exercised in handling group 1 metal amides since they are quite caustic; no toxicity studies have been performed.

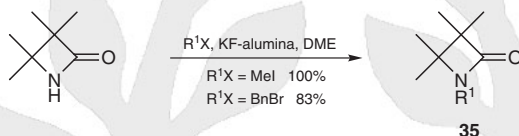
Scheme 26 Gabriel Synthesis of Primary Amines^[54]

21.12.7.1 Synthesis of Product Subclass 7

21.12.7.1.1 Method 1:
Metalation with Potassium Fluoride on Alumina

Carboxamides, lactams, and imides may be efficiently metalated using potassium fluoride on alumina.^[55] The potassium amides are not isolated. Through use of this reagent, alkylations proceed efficiently although peralkylation is common when several amides are present in the molecule. An advantage of this metalation procedure is the mild conditions used (0 °C to rt) in the preparation of compounds such as **35** (Scheme 27).

Scheme 27 Alkylation Using Potassium Fluoride–Alumina as the Metalation Agent^[55]

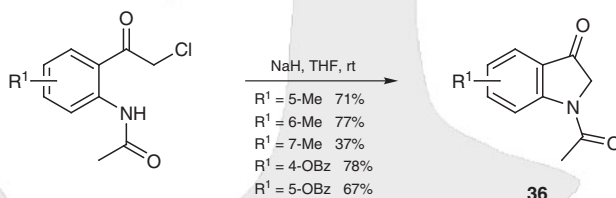
**N-Alkyl-3,3,4,4-tetramethylazetidin-2-ones **35**; General Procedure:**^[55]

A suspension of 3,3,4,4-tetramethylazetidin-2-one (0.127g, 1.0 mmol) and KF/alumina (0.38 g, 2.5 mmol KF) in DME (10 mL) was stirred at rt with a haloalkane (1 equiv) over 72 h. Isolation by chromatography (silica gel) afforded the products; yield: 83–100%.

21.12.7.1.2 Method 2:
Metalation by Metal Hydrides

Metalation of amides using metal hydrides is commonly used in the alkylation of amides. In this mild process, lithium hydride^[56] and potassium hydride^[57] have been employed to metalate amides, but the most commonly used metal hydride is sodium hydride, used for example, in the preparation of **36** (Scheme 28).^[58] These group 1 hydrides are extremely pyrophoric in the presence of moisture, and only dry, polar, non-protic solvents (i.e., THF, DME, DMF) should be used to metalate amides.

Scheme 28 Carboxamide Cyclization Using Sodium Hydride as the Metalation Agent^[58]

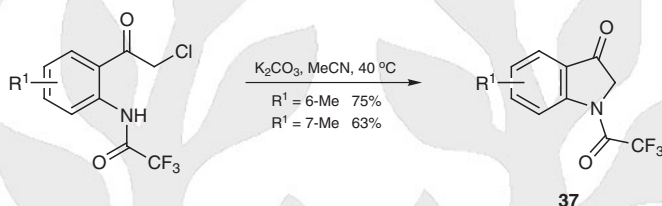
**Substituted 1-Acetyl-1,2-dihydro-3H-indol-3-ones (**36**); General Procedure:**^[58]

To a suspension of NaH (0.53g, 22.0 mmol) in abs THF under cooling was added dropwise a soln of a 2-(acetyl-amino)- α -chloroacetophenone (20 mmol) in THF. The mixture was stirred rapidly at rt until all starting material was consumed. To the mixture was added dil HCl, and the mixture was extracted with CH_2Cl_2 . The organic phase was dried (MgSO_4) before concentration. The crude solid was recrystallized (iPrOH/ H_2O) affording the products as crystalline solids; yield: 37–78%.

21.12.7.1.3

**Method 3:
Metalation with Metal Carbonates**

Metal carbonates are commonly used in the metalation of amides. Examples appear in the literature employing sodium carbonate,^[59] potassium carbonate^[58] (used to prepare **37**), and cesium carbonate.^[60] The conditions are mild; dry, polar solvents are utilized for metalation. Both imides and amides have been alkylated using this metalation method (Scheme 29). These reagents are caustic and hygroscopic, and water should be excluded from these reactions.

Scheme 29 Alkylations of Amides Using Potassium Carbonate^[58]**Alkyl-Substituted 1-(Trifluoroacetyl)-1,2-dihydro-3H-indol-3-ones **37**; General Procedure:**^[58]

To a soln of an α -chloro-2-(trifluoroacetyl-amino)acetophenone (15 mmol) in dry MeCN (75 mL) was added finely powdered K_2CO_3 (1.4 g, 10 mmol) with stirring. After stirring for 2 h, the basic suspension was heated at 40 °C for 0.5 h. The mixture was poured into H_2O , and extracted with Et_2O . The organic phase was dried ($MgSO_4$), concentrated, and the crude product recrystallized ($CHCl_3$ /hexane) to provide the products **37** as colorless crystalline solids; yields: 63–75%.

21.12.7.1.4

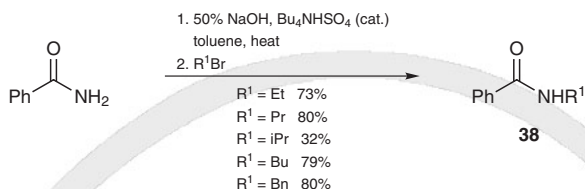
**Method 4:
Metalation with Metal Hydroxides and Metal Alkoxides**

Group 1 metal hydroxides and alkoxides have been used extensively to metalate amides and imides. Sodium hydroxide,^[61] potassium hydroxide,^[62] and potassium *tert*-butoxide^[63] are the most commonly used reagents for this type of metalation. Conditions are mild, and can employ phase-transfer catalysis.^[61,64] In another unique feature, either aqueous or polar organic solvents can be used with the metal hydroxides. The metal amides are always generated in situ with N-alkylation of the amide the ultimate goal.

21.12.7.1.4.1

**Variation 1:
With Sodium Hydroxide**

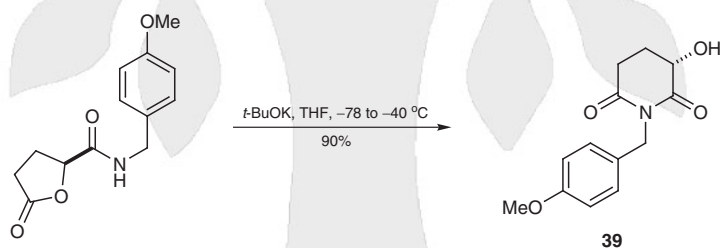
Sodium hydroxide can be used to metalate amides under aqueous^[61] or nonaqueous^[64] reaction conditions. N-Alkylation is the primary application for the resultant metal amides (Scheme 30). Use of phase-transfer catalysis can enhance the yield of the alkylation product **38**. The caustic nature of this metalation requires that base-sensitive functionality be absent.

Scheme 30 N-Alkylation of Benzamide Using Sodium Hydroxide for Metalation^[61]**N-Alkylbenzamides 38; General Procedure:**^[61]

To a refluxing suspension containing BzNH₂ (6.05 g, 50.0 mmol), 50% aq NaOH soln (50 mL), Bu₄NHSO₄ (1.7 g, 5.0 mmol), and toluene (50 mL) was added a soln of bromoalkane (53–60 mmol) in toluene (10 mL) dropwise over 1.5 h. After the addition was complete, the mixture was stirred under reflux for an additional 2.5 h. Upon cooling the mixture, H₂O (30 mL) was added, and the organic phase was washed with H₂O until neutral. The organic phase was dried (MgSO₄), concentrated, and the crude products recrystallized (Et₂O/hexane); yield: 32–80%.

21.12.7.1.4.2**Variation 2:
With Potassium *tert*-Butoxide**

Potassium *tert*-butoxide is an effective amide metalation reagent. Used in aprotic solvents such as tetrahydrofuran, selective amide deprotonation can occur at low temperatures.^[63] Potassium amides are very reactive and moisture sensitive. These metal amides are generated in situ, and immediately reacted with an alkylating or acylating agent, yielding products such as **39**. The example below shows a ring expansion via a potassium amide intermediate (Scheme 31).

Scheme 31 Ring Expansion Using Potassium *tert*-Butoxide Metalation of an Amide^[63]**(S)-3-Hydroxy-1-(4-methoxybenzyl)piperidine-2,6-dione (39):**^[63]

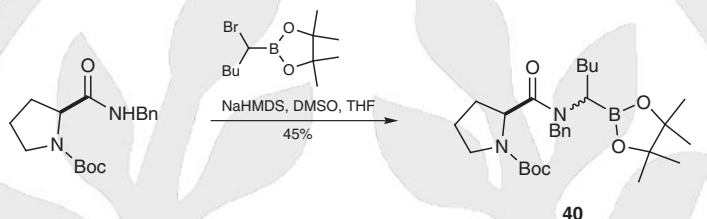
To a mixture of (S)-N-(4-methoxybenzyl)-5-oxotetrahydrofuran-2-carboxamide (4.205 g, 16.89 mmol) and *t*-BuOK (0.794 g, 7.09 mmol) was added anhyd THF (50 mL) at –78 °C under a N₂ atmosphere. The reaction was stirred for 1 h while warming to –40 °C, before being quenched with sat. NH₄Cl. The THF was removed under reduced pressure, and the residue was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, washed with sat. NaCl (15 mL), and dried (Na₂SO₄). Removal of the solvent provided the product as a white crystalline solid; yield: 3.80 g (90%); mp 98–99 °C.

21.12.7.1.5**Method 5:
Metalation with Metal Amides**

A common approach to generating group 1 metal amides uses hindered metalated secondary amines as reagents. The most frequently used reagents are lithium diisopropyl-

amide,^[65] and lithium,^[66] sodium^[67] [used in the preparation of **40** (Scheme 32)], and potassium^[68] hexamethyldisilazanes. These bases are commercially available in polar, non-protic solvents, and should be handled appropriately under anhydrous conditions under an inert atmosphere to avoid fire and burns. Because these reagents are such efficient bases, other acidic functionality within the amide molecule should be considered for possible deprotonation under the reaction conditions. As with all group 1 amide metalations, the metal amides are not isolated, but alkylated in situ.

Scheme 32 Alkylation of an Amide Using Sodium Hexamethyldisilazide^[67]



***N*-Benzyl-1-(*tert*-butoxycarbonyl)-*N*-[1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]pyrrolidine-2-carboxamide (**40**); Typical Procedure:^[67]**

To a mixture of *N*-benzyl-[2-(1-*tert*-butoxycarbonyl)pyrrolidine]-2-carboxamide (0.2 g, 0.66 mmol) and pinacol (1-bromopentyl)boronate (0.18 g, 0.65 mmol) in DMSO (5 mL) was slowly (1 drop·s⁻¹) added a 1 M soln of NaHMDS (0.7 mL, 0.70 mmol) in THF at rt. After stirring the mixture for 3 h, EtOAc (50 mL) was added, and the solid was removed by filtration. The soln was poured into an ice/brine mixture (30 mL with 10 g of ice), and the aqueous layer was extracted with Et₂O (50 mL). The organic layers were combined and dried (MgSO₄). Upon removal of the solvent under the reduced pressure, the crude product was subjected to flash chromatography (silica gel, hexane/EtOAc 1:1) to afford the product as an oil containing two diastereomers; yield: 0.15 g (45%).

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Product Class 13: *N*-Heteroatom-Substituted Alkanamides

P. R. Blakemore

General Introduction

The complete class of known *N*-heteroatom-substituted alkanamides encompasses a very large number of product subclasses. Any attempt to approach a complete coverage of these individual compound types within the limited space available would severely compromise the depth of coverage possible for each subclass. This contribution therefore focuses on the major classes of amides substituted by nitrogen, oxygen, or halogens, together with a limited selection of examples substituted by phosphorus or sulfur. An earlier comprehensive review of *N*-heteroatom-substituted alkanamides includes good coverage of amides substituted by the higher elements of groups 15 and 16.^[1] Only the most significant methods for preparation of the selected product subclasses are discussed in detail, with a bias toward more recent reports not included in the last major review.^[1]

21.13.1

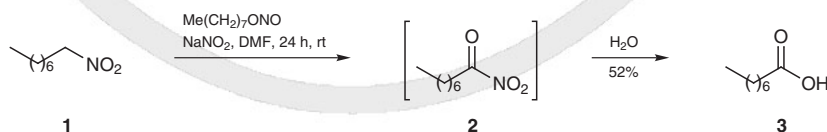
Product Subclass 1: Acyl Nitro Compounds

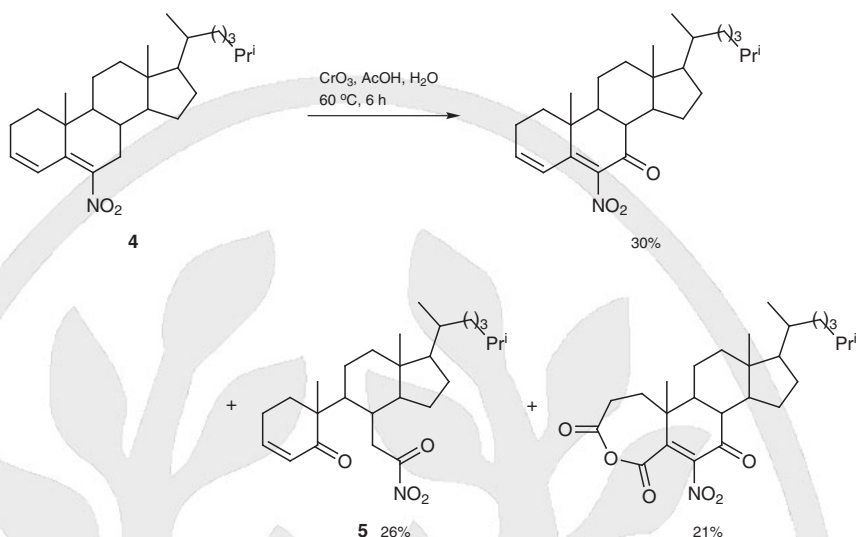
Acyl nitro compounds have been the subject of numerous theoretical investigations;^[2–5] however, genuine reports of their preparation are rare and disparate. Accordingly, only a small number of illustrative examples concerning the synthesis of this product subclass will be discussed.

α -Nitrobenzaldehyde was reported as a side product in the nitration of benzaldehyde by Lippmann and Hawliczek in 1876;^[6] hydrazones of this acyl nitro compound can be prepared indirectly from nitro(phenyl)methane and aryl diazonium salts.^[7] The Kornblum nitrosation method for the transformation of primary nitroalkanes, e.g. **1** (Scheme 1), to carboxylic acids proceeds via an initially generated nitrolic acid intermediate that is further converted into a putative acyl nitro compound, **2** (Scheme 1).^[8,9] Hydrolysis of the nitrocarbonyl compound gives the carboxylic acid, **3**. In a related process, the oxidation by ammonium persulfate of nitronate anions derived from geminal dinitroalkanes is also purported to form transient acyl nitro compounds.^[10]

Acyl nitro compounds can also be prepared by the chromic acid mediated oxidation of steroidal nitroalkenes.^[11] For example, the treatment of 6-nitrocholesta-3,5-diene (**4**) with chromium(VI) oxide in acetic acid gives a mixture of products that includes the nitrocarbonyl compound **5**. The thermal degradation of certain 2-nitrofuran derivatives, such as nitrofurazone, also yields this product subclass.^[12]

Scheme 1 Generation of Acyl Nitro Compounds^[8,11]





21.13.2

**Product Subclass 2:
Acyl Nitroso Compounds**

Acyl nitroso compounds are transient species, and no examples of this product subclass have been isolated or observed spectroscopically. Such compounds were proposed as intermediates in the oxidative cleavage of *N*-hydroxy amides (hydroxamic acids) as early as 1964,^[13] but their existence was not unequivocally established until 1973 when nitroso-carbonylmethane was trapped by a cycloaddition reaction with thebaine.^[14] In the absence of trapping agents, acyl nitroso compounds dimerize to form unstable *N,N'*-diacylazo *N,N'*-dioxides that spontaneously decay into symmetric carboxylic acid anhydrides with the loss of nitrous oxide.^[15,16]

The complex chemical reactivity of acyl nitroso compounds provides a number of useful applications. For instance, these compounds can be used as radical spin traps,^[17] and their reaction with triphenylphosphine yields the corresponding isocyanates.^[14] Of greater importance, however, are the efficient pericyclic processes in which this product subclass readily participate as a consequence of their low LUMO energies. Acyl nitroso compounds are excellent dienophiles and they react with dienes to give [4+2] hydroxamate cycloadducts (*N*-acyl 3,6-dihydro-1,2-oxazines)^[18,19] and with nonconjugated alkenes by an ene reaction to afford *N*-allylic *N*-hydroxy amides.^[20] These reactions are discussed in detail in Sections 21.13.9.1.4 and 21.13.11.1.3.

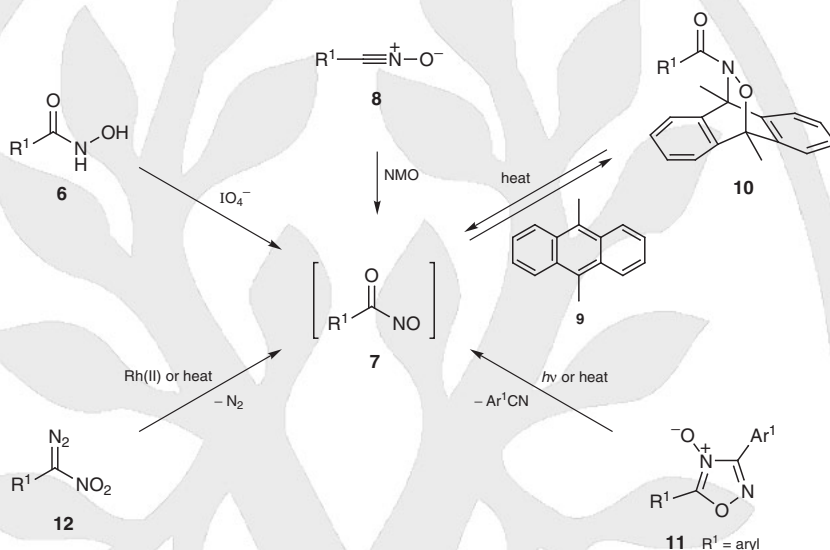
A number of methods are available for the generation of acyl nitroso compounds (Scheme 2). The method of choice is governed by the nature of the nitrosocarbonyl trapping agent and the product of the ensuing reaction. Periodate ion mediated oxidation of unsubstituted *N*-hydroxy amides **6** is the most popular method for the in situ preparation of nitrosocarbonyls **7**.^[15] Other oxidants are available for this purpose, e.g. [bis(cyclooctene)chloroiridium] dimer/hydrogen peroxide,^[21] oxalyl chloride/dimethyl sulfoxide,^[22] Dess–Martin periodinane,^[23] or (diacetoxyiodo)benzene.^[24] Treatment of nitrile oxides **8** with *N*-methylmorpholine *N*-oxide provides an alternative and particularly mild oxidative synthesis of this product subclass.^[25]

Acyl nitroso compounds can also be prepared by fragmentation and rearrangement processes. Cycloaddition of 9,10-dimethylantracene (**9**) with acyl nitroso compounds **7** (generated by oxidation of *N*-hydroxy amides) gives isolable cycloadducts **10** in good yields.^[14] Gentle heating ($\sim 80^\circ\text{C}$) of these adducts initiates a cycloreversion to release the

acyl nitroso compound **7**; this provides a simple method for generating these reactive intermediates on demand under neutral nonoxidative conditions. Cycloadducts **10** can also be significantly elaborated before thermolysis, offering access to more complex acyl nitroso compounds than are available by direct means.

The photochemical or thermal fragmentation of 1,2,4-oxadiazole 4-oxides **11** can also be applied in the synthesis of this product subclass.^[16,26] Finally, rearrangement of nitrocarbenes, derived from substituted diazonitromethanes **12** and rhodium(II) acetate, gives acyl nitroso compounds.^[27]

Scheme 2 Methods for Generating Nitroso Carbonyl Compounds^[14,16,25–27]



21.13.3

Product Subclass 3: *N*-Acyl Sulfoximides and *N*-Acyl Sulfimides

Although the general chemistry of sulfoximides^[28–30] (also known as sulfoximines and sulfonimides) and sulfimides^[31] (also known as sulfilimines and iminosulfuranes) has been studied in some detail, the *N*-acylated derivatives of these compounds have received relatively little attention. The synthetic, physical, and spectroscopic properties of *N*-acyl sulfoximides have been summarized.^[32] The *N*-acyl sulfoximide unit can be used as a unique turn-inducing motif in pseudopeptides^[33,34] and as a chiral controller group in intramolecular cycloaddition reactions.^[35] Carbonyl reduction of *N*-acyl sulfoximides with borane derivatives affords *N*-alkyl sulfoximides in good yields.^[36] Cyclic *N*-acyl vinyl sulfimides can be used as unique dienophiles for highly diastereoselective Diels–Alder reactions.^[37]

21.13.3.1

Synthesis of Product Subclass 3

In addition to the methods described below, *N*-acyl sulfoximides can also be obtained from *N*-acyl sulfimides by chemoselective S-oxidation with a variety of oxidants, including dimethyldioxirane,^[38] 3-chloroperoxybenzoate anion,^[39] or ruthenium(VIII) oxide.^[40] The reaction with dimethyldioxirane proceeds with complete retention of configuration at the sulfur atom.^[38]

21.13.3.1.1

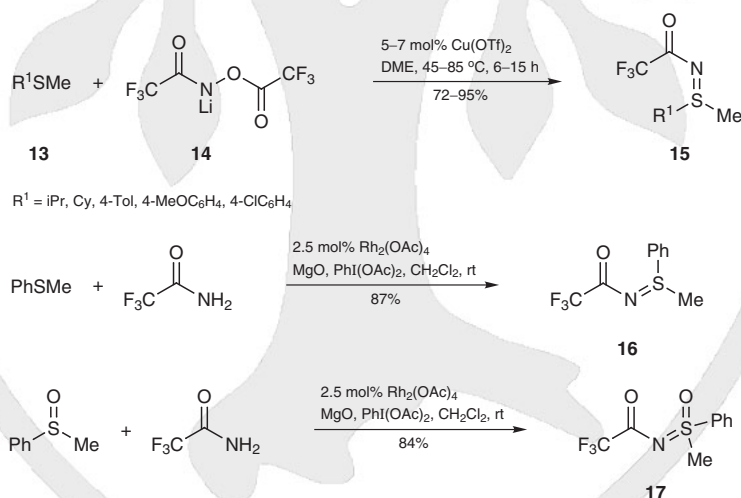
Method 1:

Oxidative Imination of Sulfoxides and Sulfides

Treatment of sulfides and sulfoxides with *N*-acyl nitrenoids or their equivalents provides a convenient synthesis of *N*-acyl sulfimides and *N*-acyl sulfoximides, respectively. *N*-Acetylminodialkylsulfonium salts are obtained in good yields from dialkyl sulfides and *N*-bromoacetamide.^[41] Deprotonation of these salts with pyridine gives the corresponding *N*-acetyl sulfimides. *N*-Phenyliodoniacarboxamide 4-toluenesulfonates can also be used in the generation of *N*-acyliminosulfonium salts from sulfides.^[42] *N*-Trifluoroacetyl nitrenoid transition-metal complexes of both copper(II) and rhodium(II) can be used to iminate sulfides and sulfoxides.^[43,44] Methyl sulfides **13** are conveniently iminated by lithium trifluoroacetoxy(trifluoroacetyl)azanide (**14**) in the presence of a substoichiometric amount of copper(II) trifluoromethanesulfonate (Scheme 3).^[43] Electron-rich sulfides give the highest yields of sulfimides **15**.

A comparatively nonhazardous reagent combination of trifluoroacetamide, (diacetoxyiodo)benzene, and magnesium oxide effects the trifluoroacetamination of methylsulfanylbenzene, in the presence of rhodium(II) acetate dimer as a catalyst, to give the sulfimide **16** (Scheme 3).^[44] The sulfoximide **17** can be similarly prepared in excellent yield from methylsulfinylbenzene. The imination of enantiomerically enriched sulfoxides shows that this oxidation reaction occurs with retention of configuration at sulfur. Furthermore, mild basic methanolysis of the *N*-trifluoroacetyl sulfoximides gives the corresponding free sulfoximides in high yields.^[44]

N-Acyl sulfimides can be synthesized enantioselectively by imination of prochiral sulfides.^[45,46] Sulfoxides containing proximal carboxy groups undergo imination with either hydrazoic acid or *O*-(mesitylsulfonyl)hydroxylamine to give heterocyclic *N*-acyl sulfoximides by concomitant lactamization.^[47–49]

Scheme 3 Imination of Sulfides and Sulfoxides^[43,44]

2,2,2-Trifluoro-*N*-[methyl(4-tolyl)-λ⁴-sulfanylidene]acetamide (**15**, R¹ = 4-Tol); Typical Procedure:^[43]

A 1.7 M soln of *t*-BuLi in pentane (21.0 mL, 35.5 mmol) was added during 10 min to a stirred soln of 2,2,2-trifluoro-*N*-[(trifluoroacetyl)oxy]acetamide (8.00 g, 35.5 mmol) in Et₂O (16 mL) at –78 °C. The resulting suspension was allowed to warm to rt, was diluted with

pentane (20 mL), and was stirred for a further 2 h. The supernatant liquor was then removed through a cannula and the remaining solvent was removed under reduced pressure to give the lithiated compound **14** as a colorless powder; yield: 7.46 g (91%).

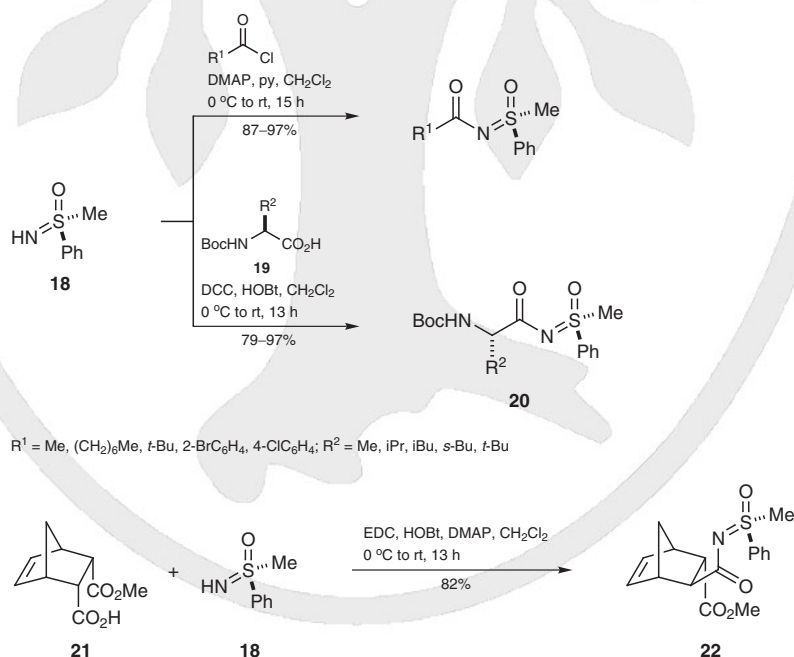
A stirred soln of sulfide **13** ($R^1 = 4\text{-Tol}$; 0.135 mL, 1.00 mmol), lithiated compound **14** (0.462 g, 2.00 mmol), and $\text{Cu}(\text{OTf})_2$ (25 mg, 0.07 mmol) in DME (10 mL) was heated at 60°C for 15 h. The resulting green soln was concentrated under reduced pressure and the residue was purified by column chromatography ($\text{EtOAc/hexanes } 2:1$) to give sulfimide **15** ($R^1 = 4\text{-Tol}$) as a colorless solid; yield: 0.191 g (77%); mp $70\text{--}72^\circ\text{C}$.

21.13.3.1.2

Method 2:**N-Acylation of Sulfoximides and Sulfimides**

Sulfoximides are acylated by acid halides or anhydrides, but acylation can also be conveniently achieved using a carboxylic acid (e.g., **19**) with a suitable carbodiimide activator to give the aminoacid sulfoximide **20**.^[32,35] Bolm and co-workers thoroughly explored the acylation of enantiomerically enriched (*S*-methylsulfonylimidoyl)benzene (**18**) (Scheme 4),^[32,33,36] a prototypical sulfoximide whose synthetic versatility was first recognized by Johnson.^[29] Acylation of **18** with the *endo-endo* cycloadduct **21** proceeds with extensive epimerization (at carbon) under mild reaction conditions, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), and produces predominantly the *exo*-*N*-acyl sulfoximide **22** (82%), together with a small quantity of the corresponding *endo*-isomer (5%).^[32] This interesting result highlights the acidifying effect of the sulfoximidyl moiety on amide carbonyl α -protons.

Free sulfimides are more nucleophilic than the analogous sulfoximides and, in addition to acid halides,^[45] acid anhydrides,^[45] and ketenes,^[50] these sulfur ylides can be acylated by esters^[51] or even by amides in the case of trichloroacetamide.^[52]

Scheme 4 Acylation of (*S*-Methylsulfonylimidoyl)benzene^[32,33,36]

Amino Acid Sulfoximides 20; General Procedure:^[33]

A stirred soln of an *N*-Boc-protected amino acid **19** (1 equiv), (*S_S*)-(*S*-methylsulfonylimidoyl)-benzene (**18**, 1 equiv), and HOBT (1 equiv) in CH₂Cl₂ (8 mL·mmol⁻¹) at 0 °C was treated with DCC (1.03 equiv) in CH₂Cl₂ (1 mL·mmol⁻¹). The resulting soln was stirred for 1 h at 0 °C and then allowed to warm to rt and stirred for a further 12 h. The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes 1:1) to afford the amino acid sulfoximide derivative **20**.

**21.13.4 Product Subclass 4:
Acyl Azides**

Previously published information regarding this subclass of products can be found in *Houben-Weyl*, Vol. 13, p 777, and in a number of reviews that cover all aspects of their chemistry.^[53–55] The great interest in this class of N-heteroatom-substituted amides stems from their many useful synthetic applications. The 1,2-nucleophilic rearrangement of acyl azides to give isocyanates (the Curtius rearrangement)^[56] is arguably the most useful reaction of this type of compound and provides an indirect route to amines, ureas, and carbamates.^[55] The azide anion possesses good properties as a nucleofugal group and, consequently, acyl azides are often used as electrophilic acylating reagents. Before the introduction of carbodiimide-based methodology,^[57] acyl azides provided the only generally applicable and satisfactory method for peptide synthesis (the “azide method”), because coupling of amines to peptidoyl azides proceeds with little or no epimerization.^[58] Acyl azides are prone to decomposition and are often generated in situ; however, many acyl azides, particularly aroyl azides, are sufficiently stable to allow straightforward isolation at room temperature.

SAFETY: In common with other organic materials containing the azido functional group, acyl azides can decompose explosively.^[59] Organic azides are most likely to suffer violent decomposition if exposed to heat, mechanical shock, or certain chemical initiators (e.g., protic acids or Lewis acids) in their pure state. Proper safety precautions should therefore be taken during the synthesis and handling of acyl azides. The isolation of low-molecular-weight aliphatic acyl azides should not be attempted.


21.13.4.1 Synthesis of Product Subclass 4**21.13.4.1.1 Method 1:
Oxidative Azidation of Aldehydes**

The direct oxidative azidation of aldehydes provides a convenient entry to the acyl azides **23** and complements traditional nonoxidative acyl substitution-based methods (Table 1).^[60–65] Oxidative azidation is typically achieved by reacting the aldehyde substrate with a source of nucleophilic azide in the presence of a suitable oxidant {e.g., sodium periodate/Dess–Martin periodinane [1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one],^[61] sodium periodate/(diacetoxyiodo)benzene,^[62] triazidochlorosilane/manganese(IV) oxide,^[63] azidotrimethylsilane/chromium(VI) oxide,^[64] or sodium azide/pyridinium chlorochromate^[65]}. The oxidant and solvent system must be chosen so that transformation of the aldehyde to the carboxylic acid is prevented.

Fundamentally different types of mechanism operate depending on the reagent combination used. A radical mechanism involving abstraction of the aldehyde hydrogen atom by the azidyl radical may occur for reagent combinations employing hypervalent iodine compounds,^[61,62] and a related radical mechanism is implicated with iodine azide.^[60] It has been postulated that combinations of transition metal oxides and silyl azides give azido transition metal oxides {e.g., diazidochromium(VI) oxide [CrO₂(N₃)₂] from azidotrimethyl-

silane and chromium(IV) oxide} that transform aldehydes to acyl azide products via the corresponding α -azidoalcohol metal esters.^[63,64] The reagent combination of sodium azide and Dess–Martin periodinane, introduced by Bose and Reddy,^[61] is the most versatile method currently available for oxidative azidation of aldehydes, and it provides excellent yields of acyl azides from a variety of aldehyde types: e.g., electron-rich aromatic aldehydes (entry 2), electron-deficient aromatic aldehydes (entry 5), α,β -unsaturated aldehydes (entry 7), or simple aliphatic aldehydes (entry 10).^[61] When conducted at slightly elevated temperatures, oxidative azidation of aldehydes may afford isocyanates, carbamoyl azide products, or both. The former are a consequence of the Curtius rearrangement of the initially generated acyl azides, whereas the latter result from nucleophilic azidation of the isocyanates themselves.^[60,65] For example, attempted azidation of aliphatic aldehydes with sodium azide and pyridinium chlorochromate at 45 °C gives carbamoyl azide products almost exclusively.^[65]

Table 1 Direct Conversion of Aldehydes into Acyl Azides^[60–63]

					
Entry	R ¹	Conditions	Yield (%)	mp ^c (°C)	Ref
1	4-Me ₂ NC ₆ H ₄	MnO ₂ , ClSi(N ₃) ₃ , ^a CH ₂ Cl ₂ , 0 °C, 2 h	78	n.r.	[63]
2	4-MeOC ₆ H ₄	DMP, ^b NaN ₃ , CH ₂ Cl ₂ , 0 °C, 1 h	95	68–70	[61]
3	4-MeOC ₆ H ₄	PhI(OAc) ₂ , NaN ₃ , CH ₂ Cl ₂ , rt, 2 h	92	68–71	[62]
4	4-O ₂ NC ₆ H ₄	MnO ₂ , ClSi(N ₃) ₃ , ^a CH ₂ Cl ₂ , 0 °C, 2 h	86	n.r.	[63]
5	4-O ₂ NC ₆ H ₄	DMP, ^b NaN ₃ , CH ₂ Cl ₂ , 0 °C, 3 h	85	64–66	[61]
6	4-O ₂ NC ₆ H ₄	PhI(OAc) ₂ , NaN ₃ , CH ₂ Cl ₂ , rt, 6 h	43	64–66	[62]
7	(E)-CH=CHPh	DMP, ^b NaN ₃ , CH ₂ Cl ₂ , 0 °C, 1 h	83	82–84	[61]
8	(E)-CH=CHPh	MnO ₂ , ClSi(N ₃) ₃ , ^a CH ₂ Cl ₂ , 0 °C, 3 h	68	n.r.	[63]
9	(CH ₂) ₆ Me	IN ₃ , ^a MeCN, rt, 2.5 h	86	oil	[60]
10	(CH ₂) ₆ Me	DMP, ^b NaN ₃ , CH ₂ Cl ₂ , 0 °C, 4.5 h	82	oil	[61]

^a Reagent prepared in situ.

^b DMP = Dess–Martin periodinane [1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one].

^c n.r. = not reported.

4-Methoxybenzoyl Azide (23, R¹ = 4-MeOC₆H₄; Table 1, Entry 2); Typical Procedure:^[61]

CAUTION: Sodium azide can explode on heating and is highly toxic. Contact of metal azides with acids liberates the highly toxic and explosive hydrazoic acid.

CAUTION: Acyl azides can decompose explosively, particularly if exposed to heat, mechanical shock, or certain chemical initiators (e.g., protic or Lewis acids) in their pure state. Proper safety precautions should therefore be taken during the synthesis and handling of acyl azides.

A soln of 4-MeOC₆H₄CHO (0.68 g, 5.0 mmol) in CH₂Cl₂ (25 mL) at 0 °C was treated with Dess–Martin periodinane (2.54 g, 6.0 mmol) and NaN₃ (1.13 g, 17.4 mmol). The resulting mixture was stirred for 1 h while the progress of the reaction was monitored (TLC). The mixture was then washed with H₂O (2 × 5 mL) and the aqueous washings were extracted with CH₂Cl₂ (2 × 10 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, EtOAc/hexanes 11:89) to give a pale yellow solid; yield: 0.84 g (95%); mp 68–70 °C; IR (KBr) $\tilde{\nu}_{\text{max}}$: 2180, 2140, 1700 cm^{−1}.

21.13.4.1.2

Method 2:**Acyl Substitution with an Azide Nucleophile**

21.13.4.1.2.1

Variation 1:**From Activated Carboxylic Acid Derivatives**

The azide anion is an excellent nucleophile and carbonyl azides can be easily prepared by direct acyl substitution reactions from suitably activated carboxy derivatives, usually acid chlorides.^[66] Sodium azide has a low solubility in most organic solvents, so reactions are often conducted by introducing a concentrated aqueous solution of the salt into a solution of the substrate in a water-miscible organic solvent such as acetone or dioxane as, for example, in the conversion of the acid chloride **24** into acyl azide **25** (Scheme 5).^[67]

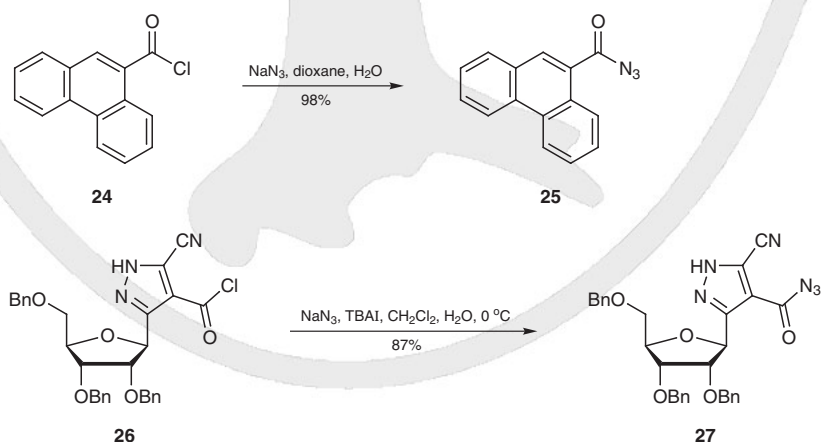
Alternative reaction conditions are required for activated carboxylic acid derivatives that undergo rapid hydrolysis. Anhydrous conditions employing a suspension of finely powdered sodium azide in an inert solvent can be used,^[68] but such protocols typically require heating of the reaction mixture, potentially initiating a Curtius rearrangement, and better solutions to this problem are available. Substrate hydrolysis can be suppressed and reactivity enhanced if the azide anion is transported to a water-immiscible organic solvent under phase-transfer catalysis conditions, as in the conversion of acid chloride **26** into the acyl azide **27** (Scheme 5).^[69]

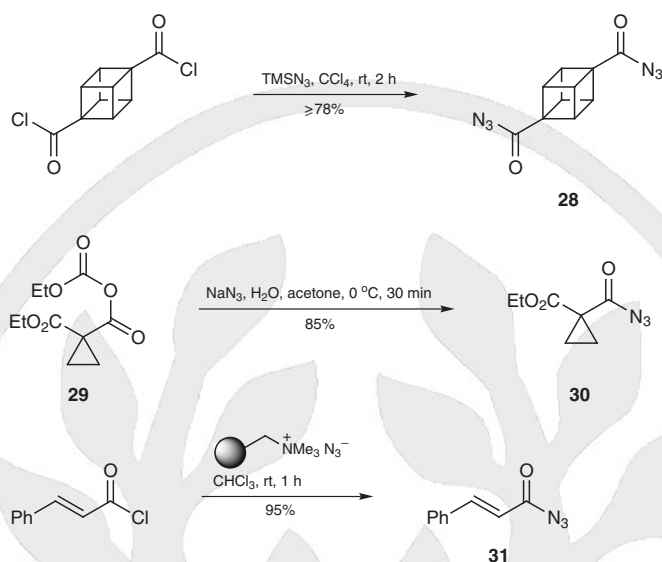
Alternatively, an organosoluble source of anhydrous azide, such as tributyltin azide^[70] or azidotrimethylsilane,^[71] can be used. The latter reagent in homogeneous carbon tetrachloride solution is well suited for the preparation of the highly energetic cubane diacylazide **28** (Scheme 5).^[72]

Mixed carboxylic–carbonic anhydrides, e.g. **29**, which are easily prepared from carboxylic acids and chloroformate esters, readily react with sodium azide to give the expected acyl azide derivatives.^[73] This approach gives the carbonyl azide **30** in excellent yield as a precursor to 1-aminocyclopropanecarboxylic acid (Scheme 5).^[74]

Acid chlorides can also be converted into azides, e.g. **31**, by treatment with a polymer-supported tetraalkylammonium azide salt (Scheme 5).^[75] Although heterogeneous, the polymer-supported azide is highly reactive in chloroform, and any excess reagent is removed by simple filtration at the end of the reaction. Similar “green” azidation protocols involve the use of sodium azide on a silica gel support^[76] or dissolved in an ionic liquid.^[77]

Scheme 5 Synthesis of Acyl Azides by Direct Acyl Substitution^[67,69,72,74,75]





(1S)-1,4-Anhydro-1-[4-(azidocarbonyl)-5-cyano-1H-pyrazol-3-yl]-2,3,5-tri-O-benzyl-D-ribitol (27); Typical Procedure:^[69]

CAUTION: Sodium azide can explode on heating and is highly toxic. Contact of metal azides with acids liberates the highly toxic and explosive hydrazoic acid.

CAUTION: Acyl azides can decompose explosively, particularly if exposed to heat, mechanical shock, or certain chemical initiators (e.g., protic or Lewis acids) in their pure state. Proper safety precautions should therefore be taken during the synthesis and handling of acyl azides.

A stirred soln of acid chloride **26** (2.43 g, 4.35 mmol) and TBAI (10 mg, 0.03 mmol) in CH_2Cl_2 (29 mL) was treated with a soln of NaN_3 (0.36 g, 5.54 mmol) in H_2O (4.9 mL) at 0°C . The resulting biphasic mixture was stirred for 2 h at 0°C . The organic layer was then separated, washed with H_2O , dried (MgSO_4), and then concentrated under reduced pressure; yield: 2.14 g (87%); IR (KBr) $\tilde{\nu}_{\text{max}}$: 2260, 2180, 2140, 1730 cm^{-1} .

21.13.4.1.2.2

Variation 2:**From Carboxylic Acids Using Diphenylphosphoryl Azide**

Diphenylphosphoryl azide (DPPA), a stable nonexplosive liquid (bp $157^\circ\text{C}/0.17$ Torr),^[78] was introduced by Yamada for the modified Curtius reaction and for peptide synthesis directly from unactivated carboxylic acids.^[79,80] Both processes involve in situ formation of acyl azide intermediates by azido transfer to the carboxy group. The acyl azides can be isolated in good to excellent yields by treating the carboxylic acid with diphenylphosphoryl azide in the presence of triethylamine at room temperature. Diphenylphosphoryl azide is compatible with a large variety of functional groups and consequently this reaction variant has been exploited to prepare many examples of particularly complex acyl azides, such as the nodulisporic acid derived acyl azide **32** (Scheme 6).^[81] The *cis*- and *trans*-cyclopropyl acyl azides **34A** and **34B**, incorporating *N*-trityl-protected imidazole moieties, can be similarly prepared in 80 and 74% yields, respectively, from imidazoles **33A** and **33B**.^[82] Both reactions proceed without epimerization.

A number of benzo-fused lactonic α,β -unsaturated acids **35**, that differ only in the protecting group (R^2) attached to the CH_2OH group, can be successfully converted into

Scheme 6 Synthesis of Acyl Azides from Carboxylic Acids with Diphenylphosphoryl Azide^[81–83,85]

Reaction 1: $R^1-CH=CH-COOH \xrightarrow{DPPA, Et_3N} R^1-CH=CH-CO-N_3$ (32, 97%)

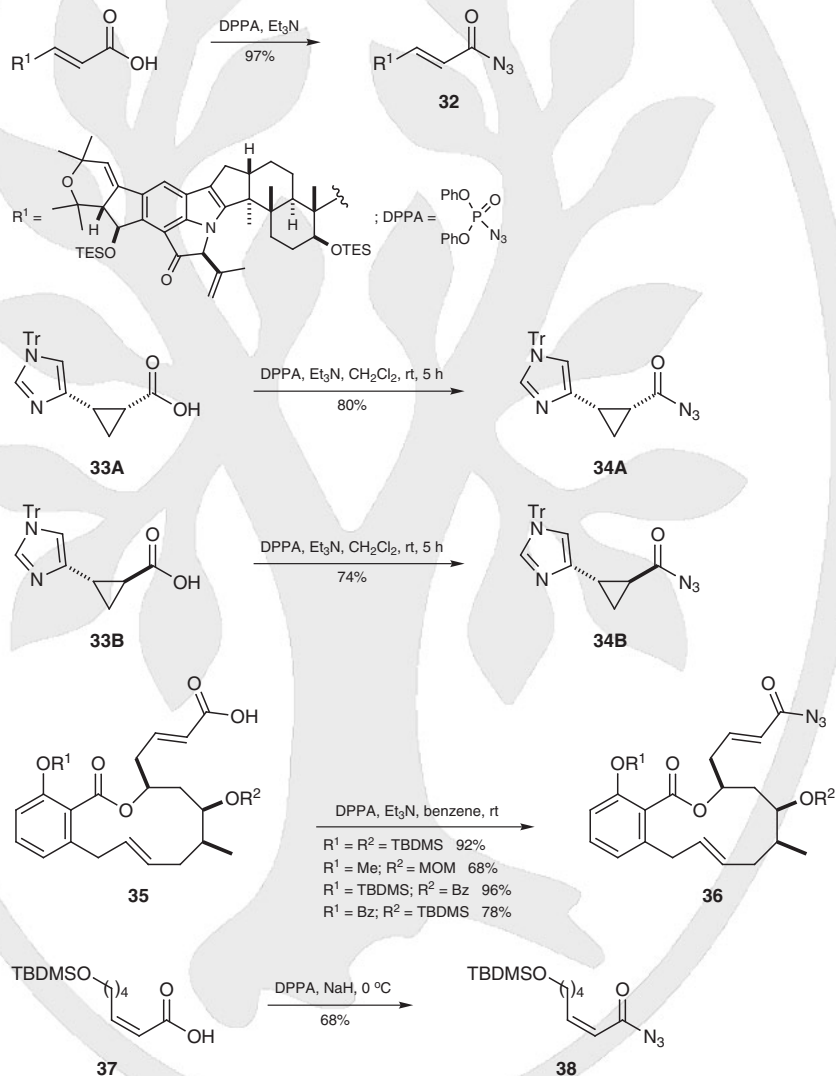
Reaction 2: $R^1-CH_2-CH_2-COOH \xrightarrow{DPPA, Et_3N, CH_2Cl_2, rt, 5 h} R^1-CH_2-CH_2-CO-N_3$ (34A, 80%)

Reaction 3: $R^1-CH_2-CH_2-COOH \xrightarrow{DPPA, Et_3N, CH_2Cl_2, rt, 5 h} R^1-CH_2-CH_2-CO-N_3$ (34B, 74%)

Reaction 4: $R^1-CH_2-CH_2-COOH \xrightarrow{DPPA, Et_3N, benzene, rt} R^1-CH_2-CH_2-CO-N_3$ (36, 92% for $R^1 = R^2 = \text{TBDMS}$)

Reaction 5: $TBDMSO-(CH_2)_4-COOH \xrightarrow{DPPA, NaH, 0^\circ C} TBDMSO-(CH_2)_4-CO-N_3$ (38, 68%)

Structure of DPPA: $PhO-P(=O)(PhO)-N_3$



Acyl Azides 40; General Procedure:^[87]

CAUTION: Sodium azide can explode on heating and is highly toxic. Contact of metal azides with acids liberates the highly toxic and explosive hydrazoic acid.

CAUTION: Acyl azides can decompose explosively, particularly if exposed to heat, mechanical shock, or certain chemical initiators (e.g., protic or Lewis acids) in their pure state. Proper safety precautions should therefore be taken during the synthesis and handling of acyl azides.

Granular NaN_3 was added to a 1 M soln of Et_2AlCl in hexanes, and the mixture was stirred at rt for 4 h. A soln of the ester in hexanes was then added and the resulting mixture was stirred at 0 °C to rt for 16–48 h (Table 2). The reaction was quenched with 2 M aq HCl. Extractive workup followed by chromatographic purification gave the acyl azide product **40**.

21.13.4.1.3

**Method 3:
Nitrosation of Hydrazides**

The successful application of the classical azide method for peptide synthesis requires a suitable preparative route to stereoisomerically homogeneous peptidoyl azides.^[58,88] The necessary acyl azides cannot usually be prepared by simple nucleophilic azidation of N^α -acylated amino acid chlorides, nor can they be prepared from similarly reactive electrophilic carboxy derivatives, because such adducts readily epimerize through formation of oxazol-5(4H)-ones.^[89] The generation of acyl azides by nitrosation of hydrazides, a method introduced by Curtius,^[56] provides a satisfactory solution to this problem, because peptide hydrazides can be conveniently prepared by hydrazinolysis of peptide esters without concomitant epimerization (see Section 21.13.16).

Although the azide method is now rarely used for peptide synthesis, the nitrosation of hydrazides continues to provide a versatile method for generating all types of carbonyl azides (Scheme 7).^[70,90–93] Nitrosation of hydrazides is generally achieved either by the original Curtius procedure using sodium nitrite and hydrochloric acid or by the milder anhydrous conditions introduced by Honzl and Rudinger (alkyl nitrite ester, hydrogen chloride in dioxane, and dimethylformamide).^[94] A fused heterocyclic acyl azide containing a potentially sensitive pyrrole moiety **43** is obtained in excellent yield by nitrosation of the precursor hydrazide **42** with sodium nitrite in aqueous acetic acid.^[90] Heating of **43** in xylenes gives the expected isocyanate that is trapped in situ by the pendant pyrrole to generate a tetracyclic pyrazinone.^[90]

The aliphatic acyl azide **45** can also be prepared from the hydrazide **44** by a nitrous acid mediated method (Scheme 7).^[91] The formation of **45** is sufficiently rapid to prevent unwanted desilylation (or silyl migration) of the *tert*-butyldimethylsilyl protecting group, which could otherwise occur under the acidic reaction conditions. Note that subsequent conversion of the acyl azide into the benzyloxy amide **46** occurs without competing β -elimination.

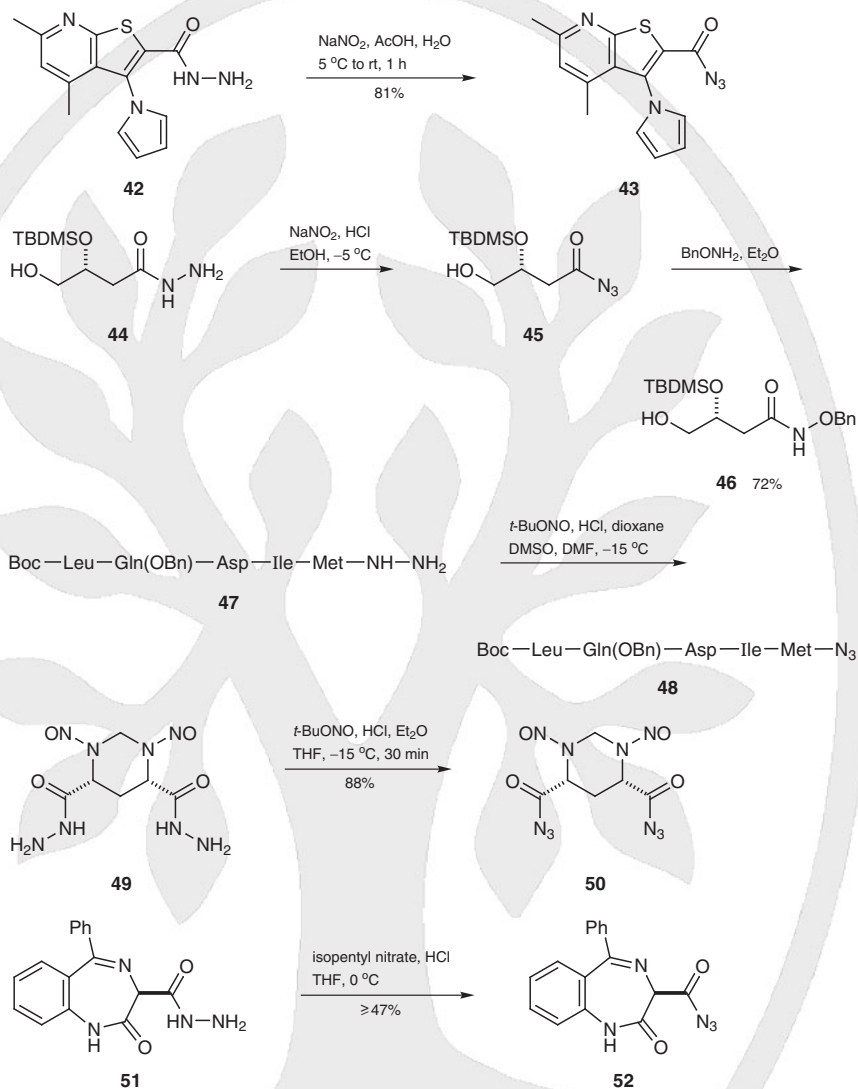
In a large-scale application of the azide method for complex peptide synthesis, the pentapeptidoyl azide **48** can be prepared from 66 g of hydrazide **47** by the Honzl–Rudinger procedure (Scheme 7).^[92] The azide is used immediately and coupled with a heptadecapeptide with a free terminal amino group to give an 85% yield of a peptide containing 22 amino acid residues, an intermediate in the preparation of the human growth hormone-releasing factor somatocrinin.

The bishydrazide **49** can be converted into the isolable diazide **50** without difficulty using *tert*-butyl nitrite as a nitrosonium ion source.^[70]

Under similar conditions, the benzodiazepine derivative **51** can be converted into the azidocarbonyl compound **52** without racemization (Scheme 7).^[93] Hydrazides can

also be converted into acyl azides with dinitrogen tetroxide,^[95] stable nitrosonium salts,^[96] or clay-supported ferric nitrate.^[97]

Scheme 7 Synthesis of Acyl Azides by Nitrosation of Hydrazides^[70,90–93]



4,6-Dimethyl-3-(1H-pyrrol-1-yl)thieno[2,3-b]pyridine-2-carbonyl Azide (43); Typical Procedure:^[90]

A stirred soln of hydrazide **42** (2.86 g, 10 mmol) in AcOH (30 mL) at 5 °C was treated dropwise with NaNO₂ (0.69 g, 10 mmol) in H₂O (2 mL). The mixture was allowed to warm to rt and stirred for 1 h. The precipitated product was isolated by filtration, washed well with H₂O, and air-dried; yield: 2.40 g (81%); mp 110 °C (dec).

21.13.5

**Product Subclass 5:
Acyl Diazenes**

Only those acyl diazenes that can genuinely be classed as *N*-heteroatom-substituted alkanamides will be considered in this section; thus, the well-known azo 1,1'-dicarboxylates

and azo 1,1'-dicarbonamides will not be discussed. Several reviews of azo group chemistry contain relevant information.^[98,99] In general, members of this product subclass are highly reactive molecules; however, certain examples, particularly the red-colored *N*-acyl *N'*-aryl azo compounds, are sufficiently stable to allow their isolation. *N*-Acyl *N'*-alkyl diazenes tautomerize to the corresponding acyl hydrazones.^[100]

Sterically unencumbered acyclic monoacyl diazenes are competent acylating reagents and can even react at the carbonyl group with poor nucleophiles such as water or 4-nitroaniline,^[101] resulting in acyl substitution. The released monosubstituted diazene nucleofuge is unstable and decomposes with evolution of nitrogen gas and the formation of a C—H bond ($\text{RN}=\text{NH} \rightarrow \text{N}_2 + \text{RH}$).^[98] This process has been developed into a useful “traceless” linker system for solid-phase organic synthesis based on polymer-supported *N*-acyl *N'*-aryl hydrazines.^[102,103]

N,N'-Diacyl diazenes are exceptionally reactive and generally have to be prepared in situ in the presence of an appropriate trapping agent, usually a diene. Both cyclic and acyclic *N,N'*-diacyl diazenes are excellent azadienophiles and participate in a wide range of hetero-Diels–Alder reactions.^[104–107]

21.13.5.1 Synthesis of Product Subclass 5

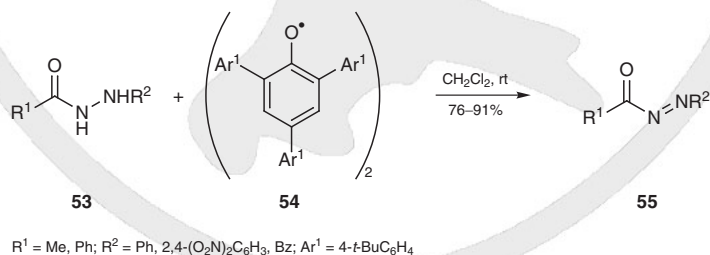
21.13.5.1.1 Method 1: Oxidation of Hydrazides

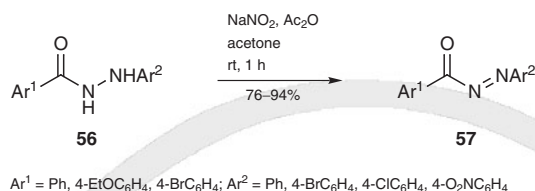
Acyl diazenes and *N,N'*-diacyl diazenes are usually prepared by the dehydrogenation of appropriate acylated hydrazine derivatives. A variety of oxidants can be used for this purpose, including lead(IV) acetate,^[100,104,106,108] *N*-bromosuccinimide,^[101,103] (diacetoxyiodo)benzene,^[105] copper(II) acetate,^[102,103] and 3-(trifluoromethyl)benzenesulfonyl peroxide.^[109]

Isolable acyl diazenes **55** are prepared by oxidation of hydrazides **53** with the dimer of 2,4,6-tris(4-*tert*-butylphenyl)phenoxy radical **54** in anhydrous dichloromethane (Scheme 8).^[110] If the substrate and product of this reaction are not water soluble, then the requisite oxy radical **54** can be conveniently generated catalytically from potassium hexacyanoferrate(III) and a substoichiometric quantity of 2,4,6-tris(4-*tert*-butylphenyl)phenol in a basic biphasic system (sodium hydroxide/water/dichloromethane).^[110]

A variety of simple reagent combinations for the easy preparation of acyl diazenes have been developed.^[111–113] The use of sodium nitrite and acetic anhydride in acetone gives excellent yields of acyl azo compounds **57** from a series of substituted *N'*-aryl benzo-hydrazides **56** (Scheme 8).^[113]

Scheme 8 Generation of Stable Acyl Diazenes by the Dehydrogenation of Hydrazides^[110,113]





Acyl Diazenes 57; General Procedure:^[113]

A mixture of a benzohydrazide **56** (1 mmol), Ac₂O (3 mmol), and NaNO₂ (3 mmol) in acetone (15 mL) was stirred at rt for 1 h while an orange-red or deep red coloration developed and the mixture became turbid. The mixture was filtered and cold H₂O was poured slowly into the filtrate. The resulting precipitated acyl diazene product **57** was collected by filtration, washed with H₂O, and dried. Recrystallization gave the pure acyl diazene **57** as yellow, orange, red, or brown prisms; yield: 76–94%.

21.13.6 Product Subclass 6: (Acylimino)phosphoranes

The chemistry of iminophosphoranes (sometimes known as phosphinimines) has been thoroughly reviewed.^[114–116] The first example of an (acylimino)phosphorane, *N*-(triphenylphosphoranylidene)benzamide, was reported by Staudinger in 1921, and was obtained from triphenylphosphine and benzoyl azide by the reaction that is now known as the Staudinger reaction.^[117] This reaction remains the major route to this product subclass and to other types of iminophosphorane.^[115] Iminophosphoranes possess multifaceted reactivity and enter into the aza-Wittig reaction with carbonyl compounds to yield imines;^[115,118] this process has been used extensively for the synthesis of heterocycles.^[119,120] (Acylimino)phosphoranes also participate in the aza-Wittig reaction;^[121,122] however, upon heating in the absence of an extraneous carbonyl component, they fragment into phosphine oxide and nitrile products ($\text{R}^1\text{CON}=\text{PR}_3 \rightarrow \text{R}^1\text{C}\equiv\text{N} + \text{O}=\text{PR}_3$). This sacrificial aza-Wittig-like process can be used for the synthesis of α,β -unsaturated nitriles.^[123] The coordination behavior of (acylimino)phosphoranes has been explored.^[124]

21.13.6.1 Synthesis of Product Subclass 6

Frøyen has provided a useful summary of preparative methods for (acylimino)phosphoranes.^[125] Besides the two methods described in Sections 21.13.6.1.1 and 21.13.6.1.2, members of this product subclass can also be conveniently obtained from amides. Aromatic *N*-unsubstituted amides and electron-deficient aliphatic *N*-unsubstituted amides give (acylimino)phosphoranes in generally good yields on treatment with diethyl azodicarboxylate and triphenylphosphine.^[126] *N*-Unsubstituted amides can also be converted into this product subclass by the Kirsanov reaction with phosphorus pentachloride, followed by addition of 3 equivalents of a Grignard reagent to the resulting (acylimino)phosphorane.^[127] In a related process, the reaction of dibromo(triphenyl)phosphorane with *N*-unsubstituted amides in the presence of triethylamine affords (acylimino)triphenylphosphoranes.^[128]

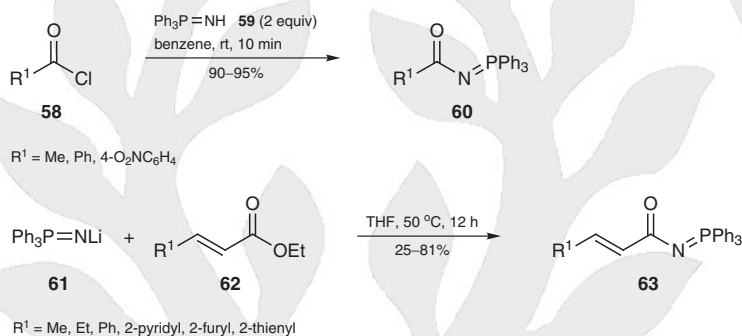
21.13.6.1.1 Method 1: N-Acylation of Iminophosphoranes

Acylation of *N*-unsubstituted iminophosphorane derivatives provides a synthesis of (acylimino)phosphoranes that does not require the preparation of potentially hazardous acyl azides, as required by the conventional Staudinger procedure. Acylation of imino(triphenyl)phosphorane (**59**) with simple acid chlorides **58** gives the expected (acylimino)-

phosphoranes **60** in excellent yields (Scheme 9).^[127] In this case, imino(triphenyl)phosphorane (**59**) is used in a two-fold excess, the additional equivalent serving as an additional base. Imino(triphenyl)phosphorane (**59**) can also be generated and acylated in situ using amino(triphenyl)phosphonium bromide as a convenient precursor.^[129]

The use of N-metalated iminophosphorane derivatives permits acylation by less-reactive acylating reagents, such as esters.^[121,123,130,131] The reaction of the lithiated iminophosphorane **61** with a range of α,β -unsaturated esters **62** gives the (acylimino)phosphorane products **63**, the result of clean 1,2-addition, in variable yields (Scheme 9).^[123] This reaction fails in the case of readily enolizable esters, which are simply deprotonated by the strongly basic lithiated imide reagent **61**.

Scheme 9 Acylation of Iminophosphoranes^[123,127]



(Acylimino)phosphoranes 60; General Procedure:^[127]

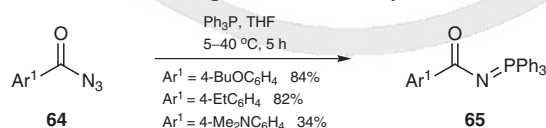
A soln of imino(triphenyl)phosphorane (**59**; 2.77 g, 10 mmol) in benzene (50 mL) (**CAUTION: carcinogen**) was added with shaking to a soln of an acid chloride **58** (5 mmol) in benzene (100 mL). The mixture was allowed to stand for 10 min while a dense precipitate formed. The mixture was refluxed for 5 min and filtered whilst hot to remove $\text{Ph}_3\text{P}^+\text{NH}_2\text{Cl}^-$. The filtrate was concentrated under reduced pressure and the residue was recrystallized (toluene/hexanes 1:3) to give the pure (acylimino)phosphorane **60**.

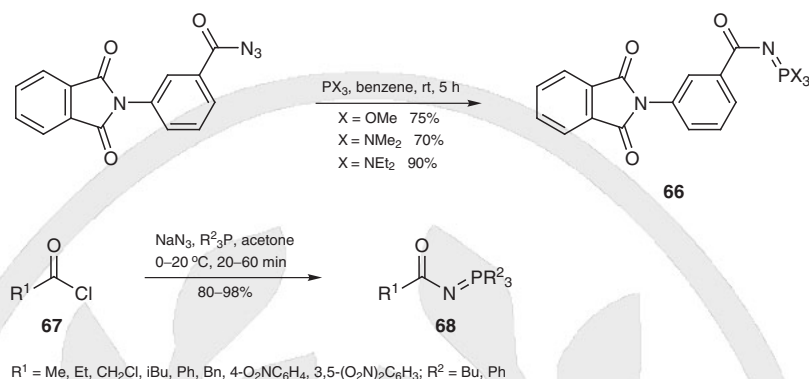
21.13.6.1.2

Method 2:
Staudinger Reaction of Acyl Azides

The Staudinger reaction^[115,118] of acyl azides, e.g. **64**, with a wide range of phosphines [including heteroatom-substituted phosphorus(III) compounds] provides a general synthesis for (acylimino)phosphoranes (e.g., **65** and **66**) (Scheme 10).^[125,132,133] Acyl chlorides **67** are directly and efficiently converted into (acylimino)phosphoranes **68** by the combined action of sodium azide and a trialkyl- or triarylphosphine in acetone.^[125] The addition of N-chlorosuccinimide to this reagent combination permits the synthesis of this product subclass directly from carboxylic acids.^[134] Both of these convenient transformations are presumed to proceed through the Staudinger reaction of intermediate acyl azides generated in situ.^[125,134]

Scheme 10 Staudinger Reactions of Acyl Azides^[125,132,133]





4-Butoxy-*N*-(triphenylphosphoranylidene)benzamide (65, Ar¹ = 4-BuOC₆H₄); Typical Procedure:^[132]

CAUTION: Acyl azides can decompose explosively, particularly if exposed to heat, mechanical shock, or certain chemical initiators (e.g., protic or Lewis acids) in their pure state. Proper safety precautions should therefore be taken during the synthesis and handling of acyl azides.

A stirred soln of Ph₃P (1.31 g, 5.0 mmol) in anhyd THF (10 mL) at 5 °C was treated with 4-butoxybenzoyl azide (**64**, Ar¹ = 4-BuOC₆H₄; 1.10 g, 5.0 mmol) in anhyd THF (5 mL). The resulting mixture was allowed to warm to rt, was stirred for 4 h, and then heated to 40 °C and stirred for a further 1 h. The solvent was then removed under reduced pressure and the residue was recrystallized [benzene (**CAUTION:** carcinogen)/hexanes] to give an analytically pure solid; yield: 1.90 g (84%); mp 154–156 °C (benzene/hexanes).

21.13.7

Product Subclass 7:

N,N-Diheteroatom-Substituted Amides (Anomeric Amides)

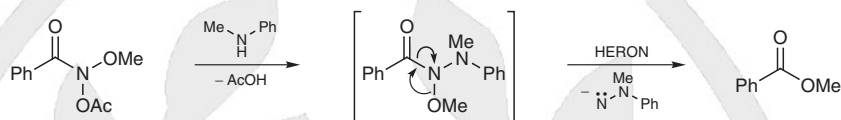
The chemistry of amides geminally disubstituted on nitrogen with two heteroatoms differs significantly from that of other classes of amide. These unusual carbonyl compounds are termed “anomeric amides” and have been the subject of extensive studies and a comprehensive review.^[135] The nitrogen atom in anomeric amides is sp³-hybridized (pyramidalization supports a stabilizing anomeric effect) and the increased s-character of the lone pair results in a poor orbital overlap with the carbonyl π-system. The carbonyl group in anomeric amides is therefore ketone-like and there is only a low energy barrier to rotation about the N—C bond.^[135]

N-Alkoxy-*N*-chloro amides can be generated from *N*-alkoxy amides by oxidative chlorination with *tert*-butyl hypochlorite.^[136] Related processes are discussed in Section 21.13.8.1.1 for the synthesis of *N*-halo amides. *N,N*-Dialkoxy and *N*-acyloxy-*N*-alkoxy amides are isolable compounds that are available from *N*-alkoxy-*N*-chloro amides by halide displacement with oxygen nucleophiles.^[137] *N*-Acyloxy-*N*-alkoxy amides are precursors to alkoxynitrenium ions and have proven mutagenic activity;^[138] these compounds also contain the most highly pyramidalized nitrogen atoms of any class of acyclic amide.^[139]

Aminolysis of *N*-acyloxy-*N*-alkoxy amides generates unstable *N*-alkoxy-*N*-amino amides that rearrange intramolecularly to esters through the so-called HERON (heteroatom rearrangement on nitrogen) process (Scheme 11).^[140] *N*-Amino-*N*-chloro and *N*-alkoxy-*N*-azido amides also readily undergo HERON rearrangements; in the case of *N*-alkoxy-*N*-azido amides, this unusual reaction has been exploited in the preparation of hindered esters.^[141]

N,N-Dihalo amides are formally classified as anomeric amides, although their behavior differs from that of other members of this product subclass.^[135] *N,N*-Dihalo amides do not readily generate nitrenium ions and their reactivity in basic solution is typified by acyl substitution^[142] and dehalogenative Hofmann rearrangement processes.^[143] *N,N*-Dihalo amides can also be prepared by oxidative halogenation of *N*-unsubstituted amides.^[142,144–146]

Scheme 11 The HERON Rearrangement of an *N*-Alkoxy *N*-Amino Amide^[140]



21.13.8

Product Subclass 8: *N*-Halo Amides

Reasonable coverage of the older literature on this product subclass can be found in a number of general reviews on amide-group chemistry.^[147,148] *N*-Halo amides are versatile oxidants and appropriate examples can be used as both electrophilic and radical sources of fluorine,^[149] chlorine,^[150–152] bromine,^[153,154] or iodine.^[155] *N*-Haloacetanilides suffer internal disproportionation by a halide translocation process (the Orton rearrangement) under a variety of reaction conditions, such as free-radical initiation or acid catalysis, to give 2'- and 4'-haloacetanilides.^[148]

Salts of *N*-halo amides derived from *N*-unsubstituted amides, particularly those of *N*-bromo amides, are thermally unstable and undergo Hofmann rearrangement upon gentle heating to give isocyanate products [$\text{RCON}^-(\text{X})\text{M}^+ \rightarrow \text{RNCO} + \text{MX}$].^[156] This process has much in common with the closely related Lossen rearrangement of *N*-acyloxy amides (see Section 21.13.10) and the Curtius rearrangement of acyl azides (see Section 21.13.4). The Hofmann reaction is usually performed in aqueous base, in which case the initially generated isocyanate products are degraded in situ to amines through decarboxylative hydrolysis.^[156]

N-Chloro amides are convenient precursors to amidyl radicals, which can undergo useful intermolecular^[157,158] and intramolecular^[159,160] addition reactions to alkenes. Photoinduced and base-induced elimination reactions from *N*-alkyl-*N*-chloro amides can be used to generate electrophilic *N*-acylimines^[161] and dehydro α -amino acid derivatives.^[162,163] Intramolecular abstraction of γ -hydrogen atoms by amidyl radicals derived from *N*-halobutyramides can be exploited in the synthesis of butyrolactones through a process that parallels the Hofmann–Löffler–Freitag reaction.^[148,155]

21.13.8.1

Synthesis of Product Subclass 8

21.13.8.1.1

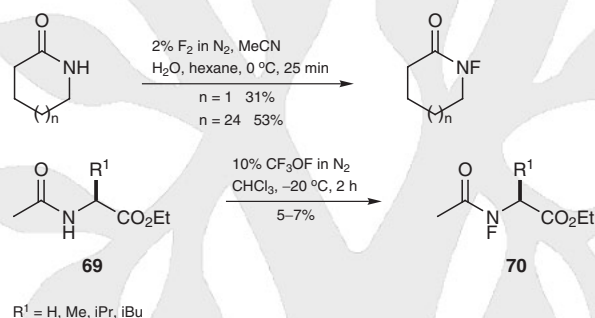
Method 1: Oxidative Halogenation of Amides

Members of this product subclass are typically prepared by the direct *N*-halogenation of appropriate amide precursors.^[147] In the case of *N*-unsubstituted amides, monohalogenation is usually achievable by careful control of reagent stoichiometry; however, certain oxidants favor the generation of *N,N*-dihalo amides.^[135]

21.13.8.1.1.1

Variation 1:
Fluorination of Amides

N-Fluoro amides are prepared from N-monosubstituted amides by careful direct fluorination. Diluted fluorine gas^[164,165] or perfluoro fluoroxy compounds [e.g., trifluoromethyl hypofluorite (for example the reaction of **69** to give N-fluoro amide **70**), difluoromethylene dihypofluorite, or pentafluorosulfur hypofluorite]^[166,167] can be successfully used for this purpose (Scheme 12).^[168,169] Surprisingly, N-fluoro amides are at least as reactive toward these reagents as their nonfluorinated precursors.^[164] The quantity of fluorinating agent delivered must therefore be precisely controlled, and the fluorinating agent is often used as the limiting reagent to allow for cleaner reactions; typically, a three-fold excess of the amide is present.^[167] Over-fluorination results in a useful synthesis of N,N-difluoroamines ($R^1CONFR^2 + F_2 \rightarrow R^1COF + R^2NF_2$).^[168] The synthesis of N-fluoro amides by the monofluorination of N-unsubstituted amides has not been reported. Fluorination of N-unsubstituted amides gives isocyanates (through the Hofmann rearrangement of the intermediate N-fluoroamide) and N,N-difluoro amide products.^[144,164] The N,N-difluoro amide product typically hydrolyzes on workup to afford the corresponding carboxylic acid and difluoroamine.^[164]

Scheme 12 N-Fluorination of N-Monosubstituted Amides^[168,169]**Ethyl N-Acetyl-N-fluorovalinate (70, $R^1 = iPr$); Typical Procedure:**^[169]

CAUTION: Special techniques are required in handling trifluoromethyl hypofluorite. The compound is known to cause bone damage in rats. It explodes on contact with short-chain alkenes and alkynes, cyclopropane, hydrogen-containing solvents, polymers, or rubber. Benzene solutions are spark- and UV-sensitive explosives. Trifluoromethyl hypofluorite forms an explosive product with pyridine.

A mixture of ethyl N-acetylvalinate (**69**, $R^1 = iPr$; 0.50 g, 2.67 mmol) and a small amount of Na_2CO_3 (ca. 5 mg) in $CHCl_3$ (125 mL) was cooled to $-20^\circ C$ and treated with gaseous CF_3OF (3.75 mmol, diluted several times with N_2) over 2 h. The mixture was allowed to warm to rt, washed successively with dil aq $NaHCO_3$ (2×100 mL) and H_2O (2×100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil was combined with that from four other identical runs and purified by column chromatography (neutral alumina, hexanes) to give an oil; yield (total from five runs): 157 mg (6%).

21.13.8.1.1.2

Variation 2:
Chlorination of Amides

Amides **71** can be N-chlorinated with a variety of oxidants [e.g., chlorine,^[170] hypochlorous acid,^[171] sodium hypochlorite,^[172] calcium hypochlorite/alumina,^[173] Oxone

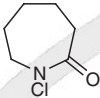
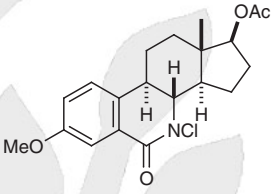
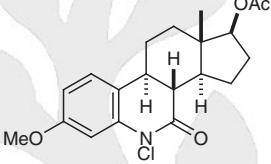
($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$)/sodium chloride,^[174] *tert*-butyl hypochlorite,^[163,175–177] *N*-chlorosuccinimide,^[160,161] or 1,3,5-trichloro-1,3,5-triazine-2,4,6-trione (trichloroisocyanuric acid)),^[178] a selection of the best of these methods are listed in Table 3.

Chlorine gas offers the most economical means to effect the transformation on a large scale (entry 3),^[170] but has limited practical value for smaller-scale applications. Sodium hypochlorite (household bleach) is also effective (entry 1),^[172] but because only dilute aqueous solutions of this reagent are available (up to 5% by weight), its use on moderate to large scales is compromised by a low active-chlorine content. A practical two-phase system employing hypochlorous acid has been patented for the preparation of *N*-chloro amides **72** on a 50-g scale (entry 2).^[171] In contrast to sodium hypochlorite, hypochlorous acid is commercially available in concentrated aqueous solutions (up to 35% by weight), which is highly advantageous for intermediate-scale work. Calcium hypochlorite and moist alumina can be used for the efficient chlorination of *N*-monosubstituted amides (entries 7 and 8).^[173] This high-yielding procedure is particularly attractive because calcium hypochlorite has a high active chlorine content and is an inexpensive solid reagent with a long shelf life. Chlorination of *N*-unsubstituted amides with calcium hypochlorite gives *N,N*-dichloro amides.^[142] 1,3,5-Trichloro-1,3,5-triazine-2,4,6-trione (trichloroisocyanuric acid), which is also an inexpensive and easily handled solid reagent, is highly effective for the *N*-chlorination of an aza steroid derivative (entry 9).^[178] Attempts to use the same reagent for *N*-chlorination of a related anilido aza steroid result in competing halogenation of the electron-rich aryl ring. In this case, a combination of potassium *tert*-butoxide and *N*-chlorosuccinimide gives the desired chemoselectivity (entry 10).^[178]

Table 3 *N*-Chlorination of *N*-Unsubstituted and *N*-Monosubstituted Amides^[160,170–174,177,178]

$\text{R}^1-\text{C}(=\text{O})\text{NHR}^2 \longrightarrow \text{R}^1-\text{C}(=\text{O})\text{N}(\text{R}^2)\text{Cl}$ <div style="display: flex; justify-content: space-around; width: 100%;"> 71 72 </div>				
Entry	Product	Conditions	Yield (%)	Ref
1	EtCONHCl	NaOCl, H ₂ O, 0 °C then aq H ₂ SO ₄ , CH ₂ Cl ₂ , 2 h	78	[172]
2		HOCl, H ₂ O, EtOAc, 1 °C, 1.5 h	98	[171]
3	Me(CH ₂) ₁₂ CONHCl	Cl ₂ , H ₂ O, 100 °C	94	[170]
4		BuLi, Et ₂ O, –78 to 0 °C then NCS, 0 °C, 2 h	47	[160]
5		<i>t</i> -BuOCl, MeOH, rt, 45 min	100	[177]
6		Oxone ^a , NaCl, moist alumina, CHCl ₃ , 45 °C, 4 h	94	[174]
7		Ca(OCl) ₂ , moist alumina, CHCl ₃ , 40 °C, 18 h	98	[173]

Table 3 (cont.)

Entry	Product	Conditions	Yield (%)	Ref
8		Ca(OCl) ₂ , moist alumina, CHCl ₃ , 40 °C, 10 h	95	[173]
9		TCTT ^b , CHCl ₃ , heat, 2 h	90	[178]
10		1. <i>t</i> -BuOK, THF, rt, 30 min 2. NCS, 3 h	90	[178]

^a Oxone = 2KHSO₅ • KHSO₄ • K₂SO₄

^b TCTT = 1,3,5-trichloro-1,3,5-triazine-2,4,6-trione.

N-Chloro Amides **72** Using Calcium Hypochlorite and Alumina (Table 3, Entries 7 and 8); General Procedure:^[173]

A suspension of Ca(OCl)₂ (2.86 g, 20 mmol) and moist alumina (10 g) in CHCl₃ (50 mL) was stirred vigorously at 40 °C for 10 min. A soln of the N-monosubstituted amide **71** (10 mmol) in CHCl₃ (10 mL) was then added and the mixture was stirred at 40 °C for 10–24 h until the starting material was completely consumed (TLC). Solids were removed by filtration and the filtrate was concentrated under reduced pressure to afford the desired N-chloro amide derivative **72**.

21.13.8.1.1.3

Variation 3: Bromination of Amides

Amides **73** can be N-brominated by various oxidants (e.g., bromine/sodium hydroxide,^[153] benzyltrimethylammonium perbromide,^[179] sodium bromide/sodium hypochlorite,^[172] sodium bromite/hydrobromic acid,^[180] sodium bromate/hydrobromic acid,^[181] *tert*-butyl hypobromite,^[182] or acetyl hypobromite^[177]); a selection of some of the better methods are listed in Table 4.^[153,177,179,181] N-Bromo amides **74** are more prone to Hofmann degradation under basic conditions than are the analogous N-chloro compounds.^[156] To avoid Hofmann rearrangement during bromination, the reaction temperature must be carefully controlled (typically in the range 0–25 °C).

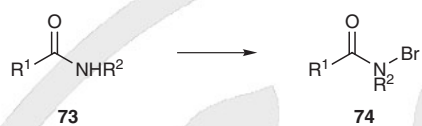
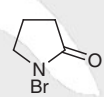
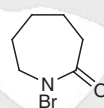
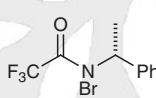
Benzyltrimethylammonium perbromide is a convenient alternative to bromine for the N-bromination of amides under basic conditions.^[179] With this reagent, aromatic and higher aliphatic N-unsubstituted amides give good yields of N-brominated products (entries 2 and 4), whereas water-soluble lower aliphatic amides do not.^[179]

A reagent combination of sodium bromate and sodium bromide, both of which are inexpensive and shelf-stable solids, in acidic media gives excellent results for most types of simple N-unsubstituted and N-monosubstituted amides (entries 1, 3, 5, and 6).^[181]

Acetylhypobromite is a superior reagent for the conversion of chiral N-monosubstituted amides into their N-bromo derivatives.^[177] For example, the attempted bromination

of 2,2,2-trifluoro-*N*-(1-phenylethyl)acetamide with *tert*-butyl hypobromite results in less than 5% conversion, whereas acetyl hypobromite rapidly effects the same transformation in 95% yield (entry 8).^[177]

Table 4 N-Bromination of N-Unsubstituted and N-Monosubstituted Amides^[153,177,179,181]

					
Entry	Product	Conditions	Yield (%)	mp (°C)	Ref
1	AcNHBr	NaBrO ₃ , NaBr, H ₂ SO ₄ , aq AcOH, rt, 30 min	90	105–108	[181]
2	Me(CH ₂) ₈ CONHBr	BnMe ₃ N ⁺ Br ₃ [−] , aq NaOH, 0°C, 4 h	66	72–74	[179]
3	Me(CH ₂) ₈ CONHBr	NaBrO ₃ , NaBr, H ₂ SO ₄ , aq AcOH, rt, 20 min	99	75–77	[181]
4	BzNHBr	BnMe ₃ N ⁺ Br ₃ [−] , aq NaOH, 0°C, 4 h	53	124–127	[179]
5	BzNHBr	NaBrO ₃ , NaBr, H ₂ SO ₄ , aq AcOH, rt, 20 min	78	124–126	[181]
6		NaBrO ₃ , HBr, aq H ₂ SO ₄ , rt, 60 min	78	113–115	[181]
7		Br ₂ , aq NaOH, 0–10°C, 2.5 h	75	64–66	[153]
8		AcOBr, CCl ₄ , rt, 1 h	95	oil	[177]

N-Bromobenzamide (74, R¹ = Ph; R² = H; Table 4, Entry 5); Typical Procedure:^[181]

Solid NaBr (690 mg, 6.7 mmol) was slowly added to a stirred soln of BzNH₂ (**73**, R¹ = Ph; 1.21 g, 10 mmol), NaBrO₃ (760 mg, 5 mmol), and concd H₂SO₄ (740 mg, 7.5 mmol) in 70% aq AcOH (7 mL), and the mixture was stirred for 20 min at rt. The resulting precipitate was collected by filtration, washed with cold H₂O, and dried to give a colorless solid; yield: 1.55 g (78%); mp 124–126°C.

21.13.8.1.1.4

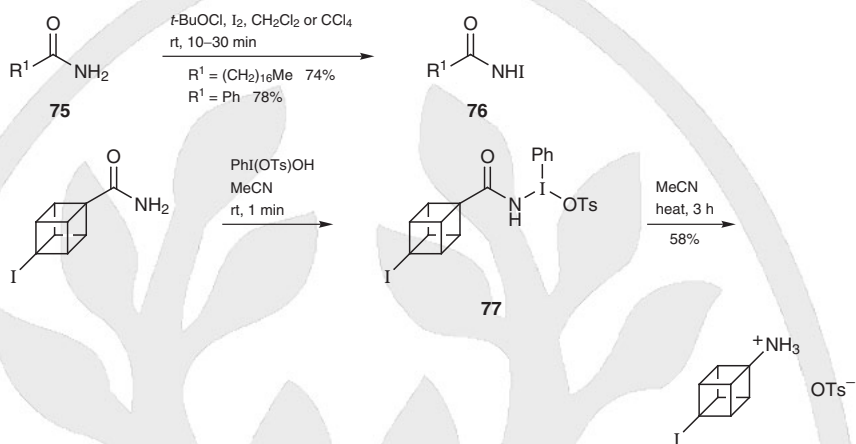
**Variation 4:
Iodination of Amides**

N-Iodo amides can also be prepared from amides by direct halogenation, but examples of this type of reaction are comparatively rare. N-Unsubstituted amides **75** can be mono-N-iodinated, e.g. to give **76**, using a reagent combination of *tert*-butyl hypochlorite and iodine (Scheme 13).^[155] The treatment of a series of anilides with this reagent pair, which forms *tert*-butyl hypoiodite as the active iodinating agent in situ, results in iodination of the aromatic ring rather than N-iodination.^[155] Other reagent combinations for N-iodination of N-unsubstituted amides include lead(IV) acetate/iodine^[155] and silver(I) oxide/iodine.^[183]

The reaction of N-unsubstituted and N-monosubstituted amides with hypervalent iodine-based oxidants results in ligand substitution and gives the expected complexes, e.g. **77** (Scheme 13).^[184] N-Phenyliodine(III) carboxamide 4-toluenesulfonates such as **77** can be

used as substrates for Hofmann rearrangement to yield bridgehead primary amines.^[184] Benziodazoles, which are stable cyclic *N*-iodine(III) amides, can be prepared by oxidation of 2-iodoanilides.^[185]

Scheme 13 Preparation of Iodine(I)- and Iodine(III)-Substituted Amides^[155,184]



***N*-Iodobenzamide (76, R¹ = Ph); Typical Procedure:**^[155]

A suspension of BzNH₂ (1.2 g, 9.9 mmol) and I₂ (3.0 g, 11.8 mmol) in CCl₄ (20 mL) (**CAUTION: toxic**) at rt was treated dropwise with *t*-BuOCl (1.3 g, 12.0 mmol) during 5 min with exclusion of light. The mixture was stirred for 30 min and the resulting precipitate was removed by filtration and washed with CCl₄. The solid was recrystallized (acetone/hexanes) to give pale yellow needles; yield: 1.9 g (78%); mp 123–124 °C (dec, acetone/hexanes).

**21.13.9 Product Subclass 9:
N-Hydroxy Amides**

Lossen reported the first examples of *N*-hydroxy amides (also known as hydroxamic acids) in 1869.^[186] Since then, several reviews have been published on the chemistry of this important product subclass.^[147,187–189] The early literature was well covered by Yale;^[187] later accounts by Challis and Challis,^[147] and Bauer and Exner^[188] are particularly useful and clarify structural aspects and nomenclature rules. The photochemistry of *N*-hydroxy amides has been comprehensively surveyed,^[190] and the medicinal chemistry and pharmacology of this product subclass has been reviewed.^[191] *N*-Hydroxy amides (R¹CONHOH and R¹CONR²OH), which typically have p*K*_a values of about 8–10, are markedly more acidic than comparable *N*-unsubstituted amides (p*K*_a 15–16).^[192] There is evidence to suggest that the deprotonated form of unsubstituted *N*-hydroxy amides is best represented by a hydroximate ion, R¹C(O[−])=NOH;^[188,192] however, this structure is disputed and is a source of controversy.^[147] Whatever their true structure, *N*-hydroxy amide anions generally react with electrophiles at the hydroxylamine-type oxygen atom (see Sections 21.13.10 and 21.13.11).

N-Hydroxy amides are effective bidentate ligands and form stable chelates with a variety of metal ions, including iron(III) and copper(II).^[193] Metal-ion complexes of *N*-hydroxy amides are often highly colored and are used extensively in colorimetric analysis.^[194] The intense purple coloration formed upon adding iron(III) chloride to *N*-hydroxy amides constitutes a very sensitive spot test for this product subclass. Many natural siderophores, e.g. ferrichrome and mycobactin, contain multiple *N*-hydroxy amide moieties that enable these molecules to sequester and solubilize ionic forms of cellular iron.^[195]

N-Hydroxy amides have an enormous potential in medicinal chemistry, and drug molecules containing this functionality have been developed for the treatment of a number of conditions, including cardiovascular disease, cancer, HIV/AIDS, malaria, tuberculosis, and metal poisoning.^[191]

21.13.9.1 Synthesis of Product Subclass 9

21.13.9.1.1 Method 1: Oxidation of Amides, Hydroxylamines, and Amines

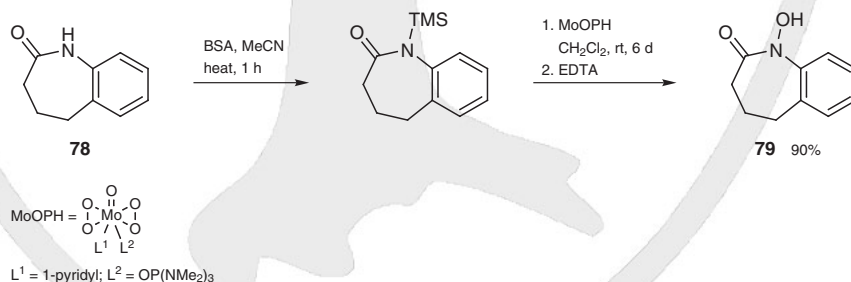
N-Monosubstituted amides, e.g. **78**, can be transformed into N-hydroxy amides, e.g. **79**, by oxidation of their N-trimethylsilyl derivatives, with (hexamethylphosphoric triamide)-oxodiperoxy(pyridine-N)molybdenum(VI) (MoOPH) (Scheme 14).^[196] This method, first introduced by Sammes for the oxidation of acyclic amides,^[197] is used extensively for the preparation of natural-product molecules containing N-hydroxypyridin-2-one moieties. Syntheses of tenellin,^[198] fusaricide,^[199] and the antitumor agent TMC-69-6H (**80**),^[200] by MoOPH oxidation establish that the Sammes method is reasonably chemoselective and tolerant of other functionalities within the pyridin-2-one precursor, e.g. phenol, ketone, and diene.

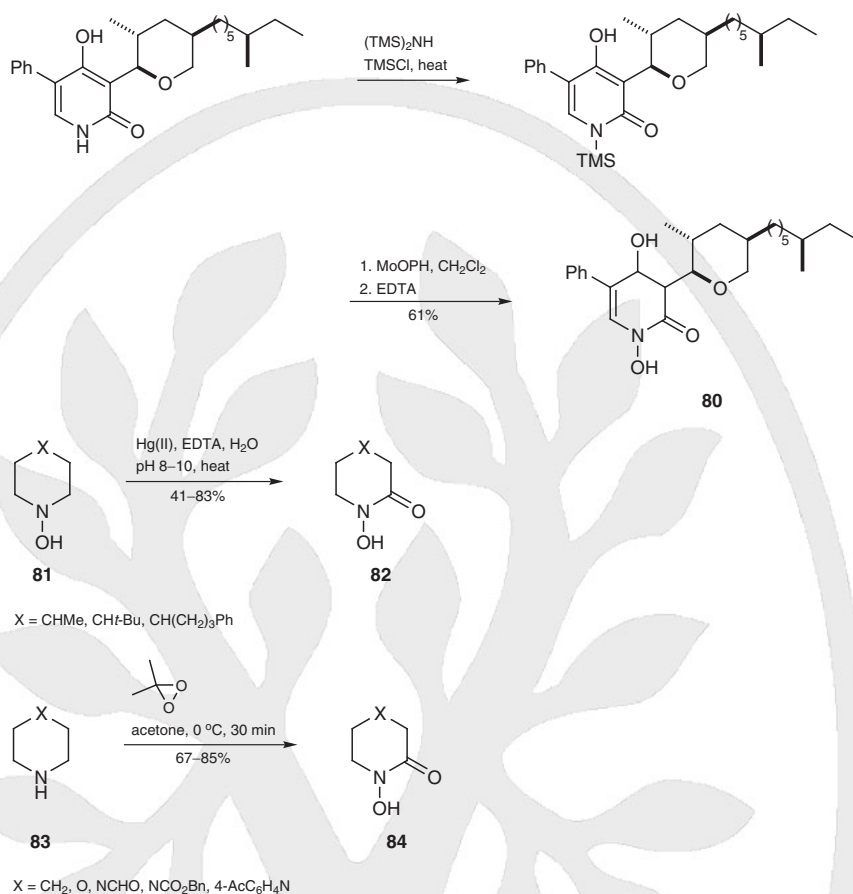
Functionalized pyridin-2-ones can also be converted into N-hydroxy amides by peracetic acid^[201] or by a reagent combination of sodium tungstate and hydrogen peroxide.^[202] Substrates beneath the oxidation level of amides can also be oxidized to N-hydroxy amides in a single step. For example, the piperidyl hydroxylamines **81** can be converted into N-hydroxy lactams **82** by the mercury(II) salt of ethylenediaminetetraacetic acid in alkaline solutions (Scheme 14).^[203]

Cyclic N-hydroxy amides can also be prepared directly from secondary amines by exhaustive oxidation with dimethyldioxirane.^[204] Six-membered cyclic amines **83** give good to excellent yields of N-hydroxy lactams **84** with this clean oxidant. Dihydroindole and 1,2,3,4-tetrahydroquinoline also give acceptable yields of N-hydroxy amides with dimethyldioxirane, but pyrrolidine and tetraisoquinoline give complex product mixtures dominated by the nitron.^[204]

Cyclic N-hydroxy amides can also be prepared from substituted 1,2,3,4-tetrahydroquinolines by tungstate-catalyzed oxidation with hydrogen peroxide.^[205]

Scheme 14 Synthesis of Cyclic N-Hydroxy Amides by Oxidation^[196,200,203,204]



**1-Hydroxy-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (79); Typical Procedure:**^[196]

A soln of lactam **78** (6.0 g, 37 mmol) and BSA (7.66 g, 37 mmol) in anhyd MeCN (36 mL) was refluxed for 1 h under N₂. The mixture was then concentrated under reduced pressure and the resulting *N*-trimethylsilyl amide was dissolved in CH₂Cl₂ (40 mL). MoOPH (10.7 g, 26 mmol) in CH₂Cl₂ (120 mL) was added to the soln of *N*-trimethylsilyl amide during 5 min. The mixture was stirred at rt under N₂ for 6 d and then concentrated under reduced pressure. The residue was dissolved in 0.1 M aq EDTA (50 mL, buffered at pH 8.0) and continuously extracted with CH₂Cl₂ (500 mL) for 24 h. The organic extract was concentrated under reduced pressure and triturated with Et₂O (40 mL) to induce crystallization. The *N*-hydroxy amide **79** was isolated by filtration as an ochre solid that gave a positive FeCl₃ test; yield: 5.90 g (90%).

21.13.9.1.2

**Method 2:
N-Acylation of Hydroxylamines**

N-Hydroxy amides are commonly prepared by the acylation of hydroxylamine derivatives **85** (Table 5).^[206-215] *N*-Unsubstituted hydroxy amides (**86**, R¹ = H) are available from the monoacylation of hydroxylamine, which occurs exclusively at the nitrogen atom in most cases.^[147,189] Hydroxylamine is an α -effect nucleophile^[216] and reacts directly with weak acyl donors, such as esters,^[206,207] lactones,^[217] and even, in some cases, amides to give *N*-hydroxy amide products in good to excellent yields. Labile esters, such as those derived from *N*-hydroxysuccinimide^[218] or phenol (entry 1),^[206] are very effective for the

clean N-monoacylation of hydroxylamine; however, simple unhindered alkyl esters (methyl or ethyl) are also suitable electrophiles for this purpose (entry 2).^[207]

Acid chlorides are not generally optimal for the synthesis of unsubstituted *N*-hydroxy amides and often give side products resulting from polyacylation of hydroxylamine. A convenient one-pot method is available for the conversion of *N*-protected amino acids into their *N*-hydroxy amides derivatives (entry 3).^[208] the carboxylic acid is activated by 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) in the presence of hydroxylamine and excellent yields of *N*-hydroxy amides are obtained without racemization. Both benzoyloxycarbonyl- and 9-fluorenylmethoxycarbonyl-protected amino acids can be used as substrates, including the derivatives of alanine, valine, phenylalanine, leucine, proline, or serine (yields 80–97%).^[208]

Substituted *N*-hydroxy amides (**86**, $R^1 \neq H$) are potentially available by acylation of *N*-substituted hydroxylamines (entries 4–12). Regioselectivity for acylation at nitrogen versus oxygen is less certain in these cases, and significant quantities of *O*-acylated products (**87**) can be formed, depending on the reaction conditions and the steric bulk of R^1 .

Substituted formyl *N*-hydroxy amides are efficiently prepared on a multi-kilogram scale using 2,2,2-trifluoroethyl formate as acyl-transfer reagent (e.g., entry 4).^[209] Traces of *O*-formylated hydroxylamine side products **87** ($R^2 = H$), formed during early stages of the reaction, isomerize to the desired *N*-hydroxy amides as the reaction progresses.

A variety of *N*-hydroxy tripeptides can be prepared by the acylation of dipeptidic *N*-hydroxy amides with *N*-(9-fluorenylmethoxycarbonyl) (Fmoc)-protected amino acid chlorides (e.g., entry 5).^[210] In this case, choice of base is crucial for obtaining the desired regiochemical outcome; the use of pyridine in place of sodium bicarbonate leads to significant quantities of unwanted *O*-acylation products (**86/87** = 65:35; $R^1 = \text{Ala-Val-OEt}$; $R^2 = \text{Fmoc-Ala}$).^[210]

Sterically encumbered *N*-substituted hydroxylamines experience *O*-acylation to a much greater extent than do unhindered examples (e.g., entries 7–10).^[212,213,215] In many such cases, formation of the *O*-acyl product is under kinetic control only and the *N*-hydroxy amide is thermodynamically favored. Reaction conditions that promote equilibration between *O*-acyl and *N*-acyl hydroxylamines can therefore be used to access the desired *N*-hydroxy amide. For example, under nonequilibrating conditions (acetic anhydride, 100 °C), exclusive *O*-acylation of a highly hindered hydroxylamine occurs (entry 9);^[215] whereas treatment of the same hydroxylamine with acetyl chloride in the presence of pyridine gives the product of *N*-acylation (which exists in the lactol form) with excellent selectivity (entry 10).

Aroyl cyanides react with moderately hindered hydroxylamines, such as *N*-phenylhydroxylamine, solely at oxygen to give *O*-acyl derivatives, e.g. entry 11.^[214] This interesting regioselectivity is not observed with methylhydroxylamine, which gives the expected *N*-hydroxy amide on reaction with (3,4-dimethoxyphenyl)(oxo)acetonitrile (entry 12).

Table 5 Acylation of Hydroxylamines^[206–215]

Entry	R ¹	R ²	X	Reaction Conditions	Yield ^b (%)		Ref
					86	87	
1	H ^a		OPh	pyridine, 30 °C, 16 h	90	n.r.	[206]
2	H ^a		OMe	MeOH, KOH, 0 °C	82	n.r.	[207]
3	H ^a		OH	TCT ^c , NMM, DMAP, CH ₂ Cl ₂ , 0 °C to rt, 12 h	97	n.r.	[208]
4	CHMePh	H	OCH ₂ CF ₃	HCO ₂ H, THF, heat, 5 h	90	n.r.	[209]
5		FmocHN-	Cl	NaHCO ₃ , CH ₂ Cl ₂ , rt, 2 h	82	n.r.	[210]
6	CH ₂ CH ₂ Ts		Cl	Et ₃ N, CH ₂ Cl ₂ , 0 °C to rt, 2 h	81	n.r.	[211]
7	EtO ₂ C-	CH ₂ Mes	Cl	NaHCO ₃ , H ₂ O, EtOAc, rt, 3 h	44	17	[212]
8		Me	OAc	pyridine, rt	n.r.	93	[213]
9		Me	OAc	Ac ₂ O, 100 °C, 15 min	n.r.	95	[215]
10		Me	Cl	Et ₂ O, pyridine, rt, 1 h	86	3	[215]
11	Ph	3,4-(MeO) ₂ C ₆ H ₃	CN	benzene, rt	n.r.	90	[214]
12	Me	3,4-(MeO) ₂ C ₆ H ₃	CN	benzene, rt	80	0	[214]

^a Introduced as hydroxylamine hydrochloride.^b n.r. = not reported.^c TCT = 2,4,6-trichloro-1,3,5-triazine.

Benzyl (2*S*)-2-[(Hydroxyamino)carbonyl]pyrrolidine-1-carboxylate (86, R¹ = H; R² = *N*-Benzoyloxycarbonylpyrrolidin-2-yl; Table 5, Entry 3); Typical Procedure:^[208]

A soln of *N*-Boc-L-Pro-OH (2.24 g, 9.0 mmol), NH₂OH•HCl (0.68 g, 9.8 mmol), and DMAP (10 mg, 0.1 mmol) in CH₂Cl₂ (20 mL) at 0 °C was treated with 2,4,6-trichloro-1,3,5-triazine (0.50 g, 3.0 mmol). The mixture was allowed to warm to rt and then stirred for 12 h. The mixture was then filtered through Celite and the filtrate was washed successively with 1 M aq HCl (3 × 15 mL) and brine. The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure; yield: 2.3 g (97%); [α]_D²⁵ –46.1 (c 0.5, MeOH).

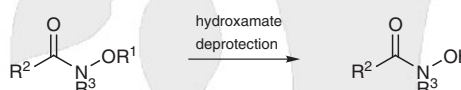
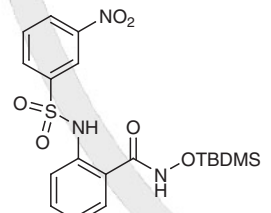
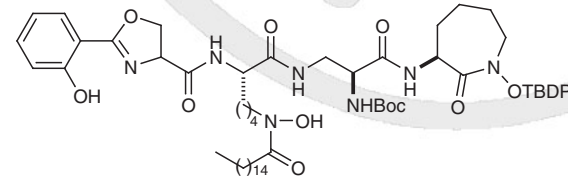
21.13.9.1.3

Method 3:**Deprotection of *N*-Siloxy, *N*-Acyloxy, or *N*-Alkoxy Amides**

The elaboration of complex *N*-hydroxy amides invariably requires that the reactive hydroxy group be protected during the synthesis and liberated at a later stage. *N*-Hydroxy amides are therefore often prepared by the O-deprotection of *N*-siloxy, *N*-acyloxy, or *N*-alkoxy amides (for the syntheses of these product subclasses, see Sections 21.13.10 and 21.13.11). Most popular types of hydroxy-protecting group^[219,220] can be successively removed to yield free *N*-hydroxy amides. The lability of such groups in this context is generally heightened as a result of the good nucleofugality of the hydroxamate anion.

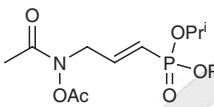
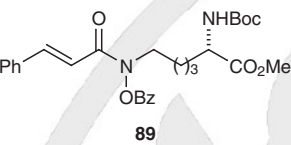
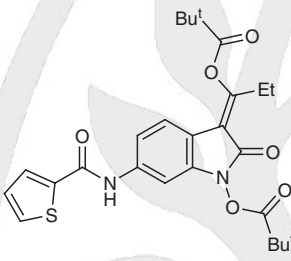
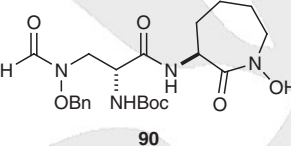
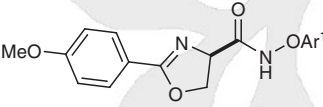
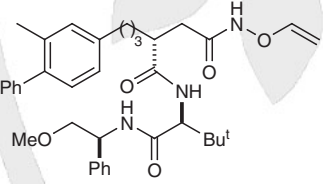
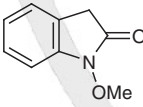
Representative examples of *N*-hydroxy amide syntheses by removal of common protecting groups are illustrated in Table 6 (e.g., **88–90**, entries 2, 4, and 6). Note that *N*-hydroxy amides are far more sensitive to degradation than are comparable alkyl amides, so appropriate care should be taken when selecting deprotection conditions. In particular, strongly basic or acidic reaction conditions should be avoided, as these can result in hydrolysis of the *N*-hydroxy amide product.^[147] In addition, certain reducing agents cleave the N—O bond of this product subclass [e.g., hydrogen/nickel, sodium amalgam, titanium(III) chloride, or samarium(II) iodide],^[230] whereas oxidants (e.g., periodate) can result in the formation of nitroso species (see Section 21.13.2) or nitroxide radicals and thence decomposition.

Table 6 O-Deprotection of *N*-Hydroxy Amide Derivatives^[221–229]

				
Entry	Hydroxamate	Deprotection Conditions	Yield (%)	Ref
1		1 M aq HCl, MeOH, rt, 1 h	81	[221]
2		TBAF, AcOH, 0 °C to rt, 1 h	84	[222]

88

Table 6 (cont.)

Entry	Hydroxamate	Deprotection Conditions	Yield (%)	Ref
3		NaOMe (cat.), MeOH, rt, 30 min	73	[223]
4	 89	10% NH ₃ , MeOH, -23 °C, 170 min	93	[224]
5		LiOH • H ₂ O, MeOH, THF, rt, 45 min	“high”	[225]
6	 90	H ₂ (1 atm), 10% Pd/C, MeOH, rt, 3 h	97	[226]
7		TFA, EtSiHMe ₂ , CH ₂ Cl ₂ , rt, 1 h	30 ^a	[227]
8		NH ₄ ⁺ HCO ₂ ⁻ , Pd(OAc) ₂ , Ph ₃ P, aq EtOH, heat, 1 h	80	[228]
9		AlCl ₃ , Me ₂ S, 0 °C to rt	80	[229]

^a Ar¹ = 2,4-(MeO)₂C₆H₃CH₂; yield over three steps.

N-((2S)-2-(tert-Butoxycarbonylamino)-3-((3S)-1-hydroxy-2-oxoazepan-3-ylamino)-3-oxopropyl)-N²-([[(4R)-2-(2-hydroxyphenyl)-4,5-dihydro-1,3-oxazol-4-yl]carbonyl]-N⁶-palmitoyl-L-lysineamide (Table 6, Entry 2); Typical Procedure:^[222]

A stirred soln of N-siloxy amide **88** (R¹ = TBDPS; 37 mg, 32 μmol) and AcOH (5.6 μL, 97 μmol) in anhyd THF (2 mL) at 0 °C was treated with a 1.0 M soln of TBAF in THF (0.1 mL, 100 μmol). The mixture was warmed to rt, allowed to stand for 1 h, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, MeOH/MeCN 11:89) to give a colorless solid; yield: 27.6 mg (84%); mp 164.5–165.5 °C.

Methyl *N*²-(*tert*-Butoxycarbonyl)-*N*⁶-hydroxy-*N*⁶-[(2*E*)-3-phenylprop-2-enoyl]-L-lysinate (Table 6, Entry 4); Typical Procedure:^[224]

A stirred soln of *N*-benzyloxy amide **89** ($R^1 = \text{Bz}$; 544 mg, 1.07 mmol) in distilled MeOH (1.4 mL) at -23°C was treated dropwise with 10 vol% NH_3 in MeOH (2.0 mL). The mixture was stirred for 170 min, the solvents were removed under a high vacuum, and the residue was purified by column chromatography (LH-20 Sephadex, EtOH/toluene 3:47); yield: 403 mg (93%).

3-[Formyl(hydroxy)amino]-*N*-[(3*R*)-1-hydroxy-2-oxoazepan-3-yl]-*N*²-butoxycarbonyl-D-alaninamide (Table 6, Entry 6):^[226]

A suspension of *N*-benzyloxy amide **90** ($R^1 = \text{Bn}$; 83 mg, 0.18 mmol) and 10% Pd/C (8 mg) in MeOH (5 mL) was stirred at rt under H_2 (1 atm) for 3 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography (C_{18} , 40–55% MeOH/ H_2O) to give a colorless solid; yield: 65 mg (97%); IR (neat) $\tilde{\nu}_{\text{max}}$: 3295, 2933, 1749, 1652 cm^{-1} .

21.13.9.1.4

**Method 4:
Ene Reactions of Acyl Nitroso Compounds**

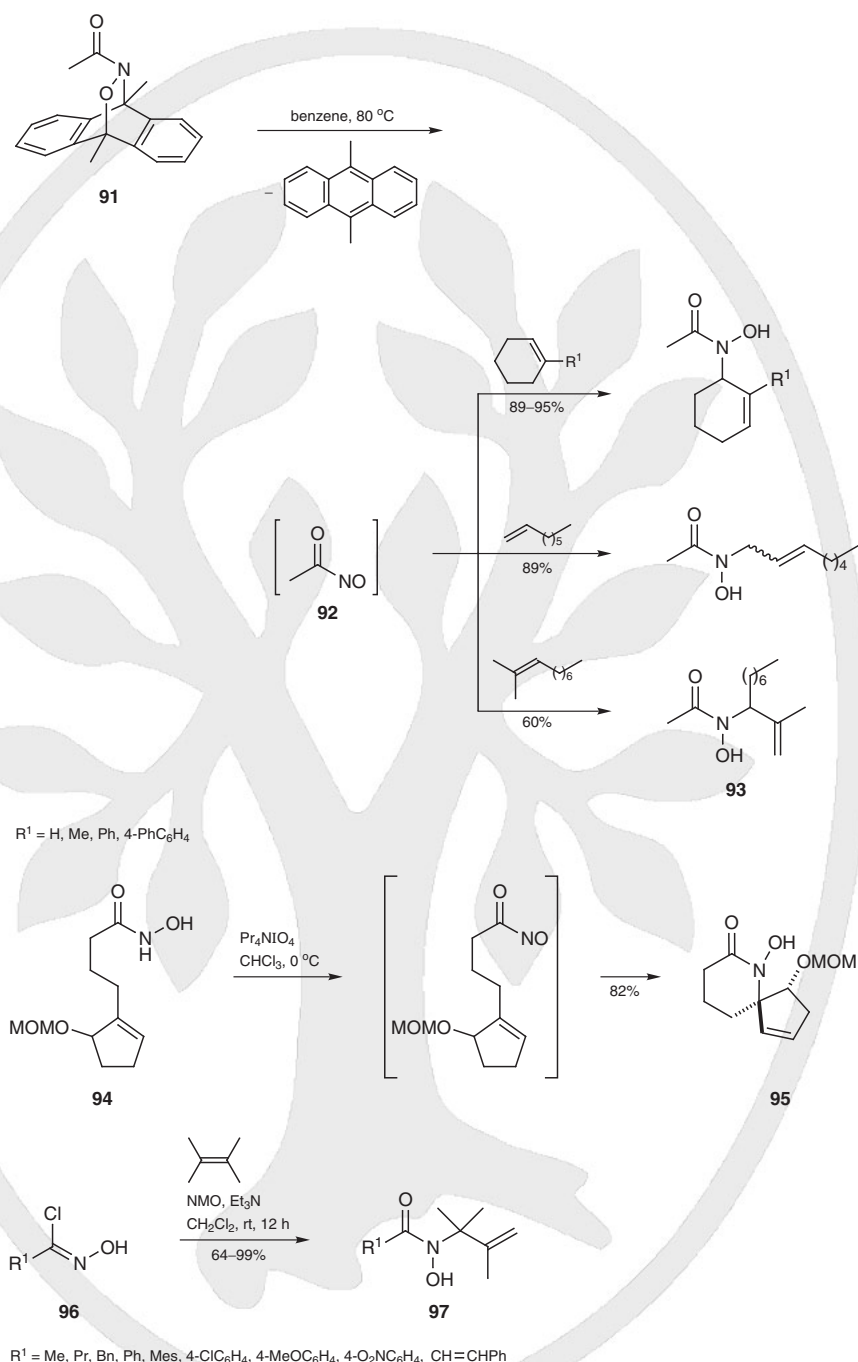
Acyl nitroso compounds effect allylic amidation of unconjugated alkenes through an ene reaction to give *N*-substituted *N*-hydroxy amides.^[14] This reaction was comprehensively studied and developed by Keck,^[231] and has been reviewed.^[20] Ene reactions of acyl nitroso compounds are typically conducted by thermal transfer of the requisite nitrosocarbonyl unit from a preformed 9,10-dimethylantracene cycloadduct (see Scheme 2, Section 21.13.2). Liberation of *N*-oxoacetamide (**92**) from its 9,10-dimethylantracene cycloadduct **91** in the presence of various alkenes gives excellent yields of the corresponding *N*-hydroxy amides, e.g. **93** (Scheme 15).^[231] With unsymmetrical internal acyclic alkenes, e.g. 2-methyldec-2-ene, the *N*-hydroxy amide product is formed by the exclusive addition of nitrogen to the less substituted unsaturated carbon atom.

Intramolecular ene reactions by nitroso transfer are also possible^[231] and this reaction has been applied to the stereoselective synthesis of complex alkaloids, such as mesembrine and dihydromaritidine.^[232]

Oxidative generation of acyl nitroso compounds for ene reactions is less common than the nitroso transfer method because the conventional oxidants that are used for this purpose (e.g., sodium periodate and tetraalkylammonium periodates) have a tendency to degrade the *N*-hydroxy amide products, resulting in poor yields.^[24,231] This is not to say, however, that such reactions cannot be successful. For example, the spirocyclic *N*-hydroxy amide **95**, representing the core of pinnaic acid, is obtained as a single diastereoisomer in 82% yield by oxidation of the oxoimide acid **94** with tetrapropylammonium periodate (Scheme 15).^[207]

(Diacetoxyiodo)benzene is another mild alternative to periodate for the production of acyl nitroso compounds from unsubstituted *N*-hydroxy amides for ene reactions.^[24]

Finally, a mild method for the generation of nitrosocarbonyl intermediates from nitrile oxides that offers excellent compatibility with ene reaction products involves the oxidation of nitrile oxides (prepared in situ by base-induced elimination from hydroximoyl halides, e.g. **96**) with *N*-methylmorpholine *N*-oxide in the presence of alkenes.^[233] Hindered alkenes, e.g. 2,3-dimethylbut-2-ene, give good-to-excellent yields of ene products, e.g. **97** (Scheme 15), although less sterically encumbered alkenes afford mixtures of ene products and dihydroisoxazoles as a result of [3+2] cycloaddition of the nitrile oxide and the alkene.^[233]

Scheme 15 Synthesis of N-Hydroxy Amides by Ene Reactions of Acyl Nitroso Compounds^[207,231,233]**N-Hydroxy-N-(1-isopropenyl)octyl)acetamide (93); Typical Procedure:**^[231]

A stirred soln of 9,10-dimethylantracene (4.0 g, 19 mmol) and Pr₄NIO₄ (11.0 g, 29 mmol) in CHCl₃ (50 mL) at 5 °C was treated dropwise with a soln of AcNHOH (2.20 g, 29 mmol) in DMF (15 mL) at such a rate that the internal temperature did not rise above 15 °C. After the addition was complete, the mixture was poured into EtOAc and washed successively with

sat. aq $\text{Na}_2\text{S}_2\text{O}_3$, H_2O , and brine. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to afford cycloadduct **91** as a crystalline solid; yield: 5.20 g (96%); mp 133–136 °C.

A soln of cycloadduct **91** (73 mg, 0.26 mmol) and 2-methyldec-2-ene (52 mg, 0.34 mmol) in benzene (0.3 mL) (**CAUTION: carcinogen**) was placed in a sealed Pyrex tube under argon and heated at 80 °C for 12 h. The mixture was then purified by column chromatography (silica gel, THF/hexanes 7:13) to give the *N*-hydroxy amide **93**; yield: 35 mg (60%).

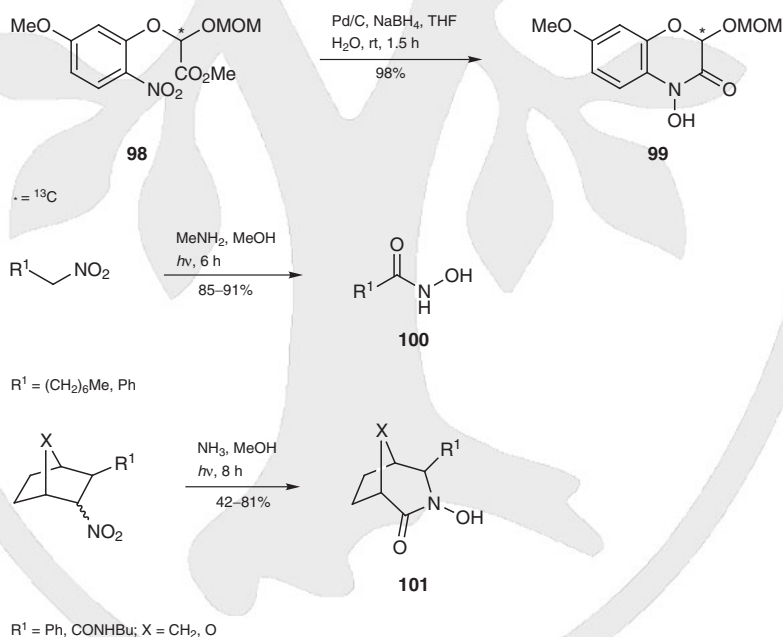
21.13.9.1.5

Method 5: Synthesis from Nitro Compounds

Nitro compounds provide some useful and easily exploited routes to *N*-hydroxy amides (Scheme 16).^[234–236] Chemoselective reduction of nitro esters with zinc leads directly to cyclic *N*-hydroxy amides through in situ intramolecular acylation of the intermediate hydroxylamines.^[237,238] This reduction can also be performed by a palladium-catalyzed route to give, for example, the cyclic *N*-hydroxy amide **99** from nitro ester **98** (Scheme 16);^[234,239] this route can also be applied in a solid-phase variant.^[240]

A useful photorearrangement of nitronate anions gives *N*-hydroxy amides, e.g. **100** (Scheme 16).^[190,235] The reaction is highly regioselective (the higher substituted and/or more electronegative β -group migrates preferentially), and stereochemistry at the migrating group is retained, for example, in the case of cyclic *N*-hydroxy amides **101**.^[236]

Scheme 16 Synthesis of *N*-Hydroxy Amides from Nitro Compounds^[234–236]



[2-¹³C]-4-Hydroxy-7-methoxy-2-(methoxymethoxy)-2H-1,4-benzoxazin-3(4H)-one (**99**):^[234]

A soln of nitro ester **98** (1.20 g, 3.99 mmol) in THF (15 mL) was added dropwise to a mixture of NaBH_4 (500 mg, 13.2 mmol) and 10% Pd/C (50 mg) in THF/ H_2O (1:1, 40 mL). The mixture was stirred for 1.5 h and the catalyst was removed by filtration. The filtrate was acidified to pH 3 with aq HCl and extracted with EtOAc (3×50 mL). The combined organic ex-

tracts were dried (MgSO_4) and concentrated under reduced pressure; yield: 1.0 g (98%); mp 142–144 °C.

21.13.10 **Product Subclass 10:** ***N*-Acyloxy Amides**

The chemistry of *N*-acyloxy amides (*O*-acyl hydroxamates) has been covered in some detail in reviews of *N*-hydroxy amides.^[147,187–189] *N*-Acyloxy amides with a free NH moiety are more acidic than the parent unsubstituted *N*-hydroxy amides ($\text{p}K_{\text{a}} \text{R}^1\text{CONHOCOR}^2 \approx 7$ vs $\text{p}K_{\text{a}} \text{R}^1\text{CONHOH} \approx 9$). Upon heating, the easily prepared salts of these compounds ($\text{R}^1\text{CON}^-\text{OCOR}^2$) suffer rearrangement with loss of the carboxylate nucleofuge (R^2CO_2^-) to yield isocyanates (R^1NCO). This useful process, named the Lossen rearrangement,^[241] is frequently employed for the preparation of amines, carbamates, and ureas (all three via the isocyanate), and represents a significant synthetic application of *N*-acyloxy amides.^[188]

21.13.10.1 **Synthesis of Product Subclass 10**

21.13.10.1.1 **Method 1:** ***O*- or *N*-Acylation**

N-Acyloxy amides are typically prepared by the acylation of *O*-acyl or *N*-acyl hydroxylamine derivatives. In each case, reaction occurs preferentially at the more nucleophilic nonacylated heteroatom. Further acylation of *N*-monoacyloxy amides ($\text{R}^1\text{CONHOCOR}^2$) usually affords *N*-acyl-*N*-acyloxy amides [$\text{R}^1\text{CON}(\text{COR}^3)\text{OCOR}^2$],^[242] although the formation of *O,O'*-diacyl hydroximates [$\text{R}^1\text{C}(\text{O}_2\text{CR}^3)=\text{NOCOR}^2$] is also known.^[243]

21.13.10.1.1.1 **Variation 1:** **By *O*-Acylation of *N*-Hydroxy Amides**

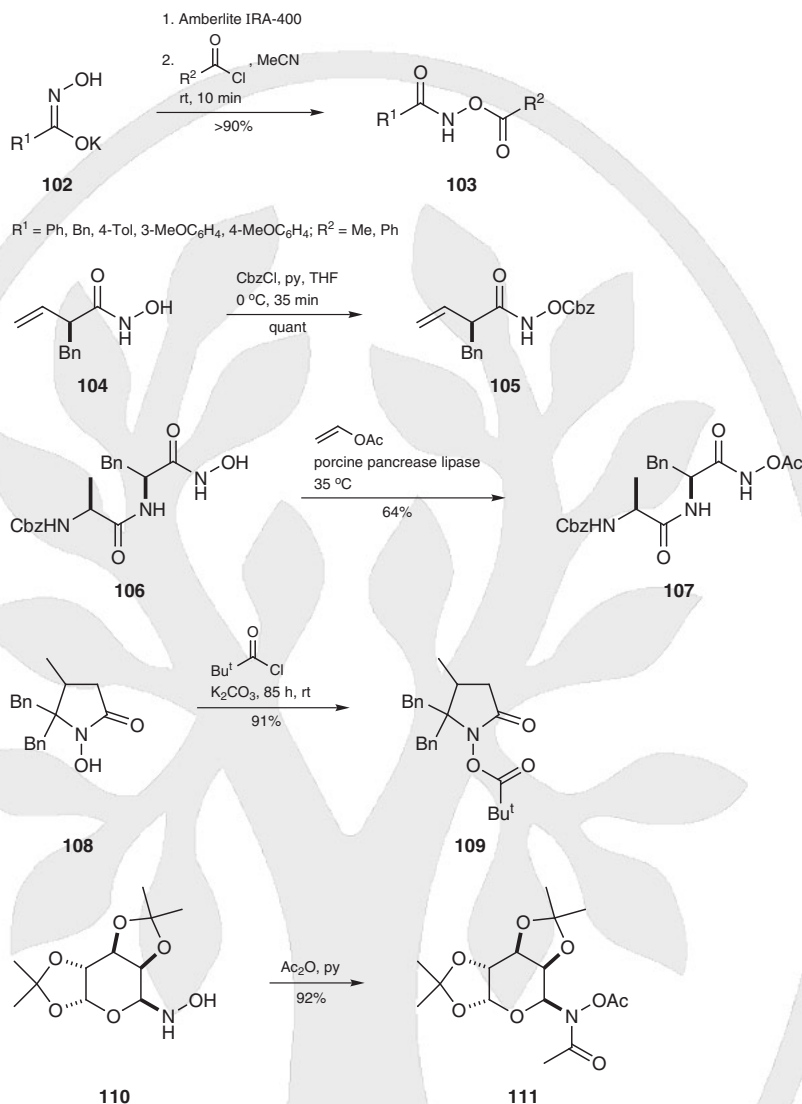
N-Hydroxy amides react with common acylating reagents (e.g., acid chlorides or carboxylic acid anhydrides) in the presence of a base to give the expected *N*-acyloxy amides.^[244] As with alkylation (see Section 21.13.11.1.1), base-mediated acylation of *N*-unsubstituted *N*-hydroxy amides occurs almost exclusively at the free hydroxy group and not at any alternative site. *O*-Acylation of potassium benzohydroxamate salts, e.g. **102**, supported on a cationic resin gives *N*-acyloxy amides in excellent yields and purities, e.g. **103** (Scheme 17).^[245]

O-Acylation of *N*-hydroxy amides is often used to introduce a temporary protecting group on the hydroxy group. For example, treatment of *N*-hydroxy amide **104** with benzyl chloroformate in the presence of pyridine gives the *O*-protected derivative **105**.^[246] An enzymatic acyl-transfer reaction catalyzed by porcine pancreas lipase can be used to prepare the *N*-acyloxy amide **107** from the *N*-hydroxy amide **106** under very mild reaction conditions (Scheme 17).^[247]

Extremely hindered *N*-acyloxy amides are available by simple acylation of *N*-hydroxy amides. Thus, the pivalate **109** is obtained in 91% yield by treating the *N*-substituted *N*-hydroxy amide **108** with neat pivaloyl chloride for an extended period of time.^[248]

N-Alkoxy amides can also be prepared by concomitant *N,O*-diacylation of hydroxylamine derivatives; e.g. the *N,O*-diacetyl derivative **111** is obtained directly from carbohydrate-derived hydroxylamine **110** (Scheme 17).^[249]

Other acyl donors used to prepare this product class from *N*-hydroxy amides include ketene dimer,^[250] acyl palladium(II) complexes derived from carbonylation,^[251] and isocyanates.^[252]

Scheme 17 O-Acylation of N-Hydroxy Amides^[245–249]**N-Acyloxy Amides 103; General Procedure:**^[245]

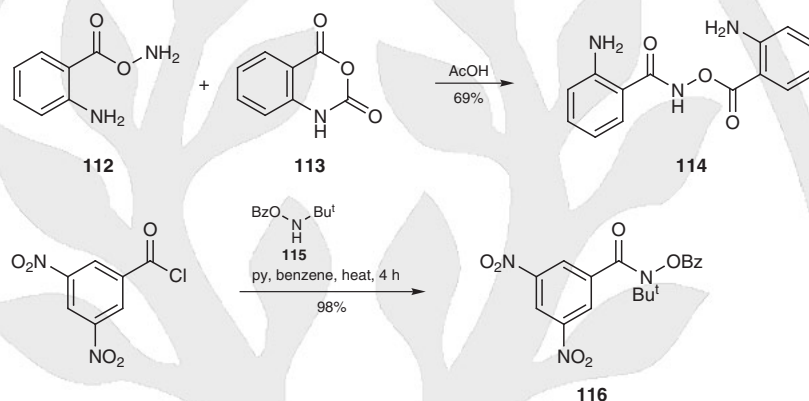
Amberlite IRA-400 (5 g, Cl[−] form) was packed in a column and washed with a 0.25 M aq soln of the potassium benzohydroxamate salt **102** until anion exchange was complete. The loaded resin was then washed successively with H₂O (100 mL), EtOH (25 mL), and Et₂O (25 mL). The resin was dried azeotropically with toluene and then at 50 °C in vacuo for 2 h. The hydroxamate ion loading of the dry resin was 1.5 mmol·g^{−1}.

A mixture of the supported benzohydroxamate ion (5 mmol) and AcCl or BzCl (5 mmol) in MeCN (20 mL) at rt was stirred in a stoppered flask for 10 min. The resin was then removed by filtration and washed with MeCN (2 × 10 mL). The filtrate and combined washings were concentrated under reduced pressure to afford essentially pure N-acyloxy amides **103**; yield: >90%.

21.13.10.1.1.2

Variation 2:***N*-Acylation of *O*-Acyl Hydroxylamines**

O-Acyl hydroxylamines possess an α -effect and the nitrogen atom of this class of amines is a competent nucleophile. For example, 2-(aminooxycarbonyl)aniline (**112**) reacts with the cyclic anhydride **113** preferentially at the hydroxylamine position to yield the *N*-acyloxy amide **114** in good yield (Scheme 18).^[253] *O*-Acyl hydroxylamines, such as **115**, react with acid chlorides to give the expected products,^[254,255] including sterically encumbered *N*-acyloxy amides, e.g. **116**.^[256]

Scheme 18 Acylation of *O*-Acyl Hydroxylamines^[253,256]***N*-(Benzoyloxy)-*N*-(*tert*-butyl)-3,5-dinitrobenzamide (**116**); Typical Procedure:**^[256]

A soln of *t*-BuNHOBz **115** (20.2 g, 105 mmol) and pyridine (16 mL) in anhyd benzene (200 mL) (**CAUTION: carcinogen**) was treated with 3,5-dinitrobenzoyl chloride (22.0 g, 95 mmol) and stirred at reflux for 4 h. The precipitated pyridinium hydrochloride was removed by filtration and the filtrate was washed successively with 2 M aq HCl (3 × 100 mL) and H₂O (3 × 100 mL). The organic phase was dried (MgSO₄) and concentrated under reduced pressure to give a pale yellow solid; yield: 36.1 g (98%); mp 100 °C.

21.13.11

Product Subclass 11:***N*-Alkoxy Amides and *O*-Siloxy Amides**

N-Alkoxy amides (*O*-alkyl hydroxamates, hydroxamic acid esters) and *N*-siloxy amides (*O*-silyl hydroxamates) have received little attention in the review literature in their own right.^[257] Nevertheless, some general accounts concerning the parent *N*-hydroxy amides (hydroxamates) contain some useful information.^[147,187,188]

Members of this product subclass with removable protecting groups on the oxygen atom are extensively employed as intermediates in the synthesis of *N*-hydroxy amides (see Section 21.13.9.1.3). *N*-Alkoxy amides are also synthetically useful for other purposes, particularly *N*-methoxy-*N*-methyl amides, which were introduced by Weinreb in 1981 as remarkable carboxy electrophiles capable of cleanly accepting a single equivalent of a variety of nucleophilic reagents.^[258] These *N*-alkoxy amides, commonly referred to as “Weinreb amides”, react with alkylolithiums and Grignard reagents to provide a high-yielding synthesis of ketones, and they are neatly reduced to aldehydes by nucleophilic hydride donors.^[257] Over-addition is not usually encountered, even if excess nucleophile is introduced, and no special techniques or experimental conditions are required. Weinreb amides can be prepared by the addition of organolithium compounds to *N,N'*-dimeth-

oxy-*N,N'*-dimethylurea.^[259] Amides can be prepared from *N*-alkoxy amides by chemoselective reductive scission of the N—O bond.^[230]

21.13.11.1 Synthesis of Product Subclass 11

21.13.11.1.1 Method 1: O-Alkylation or O-Silylation of *N*-Hydroxy Amides

Acylation is usually the preferred route to *O*-alkoxy and *O*-siloxy amides (see Section 21.13.11.1.2), but where the requisite *O*-substituted hydroxylamine derivatives are not readily available, derivatization of an *N*-hydroxy amide can offer a better option for the synthesis of *O*-substituted amides. Both *N*-substituted and *N*-unsubstituted *N*-hydroxy amides react with electrophiles predominantly at the active hydroxy group, so regioselectivity in alkylation or silylation of *N*-hydroxy amides does not present a problem.^[147] In multistep syntheses of complex *N*-hydroxy amides, it is often the case that temporary protection of the acidic hydroxy group is required; in these cases, conversion by either alkylation or silylation to form *N*-alkoxy or *N*-siloxy derivatives bearing potentially removable groups is in order.

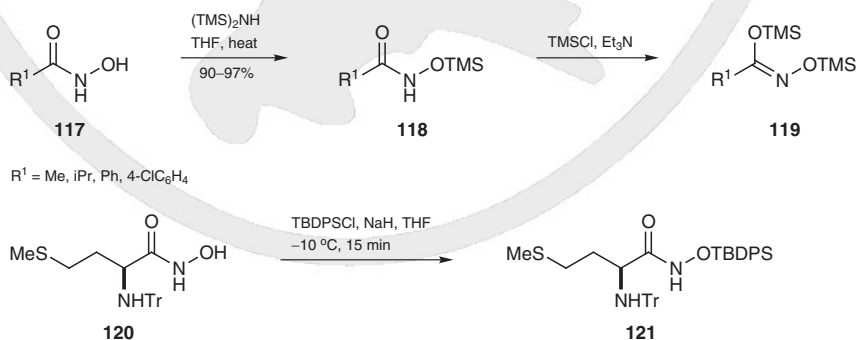
21.13.11.1.1.1 Variation 1: O-Silylation of *N*-Hydroxy Amides

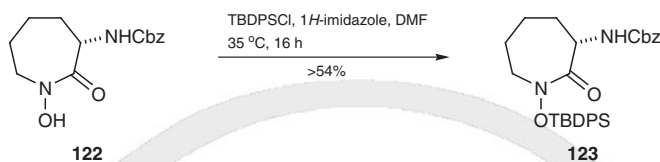
Synthesis of *N*-siloxy amides by monosilylation of *N*-hydroxy amides is straightforward and occurs almost exclusively at the hydroxy group (Scheme 19).^[260–263] *N*-Trimethylsiloxy amides, e.g. **118**, are obtained in excellent yields from simple *N*-hydroxy amides, e.g. **117**, by heating with hexamethyldisilazane in tetrahydrofuran solvent.^[260,264] Further silylation of *N*-(trimethylsiloxy)benzamide (**118**, $R^1 = \text{Ph}$) gives a product with spectral characteristics that are consistent with an imide structure **119**, rather than the result of *N*-silylation.^[260]

The *N*-siloxy amide **121** cannot be obtained by acylation of *O*-(*tert*-butyldiphenylsiloxy)hydroxylamine, but can be successfully accessed by silylation of the *N*-hydroxy amide **120**.^[262] Treatment of the sodium salt of **120** with *tert*-butylchlorodiphenylsilane in tetrahydrofuran gives **121** exclusively; however, significant amounts of an *N*-hydroxy-*N*-silyl amide accompany **121** when the same reaction is conducted in a 3:1 mixture of tetrahydrofuran and dimethylformamide.^[262]

The *N*-hydroxy lactam **122** can be protected as its *N*-*tert*-butyldiphenylsiloxy derivative **123** en route to mycobactin S;^[263] an *N*-*tert*-butyldimethylsiloxy derivative can be similarly obtained.

Scheme 19 O-Silylation of *N*-Hydroxy Amides^[260,262,263]



***N*-(Trimethylsiloxy) Amides 118; General Procedure:**^[260,264]

A mixture of an *N*-hydroxy amide **117** (10 mmol) and (TMS)₂NH (4.2 mL, 3.22 g, 20 mmol) in THF or benzene (50 mL) (**CAUTION: carcinogen**) was refluxed until evolution of NH₃ ceased (6–15 h). The solvent was then removed under reduced pressure and the residue was recrystallized; **118** (R¹ = Me): mp 37 °C; **118** (R¹ = *i*Pr): mp 106 °C; **118** (R¹ = Ph): mp 78 °C; **118** (R¹ = 4-ClC₆H₄): mp 178 °C (dec).

21.13.11.1.1.2

**Variation 2:
O-Alkylation of *N*-Hydroxy Amides**

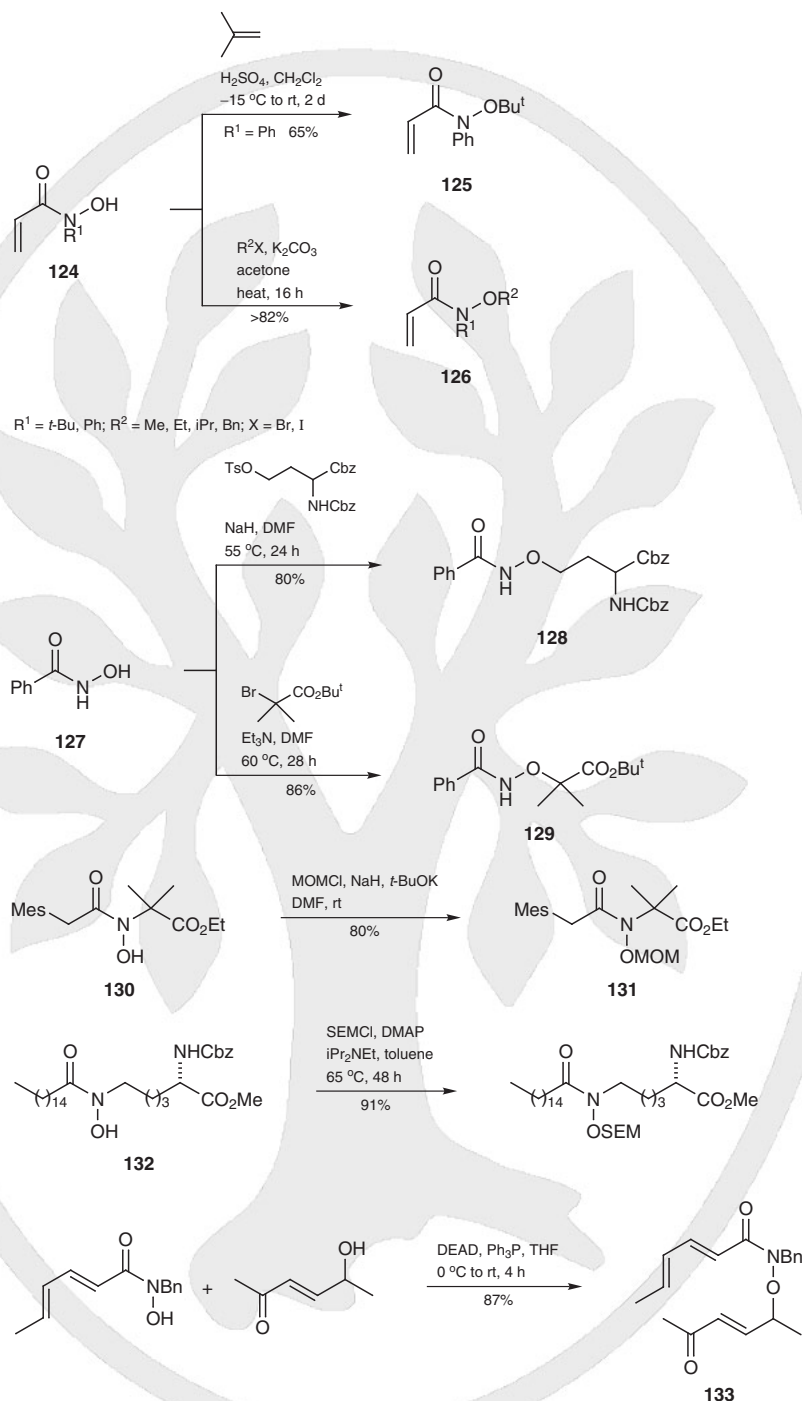
The classical Williamson-type synthesis of *N*-alkoxy amides from *N*-hydroxy amides has been extensively studied and it is well established that *N*-hydroxyamide anions are preferentially substituted at the nitrogen-bound oxygen atom by alkyl halides.^[147] Where further alkylation is possible (i.e., when *N*-unsubstituted *N*-hydroxy amides are used as the starting materials), small quantities of dialkylated material may accompany the monoalkylation product.^[265] The second alkylation can occur at either the nitrogen atom or the carbonyl oxygen atom.

N-Hydroxyacrylamides **124** are converted into the corresponding *N*-alkoxy amides **126** in high yields by simple treatment with an alkyl halide and potassium carbonate base in refluxing acetone (Scheme 20).^[266] *N*-Hydroxy amide **124** (R¹ = Ph) can also be alkylated under acidic conditions by 2-methylprop-1-ene to give the *N*-*tert*-butoxy amide **125** in moderate yield.^[266]

N-Hydroxybenzamide (**127**) can be selectively *O*-alkylated with unusual electrophiles under basic conditions to afford elaborate *N*-alkoxy amides, e.g. **128** and **129** (Scheme 20).^[267,268]

N-Hydroxy amides are often alkylated with removable groups such as methoxymethyl or (2-trimethylsilylethoxy)methyl (SEM) en route to complex *N*-hydroxy amide containing target molecules. For example, the methoxymethoxy amide **131** can be prepared in an 80% yield from the salt of *N*-hydroxy amide **130** (Scheme 20); the protective group is later removed with bromotrimethylsilane to access an insecticidal compound.^[212] (2-Trimethylsilylethoxy)methyl protection of *N*-hydroxy amide **132** is achieved in 91% yield by alkylation with [2-(chloromethoxy)ethyl]trimethylsilane and *N,N*-diisopropylethylamine in toluene as part of the synthesis of mycobactin S.^[263]

The Mitsunobu reaction^[269] provides an alternative and extremely mild process for alkylating *N*-hydroxy amides by dehydrative coupling with alcohols. Using this methodology, a series of unsaturated *N*-alkoxy amides, including **133** (Scheme 20), can be prepared as novel precursors for intramolecular Diels–Alder reactions.^[270] Cyclic *N*-hydroxy amides can also be prepared from salicyclic *N*-hydroxy amides using Mitsunobu conditions.^[271] *O*-Alkylation of *N*-hydroxy amides can also be achieved by conjugate addition^[272] and alkene haloetherification.^[273]

Scheme 20 O-Alkylation of N-Hydroxy Amides^[212,263,266–268,270]**N-Benzyloxy-N-phenylacrylamide (126, $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{Bn}$); Typical Procedure:**^[266]

A mixture of **124** ($\text{R}^1 = \text{Ph}$; 20.0 g, 120 mmol), anhyd K_2CO_3 (59.0 g, 430 mmol) and BnBr (51 mL, 73.4 g, 430 mmol) in anhyd acetone (450 mL) was stirred at reflux for 16 h (overnight). The solvent was evaporated and the residue was partitioned between CH_2Cl_2 and

1 M aq NaOH. The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 ×). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes 1:4) to give a yellow oil; yield: 25 g (82%).

21.13.11.1.2

Method 2:***N*-Acylation of *O*-Alkyl or *O*-Silyl Hydroxylamine Derivatives**

N-Alkoxy and *N*-siloxy amides are frequently prepared by the direct acylation of appropriately substituted hydroxylamine derivatives. This approach has much in common with the analogous synthesis of amides from amines, and many of the same considerations apply.^[274]

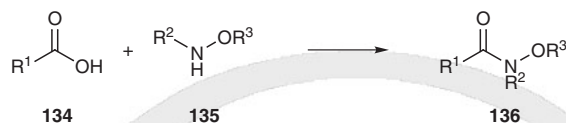
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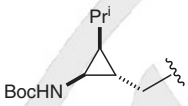
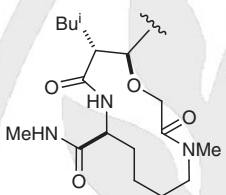
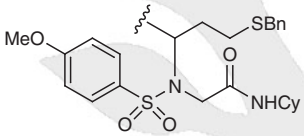
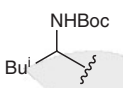
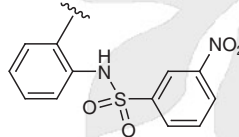


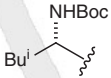
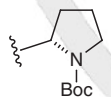
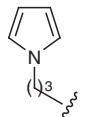
Variation 1:**With Activated Carboxylic Acid Derivatives**

O-Alkyl and *O*-silyl hydroxylamines react readily with common acylating agents, such as acid chlorides^[258] and carboxylic acid anhydrides,^[230] to give the expected products of *N*-acylation. As with the synthesis of amides from primary amines, selective monoacylation of *N*-unsubstituted *O*-alkyl- and *O*-silyl hydroxylamines is achievable in high yield without competing formation of imides. More advanced dehydrative coupling protocols, developed primarily for peptide synthesis, can also be applied in the synthesis of *N*-alkoxy and *N*-siloxy amides from hydroxylamines and carboxylic acids [e.g., 1,1'-carbonyldiimidazole, dicyclohexylcarbodiimide, dicyclohexylcarbodiimide/benzotriazol-1-ol, 1-benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP; Castro's reagent), 1-benzotriazolyloxytris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyBOP), *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethaniminium hexafluorophosphate *N*-oxide (HBTU), and *N*-[(dimethylamino)(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)methylene]-*N*-methaniminium hexafluorophosphate *N*-oxide (HATU)].^[275]

Representative examples of the synthesis of *N*-alkoxy amides **136** from carboxylic acids **134** and *O*-substituted hydroxylamines **135** are presented in Table 7.^[221,276–282] *N*-Alkoxy amides with removable protecting groups on oxygen, which are useful for subsequent conversion into *N*-alkoxy amides (see Section 21.13.9), are easily synthesized using the appropriate hydroxylamines, e.g. entries 1–5. Weinreb amides can also be prepared from carboxylic acids and *N*-methoxy-*N*-methylamine hydrochloride in the presence of a suitable coupling reagent and base, e.g. entries 6–10.

N-Alkoxy amides can be conveniently synthesized through acylation of hydroxylamines with 2-chloro-4,6-dimethoxy-1,3,5-triazine-activated carboxylic acids.^[279] *N*-Alkoxy amides derived from *N*-*tert*-butoxycarbonyl-protected amino acid substrates (including Weinreb amides) are obtained without racemization (entries 4 and 8). The reagent combination of 2,2'-disulfanediylbis(pyridine) 1,1'-dioxide (PODS) and tributylphosphine provides a mild method for the synthesis of Weinreb amides, e.g. entries 9 and 10.^[282] The method succeeds for the synthesis of a Weinreb amide bearing an electron-rich pyrrole moiety (entry 10), where other methods fail, but is less well suited for the preparation of hindered compounds.^[282]

Table 7 Condensation of O-Substituted Hydroxylamines with Carboxylic Acids^[221,276–282]

Entry	R ¹	R ²	R ³	Reaction Conditions	Yield (%)	Ref
1		H	Bn	iBuOCOCl, Et ₃ N, THF, -10 °C to rt, 12 h	79	[276]
2		H ^a	Bn	BOP ^b , iPr ₂ NEt, DMSO, 0 °C to rt, 1 h	79	[277]
3		H	Tr	EDC ^c , HOBT, CH ₂ Cl ₂ , rt, 16 h	75	[278]
4		H	TBDPS	CDMT ^d , NMM, THF, rt, 8 h	87	[279]
5		H	TBDMS	EDC ^c , CH ₂ Cl ₂ , rt, 1 h	81	[221]
6	3-pyridyl 	Me ^a	Me	DCC, Et ₃ N, CH ₂ Cl ₂ , rt, 16 h	85	[280]
7		Me ^a	Me	CDI ^e , CH ₂ Cl ₂ , rt, 16 h	99	[281]
8		Me ^a	Me	CDMT ^d , NMM, THF, rt, 8 h	97	[279]
9		Me ^a	Me	PODS ^f , Et ₃ N, Bu ₃ P, CH ₂ Cl ₂ , 0 °C to rt, 16 h	96	[282]
10		Me ^a	Me	PODS ^f , Et ₃ N, Bu ₃ P, CH ₂ Cl ₂ , 0 °C to rt, 16 h	92	[282]

^a Hydrochloride salt used in procedure.^b BOP = benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate.^c EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.^d CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine.^e CDI = 1,1'-carbonyldiimidazole.^f PODS = 2,2'-disulfanediylbis(pyridine) 1,1'-dioxide.

***N*-Methoxy-*N*-methylnicotinamide (136, R¹ = 3-Pyridyl; R² = R³ = Me; Table 7, Entry 6); Typical Procedure:**^[280]

A stirred soln of nicotinic acid (**134**, R¹ = 3-pyridyl; 26.5 g, 215 mmol), MeN(OMe)H•HCl (23.1 g, 237 mmol) and Et₃N (24.0 g, 237 mmol) in CH₂Cl₂ (200 mL) at 0 °C was treated with DCC (48.9 g, 237 mmol). The mixture was allowed to warm and was stirred overnight at rt. Hexane (400 mL) was added and the resulting precipitate was removed by filtration and washed with hexane. The combined washings and filtrate were concentrated under reduced pressure to give a colorless oil; yield: 30.6 g (85%); IR (neat) $\tilde{\nu}_{\text{max}}$: 2928, 2853, 2110, 1646, 1449, 1025, 890, 725 cm⁻¹.

21.13.11.1.2.2

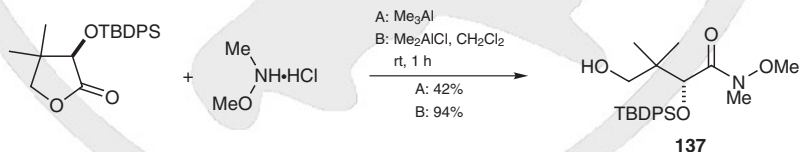
Variation 2:**Reactions of Esters and Imides with *O*-Alkyl *N*-Metalated Hydroxylamine Reagents**

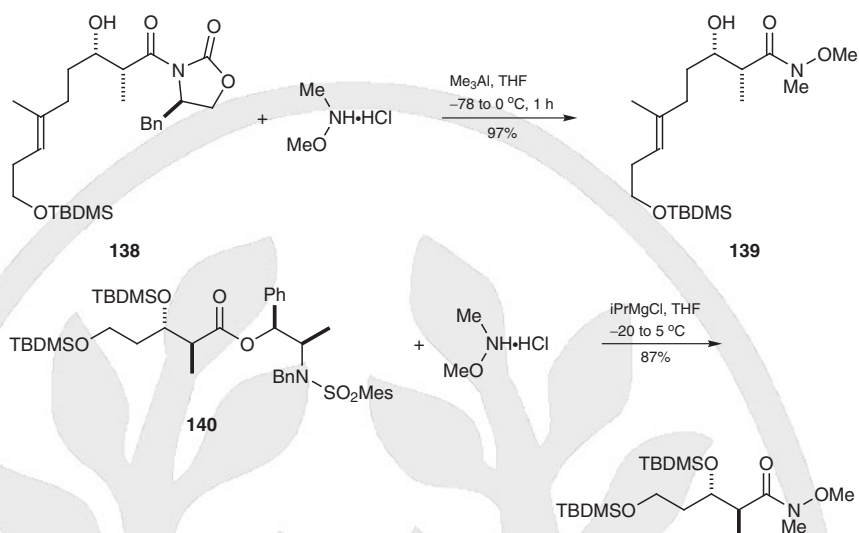
Nonactivated acyl donors, such as esters and lactones, react sluggishly, if at all, with *O*-alkyl hydroxylamines, and harsh reaction conditions are required to give acceptable yields of the *N*-alkoxy amide products. In contrast, a variety of metal amide reagents derived from *O*-alkyl hydroxylamines readily amidate esters (and in some cases imides too) at or below room temperature to give the expected *N*-alkoxy amides.

Treatment of *N*-methoxy-*N*-methylamine, or its hydrochloride salt, with trimethylaluminum or dimethylaluminum chloride,^[283,284] or related reagents,^[285] affords putative aluminum alkoxyamides that are capable of directly converting esters and lactones into their Weinreb amides, e.g. **137** (Scheme 21). A reagent combination of dimethylaluminum chloride and *N*-methoxy-*N*-methylamine hydrochloride is more efficacious for this purpose than that composed of trimethylaluminum and the same amine salt.^[284] The aluminum reagent formed in situ from *N*-methoxy-*N*-methylamine hydrochloride and trimethylaluminum is a popular one for the production of Weinreb amides from imides derived from Evans chiral auxiliaries. For successful transamidation, a β -hydroxy imide moiety is generally required.^[286] This technique can be used to prepare the Weinreb amide **139** from imide **138** (Scheme 21) in 96% yield, without epimerization, en route to the antitumor compound FR182877.^[287]

A magnesium amide reagent derived from *N*-methoxy-*N*-methylamine hydrochloride and isopropylmagnesium chloride is also available for the conversion of esters into Weinreb amides.^[288] This method is superior to other protocols, including those based on aluminum, for the amidation of Masamune ester **140**, a precursor to the cytotrienins.^[289]

Other *N*-alkoxy amides besides Weinreb amides can be prepared with the appropriate metal amide reagents, and the type of metal is not necessarily limited to aluminum or magnesium.^[290]

Scheme 21 Formation of Weinreb Amides from Esters and Imides^[284,287,289]



(2*R*,3*S*,6*E*)-9-(*tert*-Butyldimethylsiloxy)-3-hydroxy-*N*-methoxy-*N*,2,6-trimethylnon-6-enamide (139); Typical Procedure:^[287]

Neat Me_3Al (2.20 mL, 22.9 mmol) was added dropwise to a stirred suspension of $\text{MeN(OMe)H}\cdot\text{HCl}$ (2.19 g, 22.5 mmol) in THF (25 mL) at 0°C under argon. Gas evolution was observed. The resulting soln was cooled to -78°C and imide **138** (3.60 g, 7.35 mmol) in THF (15 mL) was added through a cannula. The mixture was allowed to warm to 0°C , stirred for 1 h, and then poured into sat. aq NH_4Cl (200 mL). The mixture was acidified with 1 M aq HCl (200 mL) and extracted with Et_2O (3×100 mL). The combined organic extracts were washed successively with 1 M aq HCl (100 mL), sat. aq NaHCO_3 (50 mL), and brine (100 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was triturated with hexanes/ Et_2O (10:1, 20 mL), the resulting solids were removed by filtration, and the filter cake was washed well with hexanes (3×100 mL). The combined filtrate and washings were concentrated under reduced pressure to give a colorless oil; yield: 2.66 g (97%).

21.13.11.1.3

Method 3:

Hetero-Diels–Alder Reaction of Acyl Nitroso Compounds

As noted in Section 21.13.2, acyl nitroso compounds are highly competent dienophiles and will readily engage in [4+2]-cycloaddition reactions with dienes to give cyclic *N*-alkoxy amides (*N*-acyl 3,6-dihydro-1,2-oxazines).^[14,18] The cycloadducts are often formed with reasonable levels of diastereoselectivity, particularly from intramolecular hetero-Diels–Alder reactions,^[291] and are useful in the syntheses of various alkaloids.^[19]

Acyl nitroso compounds are transient species and must be generated in situ in the presence of the diene component. Oxidation of unsubstituted *N*-hydroxy amides is commonly employed for this purpose, and nitroso compounds have been formed with a variety of diene-compatible oxidants [e.g., periodate anion,^[218,292] chlorobis(cyclooctene)iridium dimer catalyst/hydrogen peroxide,^[21] oxalyl chloride/dimethyl sulfoxide,^[22] or Dess–Martin periodinane^[23]].

Oxidation of the alanine-derived *N*-hydroxy amide **141** under Swern-type conditions gives a transient acyl nitroso compound that can be trapped with cyclohepta-1,3-diene to give the cyclic *N*-alkoxy amide **142** with good stereoselectivity (Scheme 22).^[22]

An intramolecular hetero-Diels–Alder reaction of the nitrosocarbonyl compound derived from the *N*-hydroxy amide **143** can be used to prepare oxazines **144A** and **144B** en

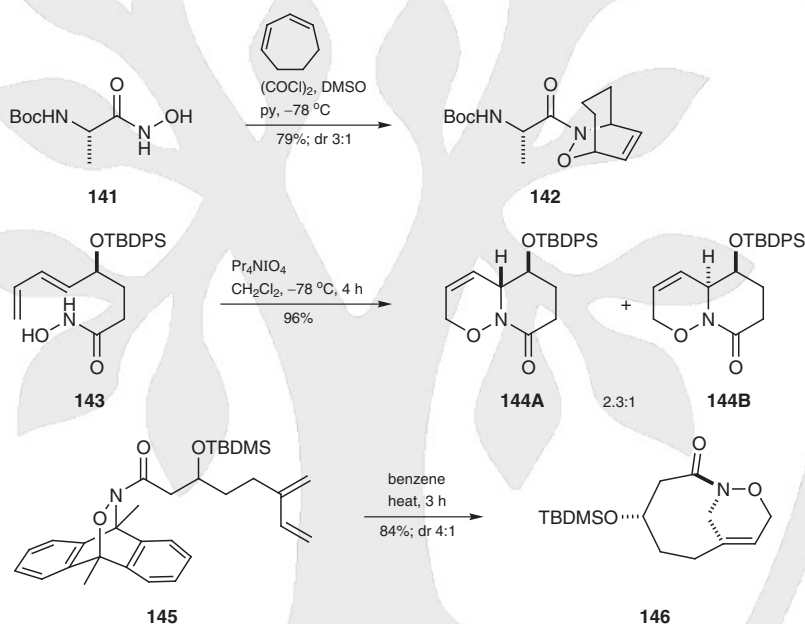
route to two isomeric indolizidines related to swainsonine (Scheme 22).^[293] Both the solvent and the temperature have a marked effect on the stereochemical outcome of this type of intramolecular cycloaddition.^[19,218,293]

Aside from oxidative protocols, acyl nitroso compounds can also be generated in situ by retro-hetero-Diels–Alder reactions of preformed cycloadducts.^[15] This method is advantageous when direct oxidation of an *N*-hydroxy amide is not compatible with the necessary reaction conditions for cycloaddition.^[294]

The cyclic *N*-alkoxy amide **145**, prepared from the cycloadduct of nitrosocarbonylmethane and 9,10-dimethylanthracene by an aldol reaction with 4-methylenehex-5-enal followed by silylation,^[295] on gentle heating undergoes fragmentation to form an acyl nitroso compound that is trapped by the pendent diene moiety to give the anti-Bredt alkene **146** in 84% yield and with good diastereoselectivity (Scheme 22).

Acyl nitroso compounds for [4+2] cycloaddition with dienes can also be generated from nitrile oxides with *N*-methylmorpholine *N*-oxide,^[25] by fragmentation of 1,2,4-oxadiazole-4-oxides^[26] and by the rearrangement of nitrocarbenes.^[27]

Scheme 22 Cyclic *N*-Alkoxy Amides by Hetero-Diels–Alder Reactions of In Situ Generated Acyl Nitroso Compounds^[22,293,295]



(4a*S*,5*R*)-5-(*tert*-Butyldiphenylsiloxy)-4a,5,6,7-tetrahydropyrido[1,2-*b*][1,2]oxazin-8(2*H*)-one (144A**); Typical Procedure:**^[293]

A soln of *N*-hydroxy amide **143** (186 mg, 0.454 mmol) in CH₂Cl₂ (5 mL) was added dropwise to a stirred soln of Pr₄NIO₄ (188 mg, 0.498 mmol) in CH₂Cl₂ (10 mL) at -78 °C. The mixture was stirred for 4 h at -78 °C and then allowed to warm to 0 °C over 30 min. The mixture was then diluted with EtOAc (50 mL), washed with sat. aq Na₂SO₃ (2 × 10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, EtOAc/hexanes 3:1) to afford a 2.4:1 mixture of diastereomeric cycloadducts **144A** and **144B** that could be separated by preparative HPLC; combined yield: 180 mg (97%); major isomer **144A**: [α]_D -75.9 (c 3.9, CHCl₃).

21.13.12 **Product Subclass 12:**
N-Sulfonyl and N-Sulfinyl Amides

The chemistry of this product subclass has been reviewed.^[296,297] N-Sulfonyl amides have many potential medicinal applications including as anticancer and anti-HIV drugs.^[298,299] The artificial sweetener saccharin [1,2-benzisothiazol-3(2H)-one 1,1-dioxide]^[300] is perhaps the best known member of this product subclass, and closely related compounds have been investigated as bactericides and enzyme inhibitors.^[301] Other heterocyclic members of this product subclass, particularly N-acylated derivatives of the well-known bornane-10,2-sultam chiral auxiliary (Oppolzer's camphor sultam, 8,8-dimethylhexahydro-3a,6-methano-2,1-benzisothiazole 2,2-dioxide), are used extensively in asymmetric syntheses.^[302,303] N-Sulfinyl amides have also been used in enantioselective synthesis,^[304] including as chiral sulfinyl transfer reagents.^[305]

21.13.12.1 **Synthesis of Product Subclass 12**

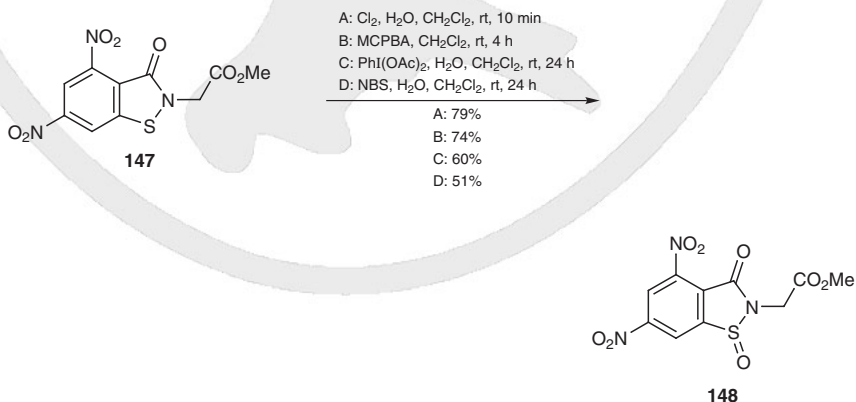
21.13.12.1.1 **Method 1:**
Oxidation of N-Sulfinyl and N-Sulfonyl Amides

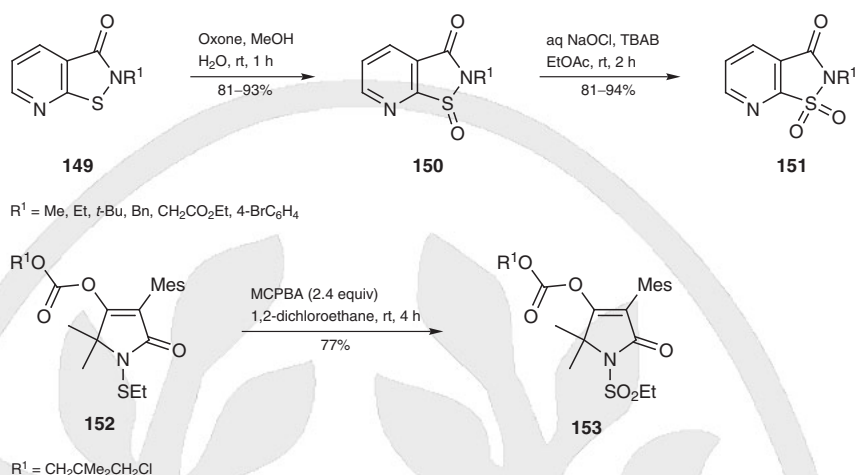
Heterocyclic N-sulfinyl and N-sulfonyl amides, particularly derivatives and analogues of saccharin [1,2-benzisothiazol-3(2H)-one 1,1-dioxide], are commonly prepared by S-oxidation of N-sulfonyl lactams.^[301,306,307] Monooxidation of (1,2-benzisothiazol-2(3H)-yl)acetates, e.g. **147**, to the corresponding (1,2-benzisothiazol-2(3H)-yl)acetate 1-oxides, e.g. **148**, can be achieved with a variety of oxidants (Scheme 23).^[301]

Oxone (2KHSO₅•KHSO₄•K₂SO₄) in aqueous methanol rapidly transforms a number of isothiazolo[5,4-*b*]pyridin-3(2H)-ones **149** to their S-monoxides **150** in excellent yields (Scheme 23).^[306] Over-oxidation of these products is negligible even if excess Oxone is used. The N-sulfinyl lactams **150** can be further converted into the corresponding S,S-dioxide derivatives **151** in similarly excellent yields by treatment with aqueous sodium hypochlorite in a biphasic mixture with tetrabutylammonium bromide as a phase-transfer catalyst.^[306]

Numerous reagent systems are available for the direct conversion of N-sulfonyl into N-sulfonyl amides [e.g., 3-chloroperoxybenzoic acid,^[307,308] peroxyacetic acid,^[309,310] periodic acid (H₅IO₆)/chromium(VI) oxide catalyst,^[311] or ammonium persulfate^[310]]. The exocyclic N-sulfonyl amide **153** is obtained in 77% yield from the N-sulfonyl amide **152** by oxidation with excess 3-chloroperoxybenzoic acid (Scheme 23).^[307] A small quantity of the intermediate N-sulfinyl amide (16%) is also isolated from this reaction.

Scheme 23 Oxidation of N-Sulfonyl and N-Sulfinyl Amides^[301,306,307]



**Isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1-Oxides (150); General Procedure:**^[306]

A stirred soln of an isothiazolo[5,4-*b*]pyridin-3(2*H*)-one **149** (9.0 mmol) in MeOH/H₂O (1:1, 30 mL) at rt was treated portionwise with Oxone (0.83 g, 13.5 mmol of KHSO₄). After stirring for 1 h, the mixture was poured into H₂O (100 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was recrystallized to afford the pure product.

21.13.12.1.2**Method 2:*****N*-Acylation of Sulfonamides and Sulfinamides**

Acylation of sulfonamides and sulfinamides provides a direct and simple route to this product subclass (Scheme 24).^[298,305,312–314] *N*-Unsubstituted sulfonamides undergo acylation under basic conditions with acid chlorides^[315] or carboxylic anhydrides,^[316] and intramolecularly with esters.^[299] Carboxylic acids can also be coupled with *N*-unsubstituted sulfonamides in the presence of a suitable activator, such as dicyclohexylcarbodiimide^[317] or 1,1'-carbonyldiimidazole.^[318]

To avoid the formation of *N,N*-diacylated side products, which are encountered in the base-mediated acylation of *N*-unsubstituted sulfonamides **154**, the *N*-acyl sulfonamides **156** are synthesized by an acid-catalyzed reaction with carboxylic anhydrides **155** (Scheme 24).^[312] This method, which relies on the generation of highly reactive acylium cation intermediates, gives monoacylated products only and it performs equally well for a wide range of substrate types, including some highly hindered examples, e.g. **156** (R¹ = 2,4,6-*i*Pr₃C₆H₂, R² = *t*-Bu), which is obtained in a 90% yield.^[312]

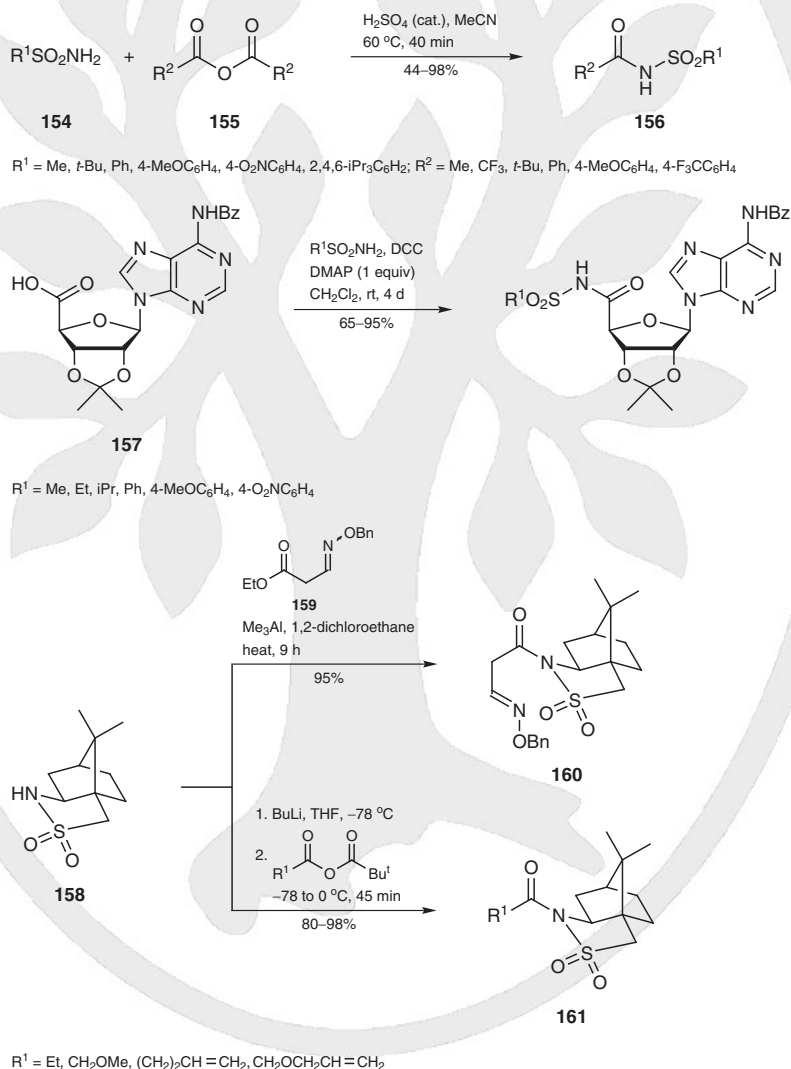
A comparison of a number of methods [1,1'-carbonyldiimidazole/1,8-diazabicyclo[5.4.0]undec-7-ene, oxalyl chloride/potassium hydroxide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/4-(dimethylamino)pyridine (catalyst), dicyclohexylcarbodiimide/4-(dimethylamino)pyridine] for the coupling of the adenosine-derived acid **157** with *N*-unsubstituted sulfonamides shows that this reaction is best accomplished using a reagent combination of dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine.^[298] *N*-Mono-substituted sulfonamides do not react at all with the acid **157** under these conditions.

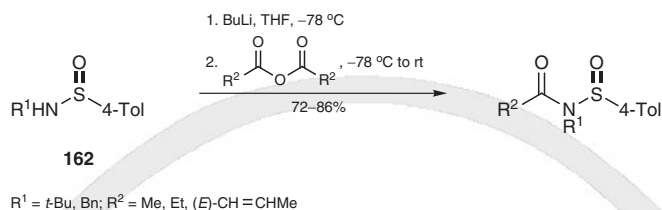
Methods for the preparation of *N*-sulfonyl amides from *N*-monosubstituted sulfonamides are exemplified by protocols successfully developed for the acylation of the sultam **158**, a widely used chiral auxiliary^[302] and a stereotypical substrate. Sultam **158** can be acylated with acid chlorides in the presence of weak bases,^[319] but in most cases acylation is best achieved by deprotonation of **158** with an appropriate strong base before the intro-

duction of the acyl donor, to give sulfonylamides such as **161**. Sodium hydride^[320] and butyllithium^[313] are among the bases commonly used for this purpose. Sultam **158** can also be acylated in excellent yields by esters, e.g. **159**, in the presence of trimethylaluminum to give the corresponding sulfonyl amides, e.g. **160** (Scheme 24).^[314] Similar methods to the above have been applied for the preparation of *N*-sulfinyl amides from sulfinamides.^[304,305,321]

When acylating enantiomerically enriched sulfinamides, care must be exercised to avoid reaction conditions that could lead to epimerization at sulfur. The sulfinamide **162** undergoes racemization when the lithium salt of this compound is acylated by the slow addition of carboxylic anhydrides.^[305] Racemization in this case is ascribed to a ligand-exchange phenomenon at sulfur and can be prevented by the rapid addition of the neat anhydride to the lithiated sulfinamide.^[305]

Scheme 24 Acylation of Sulfonamides and Sulfinamides^[298,305,312–314]





(3aS,6R)-8,8-Dimethyl-1-pent-4-enoylhexahydro-3a,6-methano-2,1-benzisothiazole 2,2-Dioxide [161, $R^1 = (\text{CH}_2)_2\text{CH}=\text{CH}_2$]; **Typical Procedure:**^[313]

A stirred soln. of pent-4-enoic acid (5.70 mL, 5.59 g, 55.8 mmol) and Et_3N (9.2 mL, 6.68 g, 66.1 mmol) in THF (100 mL) at -78°C under N_2 was slowly treated with $t\text{-BuCOCl}$ (6.90 mL, 6.76 g, 55.8 mmol). After 5 min at -78°C , the resulting soln of mixed anhydride was warmed to 0°C and stirred for 1 h.

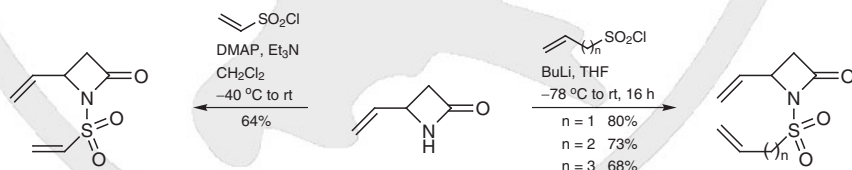
In a second flask, a soln of sultam **158** (12.0 g, 55.7 mmol) in THF (100 mL) was cooled to -78°C , treated with a 2.4 M soln of BuLi in hexanes (23.3 mL, 55.8 mmol) and stirred for 30 min. The soln of the mixed anhydride was cooled to -78°C and then treated rapidly with the cold soln of the N-lithiosultam. Stirring was continued for 15 min at -78°C and then at 0°C until the reaction was complete (TLC, ~30 min). H_2O (100 mL) was added and the aqueous layer was extracted with $t\text{-BuOMe}$. The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, $t\text{-BuOMe}/\text{cyclohexane}$ 1:2) to give a colorless solid; yield: 15.60 g (94%); mp 73°C .

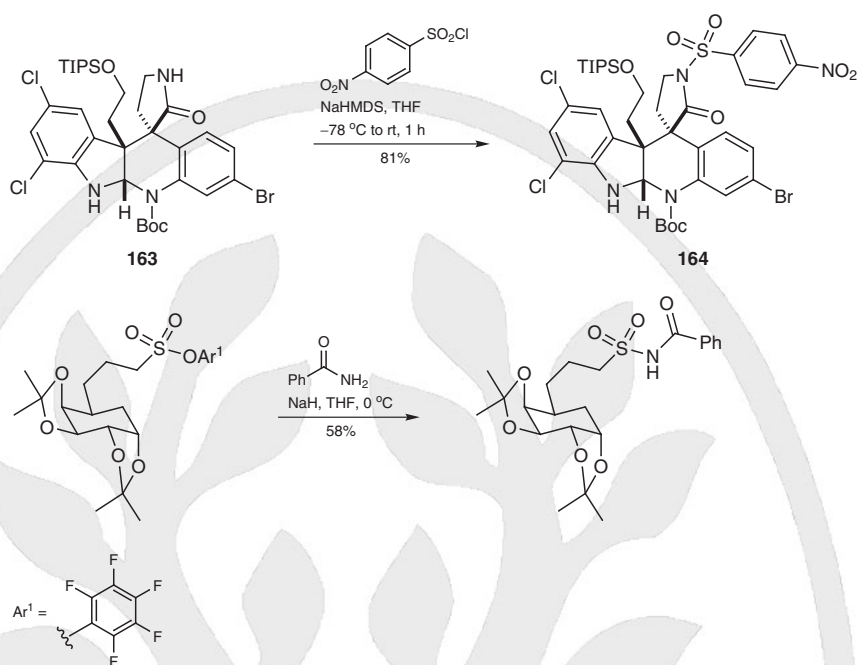
21.13.12.1.3

Method 3:
N-Sulfonylation of Amides

N-Unsubstituted and N-monosubstituted amides react with sulfonyl chlorides in the presence of a base to give the expected N-sulfonylated derivatives.^[322,323] Representative examples of N-sulfonylation are illustrated (Scheme 25).^[324–326] Amide sulfonylation can be achieved with weak bases [e.g., pyridine^[327] or triethylamine/4-(dimethylamino)pyridine^[324]], but in most cases this transformation is better accomplished by deprotonating the substrate at a low temperature with a strong base [e.g., sodium hydride,^[326,328] butyllithium,^[324] lithium hexamethyldisilazane,^[329] or sodium hexamethyldisilazane^[325] (e.g., reaction of **163** to give **164**)] before the introduction of the sulfonylating reagent to the resulting nucleophilic amide anion.

Scheme 25 N-Sulfonylation of Amides^[324–326]





(5aR,10bR,11S)-3-Bromo-5-(*tert*-butoxycarbonyl)-7,9-dichloro-1'-(4-nitrophenylsulfonyl)-10b-[2-(triisopropylsiloxy)ethyl]-5,5a,6,10b-tetrahydro-2'*H*-spiro[indolo[2,3-*b*]quinoline-11,3'-pyrrolidin]-2'-one (**164**); Typical Procedure:^[325]

A stirred soln of lactam **163** (1.34 g, 1.81 mmol) in THF (18 mL) at -78°C was treated dropwise with a 1.0 M soln of NaHMDS in THF (1.99 mL, 1.99 mmol). After 15 min, 4-nitrobenzenesulfonyl chloride (0.482 g, 2.17 mmol) was added and the soln was allowed to warm to rt over 1 h. The reaction was then quenched with H_2O and the mixture was extracted with EtOAc (3 \times). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes 1:9) to give a yellow foam; yield: 1.35 g (81%); IR (neat) $\tilde{\nu}_{\text{max}}$: 3416, 2943, 1714, 1535 cm^{-1} .

21.13.12.1.4

Method 4: Synthesis from *N*-Sulfonyl Isocyanates

N-Sulfonyl amides can be prepared in a number of ways from readily available *N*-sulfonyl isocyanates,^[330,331] such as 4-toluenesulfonyl isocyanate^[332] and chlorosulfonyl isocyanate^[333–335] (Scheme 26).^[336–339]

The decarboxylative condensation reaction of *N*-sulfonyl isocyanates with carboxylic acids, such as **165**, provides a simple and high-yielding synthesis of *N*-sulfonyl amides, e.g. **166** (Scheme 26).^[336,340]

N-Sulfonyl isocyanates react with alkenes to afford either *N*-sulfonyl 2-azetidinone [2+2] cycloadducts or acyclic *N*-sulfonyl amides, depending on the type of substrate and the reaction conditions.^[338] Acyclic amide products are obtained from a variety of nucleophilic alkenes, including enol ethers,^[338,341,342] silyl enol ethers,^[343,344] and enamines.^[337,345,346] The high-yielding carbamoylation of enamine **167** with 4-tosyl isocyanate is an example of this type of formal electrophilic substitution process.^[337] Simple alkenes react with *N*-sulfonyl isocyanates predominantly by the cycloaddition pathway to give *N*-sulfonyl β -lactam products. This reaction can have a high regio- and diastereoselectivity,

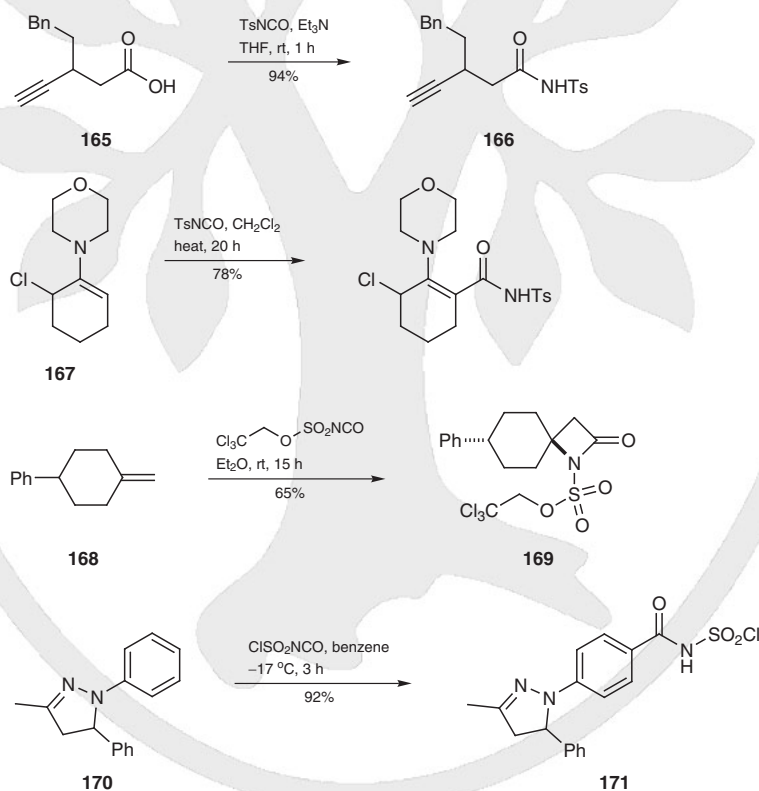
as in the case of the transformation of the alkene **168** to the *N*-sulfonyl amide **169** (Scheme 26).^[338]

The addition of chlorosulfonyl isocyanate to alkenes is particularly important because the resulting *N*-(chlorosulfonyl)-2-azetidinones can be desulfonylated under very mild conditions by reductive hydrolysis without opening of the delicate lactam ring.^[335,347,348] Other types of *N*-sulfonyl-2-azetidinones, for example, *N*-(2,2,2-trichloroethoxy)sulfonyl-2-azetidinones, such as **169**, can also be successfully desulfonylated to yield free β -lactams.^[338]

3,4-Dihydro-2*H*-pyrans react with *N*-sulfonyl isocyanates to give unstable fused bicyclic 2-azetidinones as kinetic products that readily isomerize to form ring-opened compounds.^[338,341,342] The diastereoselective [2+2]-cycloaddition reactions between protected glycols and *N*-sulfonyl isocyanates can be used in the synthesis of β -lactam antibiotics.^[349,350] Allenes, acyclic silyl enol ethers, and silyl ketene acetals also react with *N*-sulfonyl isocyanates to give azetidinone products.^[344,351] *N*-Sulfonyl isocyanates undergo hetero-Diels–Alder reactions with dienyl and heterodienyl systems.^[352,353]

Electron-rich arenes, e.g. **170**, are directly acylated by *N*-sulfonyl isocyanates to yield *N*-sulfonyl benzamides, e.g. **171** (Scheme 26).^[339,354,355] Less-reactive aromatic compounds give benzamides with these reagents under Friedel–Crafts-type conditions.^[356] *N*-Sulfonyl benzamides are also obtained by the addition of aryl Grignard reagents to *N*-sulfonyl isocyanates.^[357,358]

Scheme 26 Syntheses of *N*-Sulfonyl Amides from *N*-Sulfonyl Isocyanates^[336–339]



***N*-Tosyl-3-(2-phenylethyl)pent-4-ynamide (**166**); Typical Procedure:**^[336]

A stirred soln of the acid **165** (0.85 g, 4.2 mmol) in THF (5 mL) at rt was treated with TsNCO (0.70 mL, 0.90 g, 4.6 mmol), followed by the addition of Et₃N (0.59 mL, 0.43 g, 4.3 mmol),

which caused the immediate evolution of CO₂. After stirring for 30 min at rt, H₂O (1 mL) and Et₂O (50 mL) were added and the mixture was washed successively with 1 M aq HCl and brine. The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, Et₂O/hexanes 1:1) to give a viscous oil; yield: 1.40 g (94%); IR (CCl₄) $\tilde{\nu}_{\text{max}}$: 2116, 1727 cm⁻¹.

21.13.13 Product Subclass 13: N-Sulfanyl Amides

Reviews of sulfenamide chemistry contain pertinent information concerning this product subclass.^[359–361] N-Sulfanyl amides are used as precursors to synthetically useful amidyl radicals^[362,363] and as mild reagents for sulfanylation.^[359] 1-(Phenylsulfanyl)azepan-2-one is a superior promoter for the electrophilic activation of thioglycoside donors with trifluoromethanesulfonic anhydride.^[364] Heterocyclic derivatives of this product subclass have potential as pharmaceutical agents, particularly 1,2-benzisothiazolin-3-ones, which exhibit high antibacterial and antifungal activities.^[365,366]

21.13.13.1 Synthesis of Product Subclass 13

Aside from the following methods, members of this product subclass have also been prepared from N-chloro amides and sulfur nucleophiles.^[161,367]

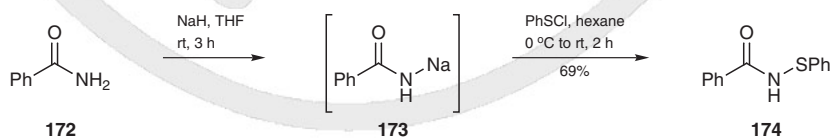
21.13.13.1.1 Method 1: N-Sulfanylation of Amides

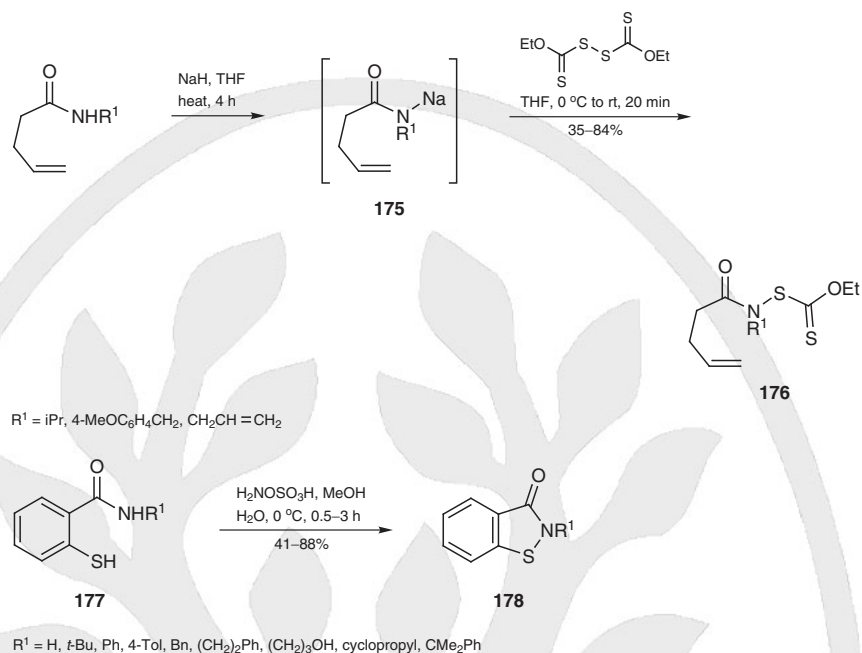
This product subclass can be oxidatively generated from amides with a variety of sulfanylation agents, including sulfanyl chlorides and dicarbonyldisulfanes (Scheme 27).^[363,368,369] Simple monofunctional amides, such as N-methylacetamide^[362] and pivalamide,^[368] can be successively sulfanylated on nitrogen with benzenesulfenyl chloride in the presence of triethylamine. For amides possessing other potential sites for electrophilic sulfanylation, such as alkenyl^[362] and aryl amides (e.g. **172**),^[368] chemoselective N-sulfanylation is best achieved at low temperatures by exploiting the enhanced nucleophilicity of their N-metalated derivatives, e.g. **173**, as shown by the synthesis of **174**.^[368]

A number of alkenyl N-xanthyl amides **176** can be prepared by treatment of the appropriate N-sodiated amides **175** with 1,1'-[disulfanediy]bis(carbonylsulfanedioxy)]diethane (Scheme 27).^[363] Radical chain reactions of these xanthates, initiated by lauroyl peroxide in refluxing 1,2-dichloroethane, give pyrrolidinone products resulting from 5-*exo-trig* amidyl radical cyclization followed by intermolecular xanthate group transfer.^[363]

N-Substituted 1,2-benzisothiazolin-3-ones **178** can be prepared by a chlorine-free route using oxidative cyclization of thiosalicylamides **177** with either hydroxylamine-O-sulfonic acid or chloramine-T.^[369] With hydroxylamine-O-sulfonic acid, cyclization occurs through transamination of intermediate sulfenamides.

Scheme 27 Sulfanylation of Amides^[363,368,369]



**N-(Phenylsulfanyl)benzamide (174); Typical Procedure:**^[368]

A soln of BzNH₂ (**172**, 200 mg, 1.65 mmol) in anhyd THF (15 mL) at rt was treated with NaH (79 mg, 60 wt% dispersed in oil, 2.00 mmol) and the resulting mixture was stirred for 3 h. The mixture was cooled to 0 °C and treated in one portion with a soln of freshly distilled PhSCl (290 mg, 2.00 mmol) in anhyd hexane (1 mL). After stirring for 2 h at rt, Et₃N (0.5 mL) was added and stirring was continued for a further 30 min. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography [silica gel, EtOH/benzene (**CAUTION: carcinogen**) 1:99] to give a solid that was recrystallized (benzene/hexane); yield: 260 mg (69%); mp 123–124 °C (benzene/hexane).

21.13.13.1.2

Method 2:**N-Acylation of Sulfenamides**

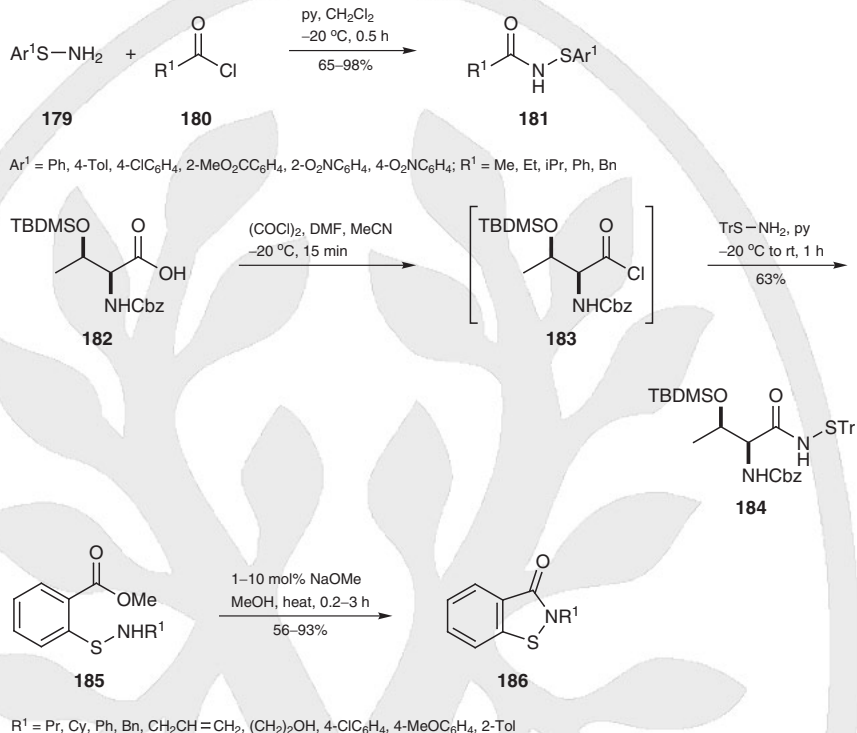
N-Sulfanyl amides can be prepared in good yields by acylation of sulfenamides (Scheme 28).^[370–372] Acylation does not necessarily follow a simple course: alkenyl and aryl sulfenamides react with acetic anhydride to afford disulfenylamines rather than N-sulfanyl acetamide products [i.e., 2R¹SNHR² + Ac₂O → (R¹S)₂NR² + AcNHR² + AcOH]^[359] Analogous behavior occurs with other acylating agents.^[370,373] The formation of disulfenylamines can be largely avoided and N-sulfanyl amides can be obtained in good yields if acylation is conducted at sub-ambient temperatures with reactive acyl donors, such as perfluorocarboxylic anhydrides or acid chlorides.^[370]

Arenesulfenamides **181**, which exist in equilibrium with their imidate tautomers, can be efficiently prepared by low-temperature acylation of sulfenamides **179** with a range of acid chlorides **180** (Scheme 28).^[370] The N-sulfanyl amide **184** cannot be obtained directly from the threonine derivative **182** using carbodiimide methodology, but can be obtained via the acid chloride **183**.^[371]

Intramolecular acylation of sulfenamides is easily controlled and 1,2-benzisothiazolin-3-ones **186** are obtained by straightforward base-catalyzed lactamization of sulfen-

amides **185** derived from thiosalicylate esters.^[372] N-Unsubstituted 1,2-benzisothiazolin-3-ones can be prepared in an analogous manner.^[374]

Scheme 28 Acylation of Sulfenamides^[370–372]



N-Sulfanyl Amides **181**; General Procedure:^[370]

A stirred soln of an arenesulfenamide **179** (0.5 mmol) and pyridine (60 mg, 0.75 mmol) in CH₂Cl₂ (6 mL) at –20 °C was treated with an acid chloride **180** (0.6 mmol). The mixture was stirred for 30 min and then the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (silica gel, EtOAc/CH₂Cl₂ 1:19 to 9:81 gradient) to afford the pure N-sulfanyl amide **181**.

21.13.14

Product Subclass 14: N-Nitro and N-Nitroso Amides

N-Nitro and N-nitroso amides are grouped here into a single product subclass, as they exhibit comparable reactivity and are obtained by analogous synthetic methods. Their chemistry has been reviewed.^[147,244] Both types of amide generally undergo nucleophilic attack at the carbonyl group and readily engage in acyl substitution reactions with a variety of nucleophiles.^[375] An example of this reactivity mode, the basic hydrolysis of N-alkyl N-nitroso amides, provides a well-known synthesis of diazoalkanes through tautomerization/dehydration of the resulting N-alkyl-N-nitrosoamine nucleofuge.

As expected, N-nitro amides are more reactive toward nucleophiles than are N-nitroso amides;^[375] however, N-nitro amides possess a greater thermal stability than the related nitroso compounds. N-Nitroso amides rearrange, with loss of nitrogen, at ambient temperatures to generate ester or carboxylic acid products (lactones are produced from N-nitroso lactams).^[376,377] The analogous rearrangement from N-nitro amides is also possible but requires slightly higher temperatures and longer reaction times.^[378] Stable N-nitro

and *N*-nitroso derivatives of *N*-unsubstituted amides are very unusual (most such compounds spontaneously deaminate to give carboxylic acids), and the majority of isolable compounds belonging to this product subclass are formally derived from *N*-monosubstituted amides.

SAFETY: *N*-Nitroso amides are potent carcinogens and proper care should be taken during their preparation and handling to eliminate the possibility of exposure.

21.13.14.1 Synthesis of Product Subclass 14

Besides the preparative methods outlined in Sections 21.13.14.1.1 and 21.13.14.1.2, *N*-nitro and *N*-nitroso amides are occasionally prepared by the respective acylation reactions of *N*-nitro and *N*-nitroso *N*-alkyl metal amides with acid chlorides.^[379,380]

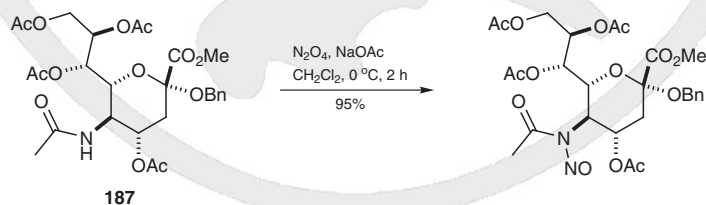
21.13.14.1.1 Method 1: Nitration and Nitrosation of Amides

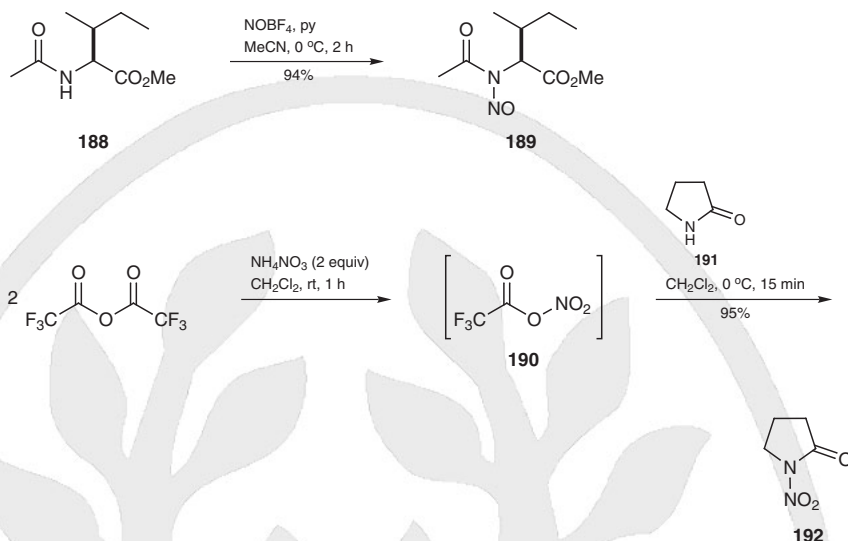
N-Nitroso amides are typically prepared by direct nitrosation of *N*-monosubstituted amides with a suitable source of the nitrosonium cation or its synthetic equivalent. The transformation is often achievable in near-quantitative yield and without interference from neighboring functional groups. Dinitrogen tetroxide (N_2O_4) is a superior reagent for this purpose,^[381] and amides, e.g. **187**, are rapidly nitrosated by a stream of this gas below 0°C in the presence of anhydrous sodium acetate (Scheme 29).^[382] Dinitrogen tetroxide is commercially available or, alternatively, it can be conveniently prepared by the action of concentrated nitric acid on copper wire.^[375]

Some hindered amides react sluggishly, if at all, with dinitrogen tetroxide, and potentially recalcitrant substrates are best nitrosated with a reagent combination of nitrosonium tetrafluoroborate and pyridine.^[383] Thus, methyl *N*-acetyl-L-isoleucinate (**188**), which fails to give any *N*-nitroso amide after prolonged treatment with dinitrogen tetroxide, is converted into the nitroso derivative **189** in near-quantitative yield by the nitrosonium salt-based protocol (Scheme 29).^[383] Nitric oxide (NO)^[384] and calixarene-encapsulated nitrosonium cations^[385] are also suitable reagents for the nitrosation of amides.

Nitration of amides is harder to achieve than nitrosation, and such reactions often give side products or else fail to go to completion. Various sources of a nitronium electrophile can be used for this purpose [e.g., nitric pentoxide (N_2O_5), nitrosonium tetrafluoroborate (NOBF_4), nitric acid/acetic anhydride, or copper(II) nitrate/acetic anhydride];^[375] however, trifluoroacetyl nitrate (**190**), prepared in situ from ammonium nitrate and trifluoroacetic anhydride, provides by far the best results.^[386] The nitration of pyrrolidin-2-one (**191**) with this reagent gives the *N*-nitro amide derivative **192** in 95% yield (Scheme 29).

Scheme 29 Nitrosation and Nitration of Amides^[382,383,386]





Methyl N-Acetyl-N-nitroso-L-isoleucinate (**189**); Typical Procedure:^[383]

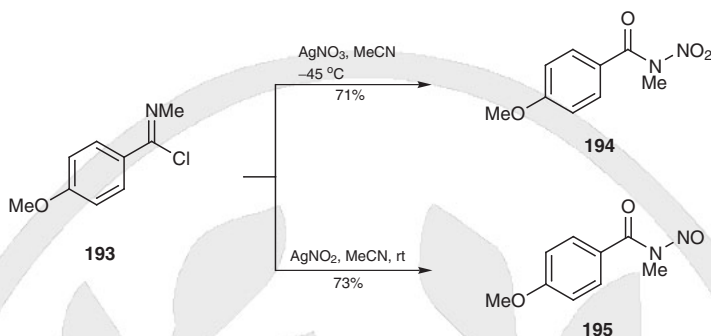
CAUTION: N-Nitroso amides are potent carcinogens and proper care should be taken during their preparation and handling to eliminate the possibility of exposure. Nitrosyl tetrafluoroborate is irritating to the eyes, respiratory system, and skin.

A stirred soln of methyl N-acetyl-L-isoleucinate (**188**; 187 mg, 1.0 mmol) and anhyd pyridine (163 μL , 160 mg, 2.0 mmol) in MeCN (5 mL) at -20°C was treated with NOBF_4 (232 mg, 2.0 mmol). The resulting mixture was allowed to warm to 0°C and stirred for 2 h. CH_2Cl_2 and ice were then added, followed by cold H_2O . The layers were separated and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure without heating. The residue was purified by chromatography (silica gel) to give a yellow oil; yield: 203 mg (94%).

21.13.14.1.2 Method 2: Synthesis from Imidoyl Chlorides

The addition of silver nitrate or silver nitrite to imidoyl chlorides **193** provides a convenient synthesis of N-nitro and N-nitroso amides, respectively (Scheme 30).^[387] The reactions proceed via putative imidoyl nitrates and nitrites (formed by nucleophilic displacement of chloride) that rapidly isomerize to the desired amide products. The method is particularly advantageous for the synthesis of N-nitro amides that bear electron-rich arene groups; attempted syntheses of the same targets by direct amide nitration, as described in Section 21.13.14.1.1, results in unwanted ring nitration.^[388] The electron-rich imidoyl chloride **193** is converted into N-nitro amide **194** in 71% yield with silver nitrate; the same substrate is transformed into the N-nitroso amide **195** in 73% yield by treatment with silver nitrite (Scheme 30).

The synthesis of N-nitro amides by the addition of silver nitrate to imidoyl chlorides can be complicated by the formation of small quantities of N-nitroso amides. The mechanism for this side reaction is not well understood; however, it is suppressed at lower temperatures and in the absence of light.^[389]

Scheme 30 *N*-Nitro and *N*-Nitroso Amides from Imidoyl Chlorides^[387]

Conversion of Imidoyl Chlorides **193 into *N*-Nitro Amides **194** or *N*-Nitroso Amides **195**; General Procedure:**^[387]

An imidoyl chloride **193** (1–10 mmol) was added to a stirred soln of either AgNO_2 (for *N*-nitroso amide synthesis) (1 equiv) or AgNO_3 (for *N*-nitro amide synthesis) (1 equiv) in MeCN (25 mL) at rt or -45°C , respectively, with exclusion of light. After stirring for 30 min, the mixture was filtered and concentrated under reduced pressure to afford the corresponding crude *N*-nitro amide **194** or *N*-nitroso amide **195** (as appropriate). These were further purified by column chromatography (silica gel).

21.13.15

Product Subclass 15:
Acyl Hydrazones

Acyl hydrazones are crystalline materials that were once used extensively for the identification and purification of carbonyl compounds.^[390] Members of this product subclass also serve as synthetic surrogates for imines^[391,392] and as precursors for the syntheses of heterocycles.^[393–397] Acyl hydrazones possess a good electrophilicity at the imine-like carbon atom and are easier to prepare and more stable toward hydrolysis than are the analogous Schiff bases. Enantioselective addition to acyl hydrazones is facilitated by their ability to offer two-point binding to chiral metal reagents. This chelation mode provides ordered transition-state assemblies and can lead to the attainment of a high enantioselectivity.^[392,398,399] The addition of nucleophiles to acyl hydrazones to give hydrazides is discussed in Section 21.13.16.1.4.

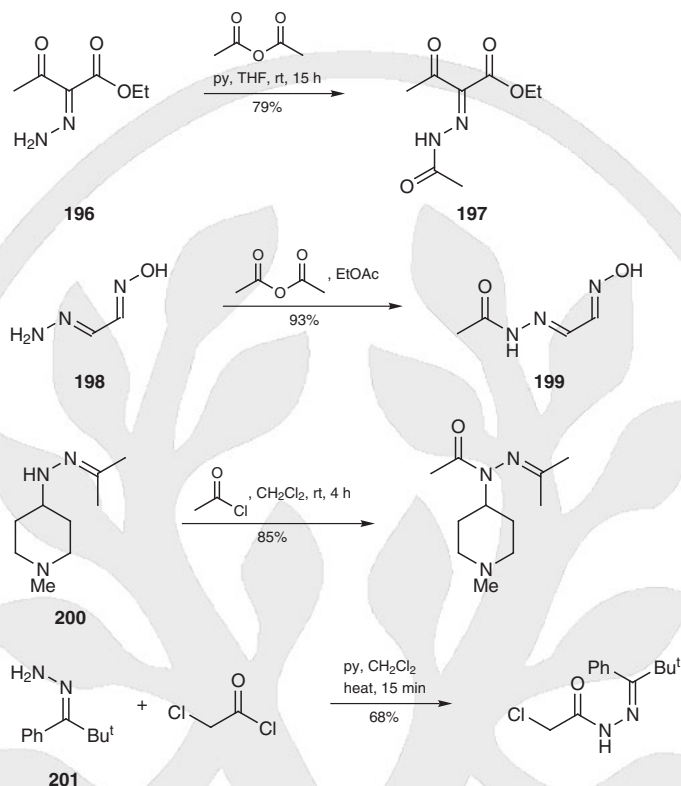
21.13.15.1

Synthesis of Product Subclass 15

21.13.15.1.1

Method 1:
Acylation of Hydrazones

Hydrazones, such as **196**, derived from either aldehydes or ketones react with common acylating agents, such as acid chlorides and carboxylic anhydrides, to give the expected acyl hydrazone products, e.g. **197** (Scheme 31).^[394] *N*-Unsubstituted hydrazones can usually be cleanly monoacylated; however, the use of excess acylating agent can lead to the formation of *N*,*N*'-diacylated hydrazones^[400] or isomeric 2,3-dihydro-1,3,4-oxadiazoles.^[393] Hydrazone amino groups are powerful neutral nucleophiles and can be selectively acylated in the presence of other heteroatoms. The mixed oxime hydrazone derived from glyoxal **198** is acetylated on the hydrazone amino group with complete chemoselectivity to give acyl hydrazone **199** in 93% yield: this can subsequently be transformed into 1,2,3-triazole.^[396] Hindered hydrazones, such as **200** and **201**, can also be acylated in good yields with acid chlorides.

Scheme 31 Acylation of Hydrazones^[394,396,401,402]**Ethyl 2-(Acetylhydrazono)-3-oxobutanoate (197); Typical Procedure:**^[394]

A soln of the hydrazone **196** (300 mg, 1.90 mmol) in THF (5 mL) at rt was treated with Ac₂O (0.20 mL, 214 mg, 2.10 mmol) and pyridine (0.17 mL, 170 mg, 2.15 mmol). The resulting soln was stirred overnight, then diluted with EtOAc (30 mL) and washed successively with 0.1 M aq HCl (20 mL) and H₂O (30 mL). The organic phase was concentrated under reduced pressure and purified by column chromatography (silica gel, hexane/CHCl₃/THF 6:2:1) to give a solid; yield: 300 mg (79%); mp 70–74 °C.

21.13.15.1.2

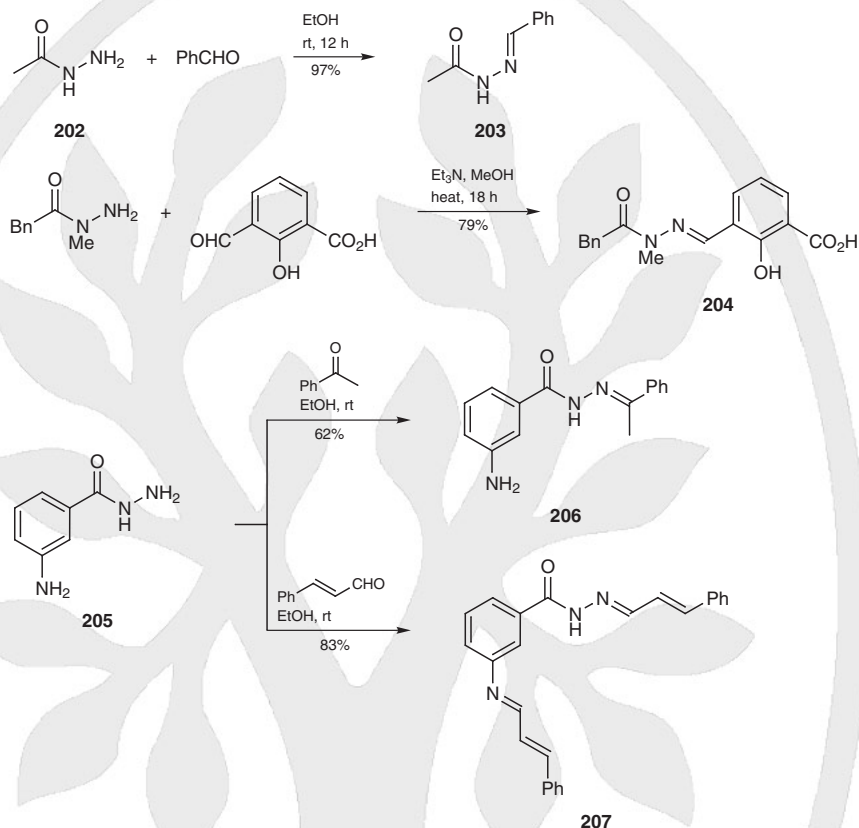
Method 2:**Synthesis from Hydrazides and Carbonyl Compounds**

Condensation reactions between N^β-unsubstituted hydrazides and carbonyl compounds proceed readily to afford acyl hydrazones, e.g. **203**, in excellent yields.^[390] In many cases, for example acetohydrazide **202** and benzaldehyde, no acid catalyst is needed for dehydrative coupling to take place and the reactants are simply mixed together in an appropriate solvent, usually ethanol (Scheme 32).^[392] Both aldehydes and ketones are suitable substrates for the reaction and an N^α-substituent on the hydrazide is tolerated, for example in the preparation of the N-acylhydrazone **204**.^[403]

The hydrazide amino group is a powerful nucleophile and chemoselectivity for reaction at this site in the presence of other amino groups is possible. For example, aniline **205** reacts preferentially at the hydrazide amine with acetophenone to give hydrazone **206** in 62% yield.^[404] Treating the same compound with an excess of cinnamaldehyde resulted in reaction at both amino groups to afford iminohydrazone **207** in 83% yield (Scheme 32).

The condensation of unsubstituted hydrazides with 1,3-dicarbonyl compounds provides a synthesis of acyl pyrazoles;^[405] similar reactions lead to other heterocyclic systems with embedded acyl hydrazone motifs.

Scheme 32 Formation of Acyl Hydrazones from Hydrazides and Carbonyl Compounds^[392,403,404]



N'-Benzylideneacetohydrazide (203); Typical Procedure:^[392]

A soln of AcNHNH₂ (**202**; 2.50 g, 33.8 mmol) in EtOH (70 mL) was treated with PhCHO (3.50 mL, 3.64 g, 34.3 mmol) and the mixture was stirred for 12 h at rt. The mixture was then concentrated in vacuo, and the residue was purified by column chromatography (silica gel, acetone/CH₂Cl₂ 1:9 to 3:17 gradient) to give a colorless solid; yield: 5.32 g (97%).

21.13.16

**Product Subclass 16:
Hydrazides**

The chemistry of hydrazides (acyl hydrazines) is fairly extensive and the older literature has been thoroughly reviewed.^[390,406] Members of this product class often exhibit biological activity (e.g., isonicotinohydrazide is a tuberculostatic), and hydrazides are common target molecules. They also constitute a group of versatile synthetic intermediates: for example, hydrazides are used extensively as precursors to acyl azides for use in peptide synthesis (see Section 21.13.4),^[88] whereas reductive cleavage of the hydrazino bond under dissolving-metal conditions provides a convenient entry to amines.^[407] Hydrazides can also be used as precursors to acyl radicals.^[408]

21.13.16.1 Synthesis of Product Subclass 16

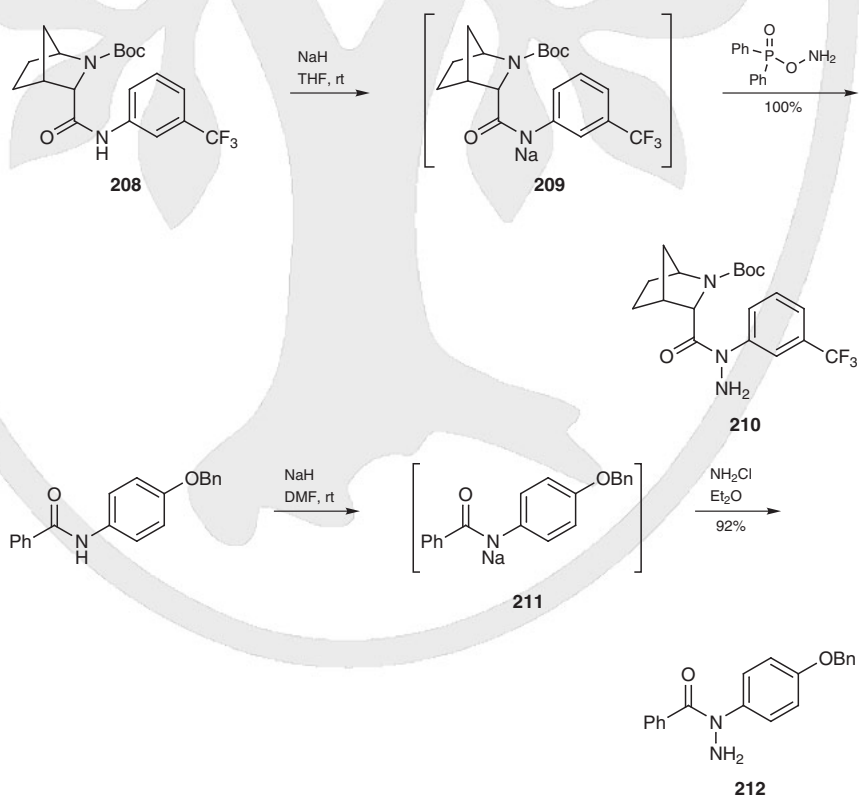
Notable methods for the preparation of members of this product subclass that are not listed below include nucleophilic amination of *N*-chloro amides,^[409] [3 + 2] cycloaddition between glyoxylic ester derived acyl hydrazones and alkenes,^[397] and [2 + 2] cycloaddition between ketenes and hydrazones.^[410]

21.13.16.1.1 Method 1:
Electrophilic Amination of Amides

Hydrazides are generally available in good yields by the oxidation of *N*-monosubstituted amides with hydroxylamine-based electrophilic amination reagents such as hydroxylamine-*O*-sulfonic acid,^[411,412] *O*-(mesitylenesulfonyl)hydroxylamine,^[413,414] or *O*-(diphenylphosphinyl)hydroxylamine.^[415] The last reagent can be used to prepare hydrazide **210** in a quantitative yield from the sodiated anilide **209**, prepared from the amide **208** and sodium hydride, the *tert*-butyloxycarbonyl amine-protecting group survives under these conditions (Scheme 33).^[416]

Other nitrenium cation equivalents can also be used to prepare hydrazides. For example, chloramine, which can be conveniently prepared in situ from domestic bleach (sodium hypochlorite) and ammonium hydroxide can be used to prepare the *N*-amino anilide **212** in 92% yield from the amide sodium derivative **211** on a 0.25-mol scale.^[417]

O-(4-Nitrobenzoyl)hydroxylamine is a superior electrophilic amination reagent for the preparation of *N*-amino-2-oxazolidinones from Evans-type chiral auxiliaries.^[418] The findings of Shen and Fristad, which pertain to the preparation of *N*-aminocarbamates, are also likely to be applicable to the preparation of hydrazides from amides.

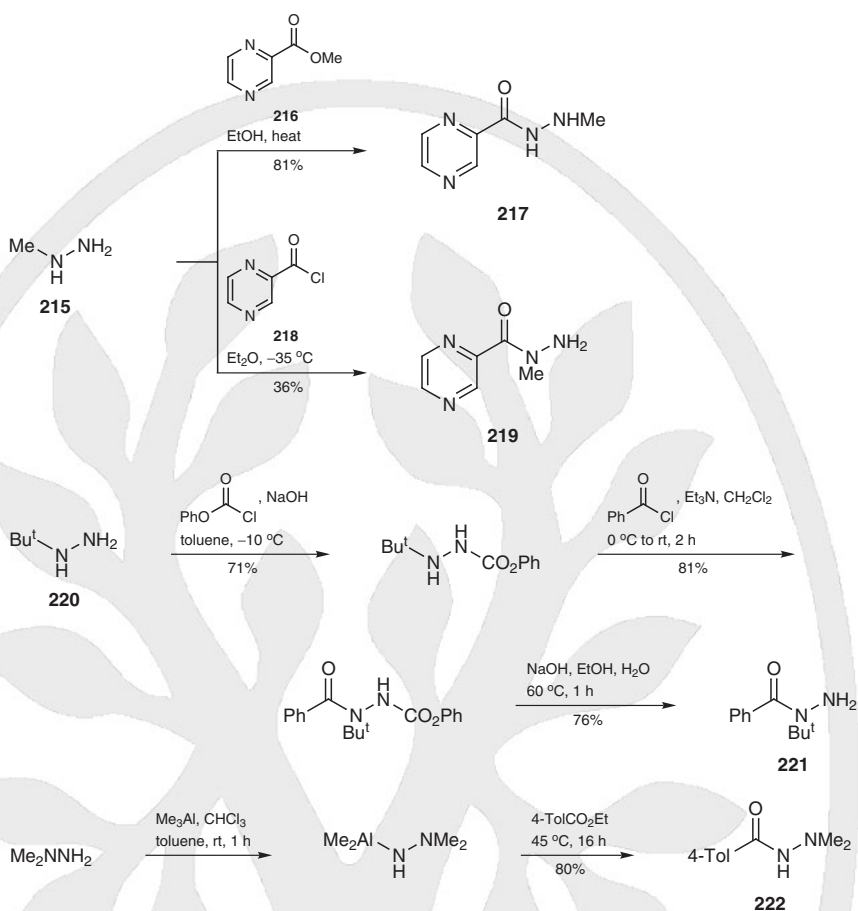
Scheme 33 Electrophilic Amination of *N*-Monosubstituted Amides^[416,417]

2-(tert-Butoxycarbonyl)-N-(4-trifluoromethylphenyl)-2-azabicyclo[2.2.1]heptane-3-carbohydrazide (210); Typical Procedure:^[416]

A soln of amide **208** (308 mg, 0.80 mmol) in THF (15 mL) was treated with NaH (38 mg of 60 wt% oil dispersion, 0.95 mmol), and the mixture was stirred for 15 min at rt. $\text{Ph}_2\text{P}(\text{O})\text{ONH}_2$ (224 mg, 0.96 mmol) was then added and stirring was continued for a further 1 h. H_2O was added and the mixture was extracted with CH_2Cl_2 . The combined organic extracts were dried and concentrated under reduced pressure to give a semi-solid that could be used without further purification; yield: 319 mg (100%).

21.13.16.1.2 Method 2: Acylation of Hydrazine Derivatives

The acylation of hydrazine and its derivatives provides a straightforward and much exploited route to hydrazides; this chemistry has been reviewed.^[55,419] Unsubstituted hydrazides are readily available from the reactions of hydrazine hydrate with a wide variety of carboxy compounds. Because of the high nucleophilicity of hydrazine, suitable acyl donors need not be particularly electrophilic, and even amides will react with hydrazine to give hydrazides, albeit only at high temperatures.^[55] The hydrazinolysis of esters in an alcohol solvent generally gives very good yields of hydrazides, e.g., benzohydrazide (**214**) is obtained in 88% yield from methyl benzoate (**213**) by this simple method (Scheme 34).^[408]



Benzohydrazide (214); Typical Procedure:^[408]

A stirred soln of methyl benzoate (**213**; 0.20 mL, 219 mg, 1.61 mmol) in MeOH (1.1 mL) was treated with $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$ (0.32 mL, 330 mg, 6.60 mmol) and refluxed for 6 h. The mixture was then concentrated under reduced pressure. The residue was dissolved in EtOAc (20 mL), washed with brine (20 mL), dried (MgSO_4), and then concentrated again under reduced pressure to give a colorless crystalline solid; yield: 193 mg (88%); mp 109–113 °C.

21.13.16.1.3

Method 3: Reductive Processes

Hydrazides can be obtained by chemoselective reduction of *N*-acyl hydrazones, *N*-acyl diazenes, or *N*-nitroso amides. The transformation of *N*-acyl hydrazones to *N*-hydrazides can be accomplished with a variety of reagents without unwanted reduction at the carbonyl group or cleavage of the hydrazino linkage. Common sources of nucleophilic hydride, such as sodium borohydride^[426] or sodium cyanoborohydride,^[403] give good results. Ionic reduction with a reagent combination of triethylsilane and trifluoroacetic acid is also possible.^[427]

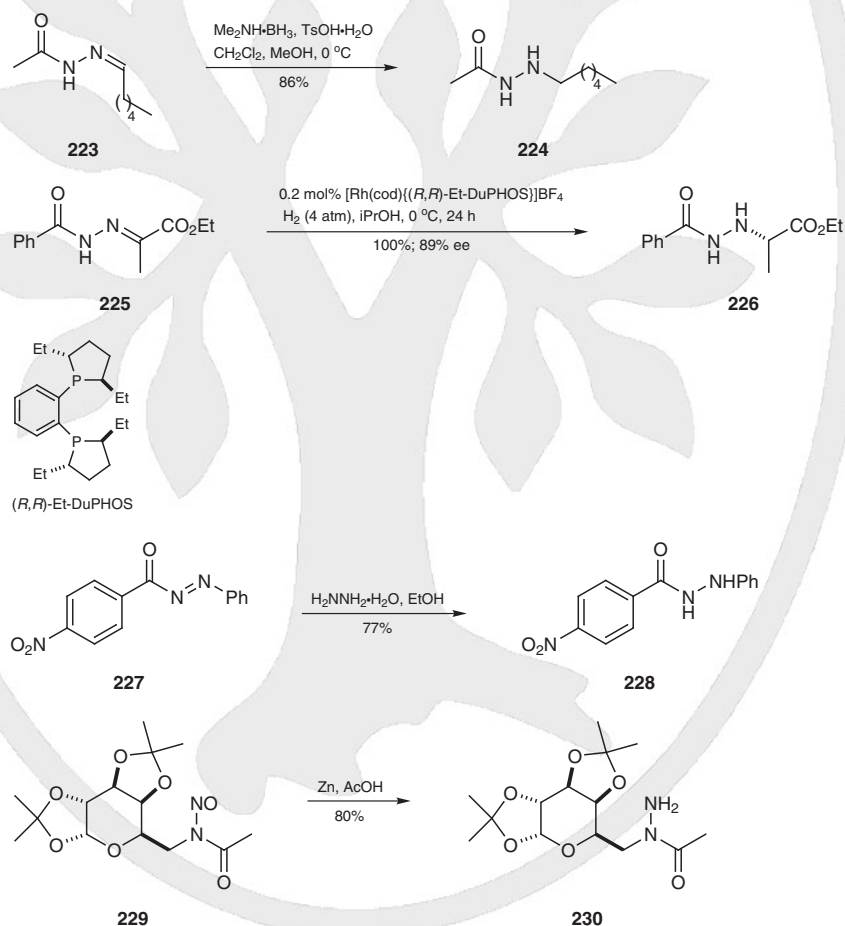
The reduction of *N*-acyl hydrazones, e.g. **223**, by dimethylamine–borane complex in the presence of 4-toluenesulfonic acid gives excellent yields of the expected hydrazides, e.g. **224** (Scheme 35).^[428] The selective 1,2-reduction of α,β -unsaturated *N*-acyl hydrazones to give allylic hydrazides is also possible.^[428]

The imine bond of *N*-acyl hydrazones can be selectively reduced by transition-metal-catalyzed hydrogenation: palladium,^[429] platinum,^[430] nickel,^[431] and rhodium^[432] are all effective catalysts for this purpose. A highly chemoselective and enantioselective procedure for the preparation of nonracemic chiral hydrazides involves the hydrogenation of *N*-acyl hydrazones catalyzed by a cationic rhodium complex of (2*R*,5*R*,2'*R*,5'*R*)-1,1'-(1,2-phenylene)bis(2,5-diethylphospholane) [(*R,R*)-Et-DuPHOS].^[433] For reasonable enantioselectivity to be achieved, the *N*-acyl hydrazone substrate must possess a free NH group. The reduction of the oxo ester-derived *N*-benzoylhydrazone **225** by this method gives the hydrazide **226** in a quantitative yield and 89% ee (Scheme 35). The hydrazide **226** can be further converted into (*S*)-(+)-alanine in two steps.

Hydrazides are less commonly prepared by the reduction of *N*-acyl diazenes^[434] and *N*-nitroso amides.^[435] The chemoselective reduction of acyl diazene **227** with hydrazine hydrate gives the hydrazide **228** without concomitant reduction of the nitro group.^[434]

Zinc in acetic acid is the most effective reagent combination for effecting the transformation of *N*-nitroso amides, e.g. **229**, to hydrazides, e.g. **230**.^[435]

Scheme 35 Hydrazides by Reduction of *N*-Acyl Hydrazones, *N*-Acyl Diazenes, or *N*-Nitroso Amides^[428,433–435]



***N*'-Hexylacetohydrazide (224); Typical Procedure:**^[428]

A stirred soln of hydrazone **223** (156 mg, 1.0 mmol) and $\text{Me}_2\text{NH}\cdot\text{BH}_3$ (94 mg, 1.6 mmol) in CH_2Cl_2 (2 mL) at 0°C was treated with TsOH (1.14 g, 6.6 mmol) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (3:1, 2 mL).

After 30 min, 10 wt% aq Na_2CO_3 (6 mL) and MeOH (2 mL) were added and the mixture was refluxed for a further 30 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 . The combined organic phases were dried (MgSO_4) and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, Et_2O /hexanes) to give a colorless oil; yield: 136 mg (86%); IR (neat) $\tilde{\nu}_{\text{max}}$: 1648 cm^{-1} .

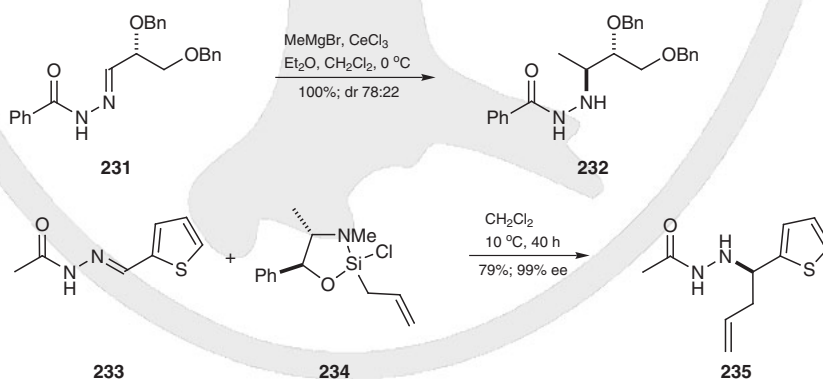
21.13.16.1.4

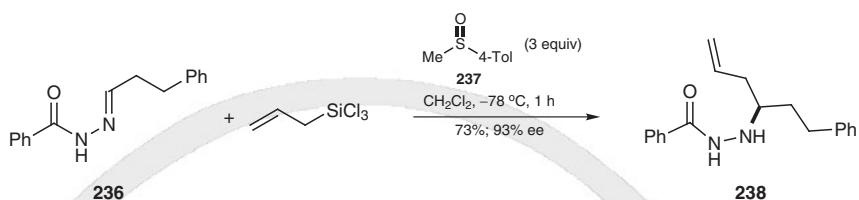
Method 4:**Addition of Carbon-Centered Nucleophiles to N-Acyl Hydrazones**

Substituted hydrazides are available by addition of carbon nucleophiles to the electrophilic imine moiety of N-acyl hydrazones.^[436] A variety of stereocontrolled versions of this type of reaction are available that enable the synthesis of enantiomerically enriched chiral hydrazides. The glyceraldehyde-derived N-acyl hydrazone **231** is a versatile synthon for the preparation of α -hydrazino acids (Scheme 36).^[437] Addition of methylmagnesium bromide to hydrazone **231** in the presence of cerium(III) chloride occurs with reasonable diastereoselectivity to afford 72% of the *anti*-hydrazide **232**, after separation from its minor *syn*-epimer.^[437]

Acetyl hydrazones undergo a practical, reagent-controlled, asymmetric allylation reaction with the chiral allylsilane **234**.^[392] The allylsilane **234** is readily prepared from allyltrichlorosilane and pseudoephedrine; large quantities (>100 g) of this relatively inexpensive reagent can be prepared in a single batch. Allylation with allylsilane **234** is possible on a reasonable scale and a high enantioselectivity is obtainable for hydrazones derived from aromatic aldehydes; e.g. the allylation of hydrazone **233** (5 g) with allylsilane **234** gives the hydrazide **235** in 79% yield and with 99% ee after recrystallization (the enantiomeric excess is 89% before recrystallization) (Scheme 36).^[392]

A variety of useful and innovative catalytic methods are available for the production of enantiomerically enriched hydrazides from acyl hydrazones.^[438,439,391] For example, methyl 4-tolyl sulfoxide (**237**) acts as a neutral coordinating organocatalyst in promoting the enantioselective addition of allyltrichlorosilane to benzoyl hydrazones.^[439] The chiral sulfoxide promoter is used in a stoichiometric quantity, but can be recovered from the reaction mixture. Benzoyl hydrazones derived from nonconjugated aldehydes are superior substrates for this reaction, e.g. hydrazone **236** is converted into the hydrazide **238** in 73% yield and with 93% ee, with recovery of sulfoxide **237** in over 90% yield (Scheme 36). An analogous crotylation reaction is also available.^[439]

Scheme 36 Stereocontrolled Nucleophilic Addition to N-Acyl Hydrazones^[439,437,392]



N'-[(R)-1-(2-Thienyl)but-3-en-1-yl]acetohydrazide (235); Typical Procedure:^[392]

A soln of allylsilane **234** (9.90 g, 37.0 mmol) in CH₂Cl₂ (300 mL) at 10 °C was treated with hydrazone **233** (5.0 g, 29.7 mmol) and stirred for 40 h. MeOH (40 mL) was added and stirring was continued for 15 min. The mixture was then partitioned between EtOAc (150 mL) and H₂O (500 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with H₂O (2 × 200 mL) and brine (200 mL), then dried (MgSO₄) and concentrated under reduced pressure. The residue was dissolved in boiling toluene (50 mL) and the resulting soln was allowed to cool to rt. Pentane (200 mL) was layered on top of the toluene soln and the mixture was allowed to stand at rt overnight. The resulting precipitate was collected by filtration, washed with pentane/toluene (5:1), and dried to give colorless crystals; yield: 4.94 g (79%); [α]_D +178.0 (c 1.0, CHCl₃).

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Product Class 14: Acylphosphorus Compounds

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General Introduction

This product class has not been reviewed previously in the *Houben–Weyl* series. Up until 1996, only two seminal reviews on acylphosphorus compounds were published,^[1,2] and another review on oxo phosphonates appeared in 2002.^[3] This section covers material regarding the synthesis and applications of acylphosphorus compounds since the 1996 review.^[2]

The unique reactivity pattern of acylphosphorus compounds is evident in the array of applications for which they have been utilized. Acylphosphorus compounds have been widely employed for the generation of phosphorus-containing analogues of biologically active compounds. In addition to their significance as biological analogues, acylphosphorus compounds, and most specifically, acylphosphonates, have been applied to the synthesis of non-phosphorus-containing substrates. An increased interest in the unique reactivity of the acylphosphonate subclass of acylphosphorus compounds is indicative of their broad applicability. As a result of this focused interest in acylphosphonates, the bulk of the work in the realm of acylphosphorus chemistry, subsequent to previous reviews, has been aimed at this product subclass. This section is therefore centered on newer methods for the preparation and reactions of acylphosphonates. A brief section on the synthesis and applications of tricoordinate acylphosphorus compounds is also included.

21.14.1

Product Subclass 1: Tetracoordinate Acylphosphorus Compounds

The unique reactivity of acylphosphonates, owing to their particular physical properties, is evident in the renewed interest in this class of compounds as reagents and synthetic intermediates. Some key features include the *s-trans* relationship between P=O and C=O, which is the lowest energy conformer, the lower pK_a values α to the carbonyl, and the instability of the C—P bond toward hydrolytic and acidic conditions. This high reactivity requires careful handling procedures to avoid product decomposition via hydrolysis and rearrangement pathways. The interesting reactivity pattern of acylphosphonates is largely dependent on the phosphorus substituents. The commonest methods for assembling acylphosphonates include the Arbuzov reaction of an acyl chloride with a trialkyl phosphite and the oxidation of α -hydroxy phosphonates. α -Hydroxy phosphonates can be readily generated from the Pudovik reaction of an aldehyde with a trialkyl phosphite. Examples of oxidations of α -hydroxy phosphonates, however, are much less prevalent in the literature than Arbuzov reactions and also lack broad applicability.

21.14.1.1

Synthesis of Product Subclass 1

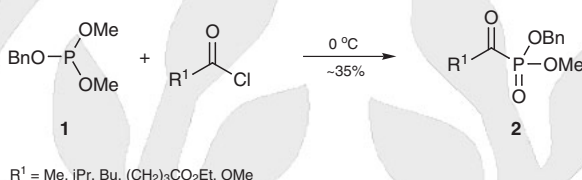
21.14.1.1.1

Method 1: The Arbuzov Reaction: Acylation of Phosphorus(III) Compounds

The most general approach to this subclass of compounds is the Michaelis–Arbuzov reaction of trialkyl or triaryl phosphites with acyl chlorides; it remains the most widely employed route for the generation of acylphosphonates (see Sections 21.14.1.2.1.3,

21.14.1.2.2.3, 21.14.1.2.3.1, 21.14.1.2.7, and 21.14.1.2.7.2). While having been extensively studied, areas of interest remain. One area of continued investigation is the generation of nonsymmetrically substituted acylphosphonates from mixed phosphite precursors.^[4] This method requires differentiated reactivity between the different phosphite substituents. For example, treatment of benzyl dimethyl phosphite (**1**) with an acid chloride gives a mixture of symmetric and nonsymmetric acylphosphonates, separable by distillation, resulting in the nonsymmetric acylphosphonate **2** in moderate yield (Scheme 1).^[4]

Scheme 1 Nonsymmetric Acylphosphonates via the Arbuzov Reaction^[4]



Benzyl Methyl Acylphosphonates **2**; General Procedure:^[4]

An acid chloride (1 equiv) was added to benzyl dimethyl phosphite (**1**; 1 equiv) under a stream of N_2 (**CAUTION: the reaction is very exothermic**), at a temperature maintained between -10 and 0 °C. At the end of the addition, the mixture was stirred for 2 h at rt until the alkyl chloride was completely released. The symmetric acylphosphonate, $\text{R}^1\text{COPO(OMe)}_2$, was separated out by distillation. The nonsymmetric acylphosphonate **2** was then extracted with Et_2O , and recovered in the form of a colorless liquid upon removal of the solvent; yield: ca. 35%.

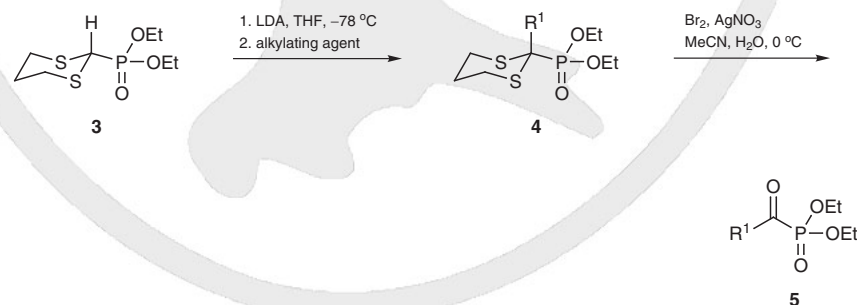
21.14.1.1.2

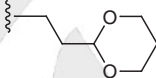
Method 2:

Dithiane Alkylation, Followed by Hydrolysis

While Swern and analogous oxidations are known to be viable nonmetal routes to acylphosphonates,^[5–7] alternative routes have been reported. Alkylation of (dialkoxyphosphoryl)dithianes such as **3** under basic conditions provides substituted masked oxo phosphonates **4** (Scheme 2).^[8] Hydrolysis of the dithioketals **4** with bromine and silver nitrate in aqueous acetonitrile gives an array of acylphosphonates **5** in good yield. This method provides a mild, nonthermal alternative to metal-promoted oxidations (see Section 21.14.1.1.3) allowing for broad functional group compatibility.

Scheme 2 Acylphosphonates by Dithiane Alkylation, Followed by Hydrolysis^[8]



R ¹	Yield (%) of 4	Yield (%) of 5	Ref
Me	78	78	[8]
Et	76	79	[8]
(CH ₂) ₅ Me	74	80	[8]
(CH ₂) ₂ CH=CH ₂	74	76	[8]
Bn	80	77	[8]
CH ₂ CO ₂ Et	81	74	[8]
	34	77	[8]

Diethyl Acylphosphonates **5**; General Procedure from Dithiane **3**:^[8]

CAUTION: Bromine is a severe irritant of the eyes, mucous membranes, lungs, and skin. Liquid bromine causes severe and painful burns on contact with eyes and skin.

A commercially available soln of LDA in hexane/THF (0.02 mol) was added to a stirred soln of diethyl 1,3-dithian-2-ylphosphonate (**3**; 2.56 g, 0.01 mol) in THF (20 mL) maintained under anhydrous conditions at -78°C . After 5 min the alkylating agent was added (0.02 mol) and the mixture was stirred for 30 min before being warmed to rt. H₂O (10 mL) was added, and the organic products were extracted with Et₂O (2 \times 10 mL) and dried (MgSO₄). The concentrated product **4** was purified by column chromatography; yield: 34–81%.

AgNO₃ (0.760 g, 4.5 mmol) was added to a stirred soln of Br₂ (0.64 g, 4.0 mmol) in MeCN (20 mL) at 0°C and the mixture was stirred to form a suspension. A mixture of MeCN (2 mL) and H₂O (2 mL) was added, followed by the diethyl 2-alkyl-1,3-dithian-2-ylphosphonate **4** (1.0 mmol). The soln was stirred for 30 min at 0°C and then allowed to warm to rt and stirred for an additional 30 min. The soln was filtered and to the filtrate was added 10% aq NH₄OAc (10 mL) and 10% aq Na₂S₂O₃ (10 mL). The aqueous layer was extracted with Et₂O (3 \times 20 mL) and the combined extracts were washed with brine (20 mL) and H₂O (20 mL), and dried (MgSO₄). The product **5** was obtained upon removal of the solvent under reduced pressure; yield: 74–80%.

21.14.1.1.3

Method 3:

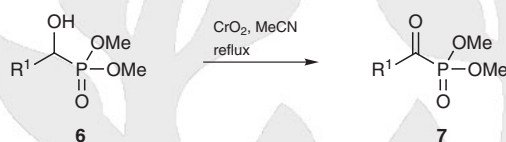
Metal-Mediated Oxidations of α -Hydroxy Phosphonates

While the assembly of acylphosphonates via the Arbuzov reaction represents a rapid approach toward this class of compounds (see Section 21.14.1.1.1), the Arbuzov reaction can be problematic for systems containing alternate electrophilic sites (e.g., β,γ -unsaturated acylphosphonates) and cases where the products may be unstable to acid or thermal conditions.^[2] In order to circumvent these problems, methods focusing on the oxidation of generally more stable α -hydroxy phosphonates have been developed. The α -hydroxy phosphonate precursor can be readily derived from the Pudovik reaction of an aldehyde with a trialkyl phosphite. Oxidation procedures have utilized a variety of metal-mediated approaches under various conditions, ranging from both homogeneous/heterogeneous to solvent-free conditions. Nonmetal routes include the Parikh–Doering, Pfitzner–Moffatt, and Swern oxidations.^[5–7] These methods provide milder reaction conditions and avoid the use of excess amounts of toxic metal oxidants. Ongoing research in this area has been spurred by the necessity for reactions requiring less substrate specificity. Common problems encountered include retro-Pudovik reactions, in addition to rearrangements of the α -hydroxy phosphonate precursors.

21.14.1.1.3.1

**Variation 1:
Heterogeneous Reactions**

Heterogeneous oxidations are an attractive approach to acylphosphonates due to the ease of post-reaction workup which, depending on reaction completion, can be as simple as filtration. Earlier work has shown manganese(IV) oxide in toluene to be suitable conditions for the oxidation of di-*tert*-butyl hydroxy(phenyl)methylphosphonates.^[9] Subsequently reported conditions, such as chromium(IV) oxide in refluxing acetonitrile, result in quantitative conversions of **6** into the acylphosphonates **7** with improved functional group compatibility (Scheme 3).^[10] Potassium permanganate in benzene at room temperature is effective for the oxidation of aryl-substituted α -hydroxy phosphonates in good to excellent yield.^[11]

Scheme 3 Acylphosphonates via Heterogeneous Oxidation of α -Hydroxy Phosphonates^[10]

R ¹	Conversion (%)	Ref
	100	[10]
Cy	85	[10]
CH ₂ CH ₂ Ph	50	[10]
CH=CHMe	100	[10]
CH=CHPh	100	[10]
	87	[10]
Ph	100	[10]
4-BrC ₆ H ₄	100	[10]
	100	[10]

Dimethyl Acylphosphonates 7; General Procedure for Chromium(IV) Oxide Oxidations:^[10]

An α -hydroxy phosphonate **6** was refluxed in MeCN with CrO_2 (20–30 equiv). Upon completion of the reaction, the mixture was filtered to remove the insoluble metal oxides and the solvent was removed by evaporation; conversion: 50–100%.

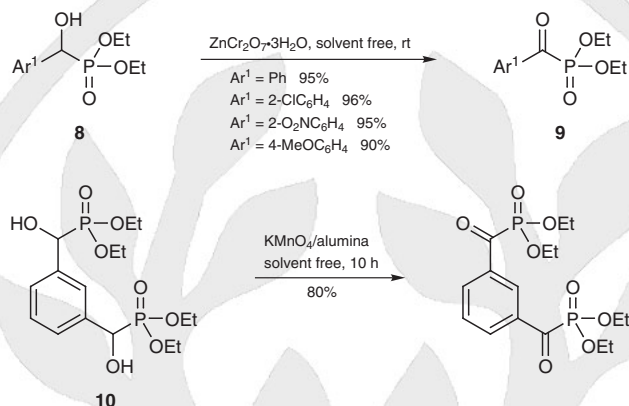
21.14.1.1.3.2

**Variation 2:
Solvent-Free Reactions**

As with heterogeneous reaction conditions (see Section 21.14.1.1.3.1), solvent-free conditions provide ease of purification and mild reaction conditions compared to their homogeneous counterparts. Under solvent-free conditions both zinc and chromium reagents, as well as potassium permanganate/alumina, are suitable oxidants for a variety of substi-

tuted α -hydroxy phosphonates, e.g. **8** and **10** (Scheme 4).^[12,13] Using microwave irradiation, alumina-supported chromium(IV) oxide under solvent-free conditions is also capable of oxidizing allyl-, aryl-, and aliphatic-substituted α -hydroxy phosphonates under very short reaction times and in excellent yields.^[14]

Scheme 4 Acylphosphonates via Solvent-Free Oxidations of α -Hydroxy Phosphonates^[12,13]



Diethyl Aroylphosphonates **9**; General Procedure for Zinc Dichromate Oxidations:^[12]

A mixture of an α -hydroxy phosphonate **8** (5 mmol) and $\text{ZnCr}_2\text{O}_7 \cdot 3\text{H}_2\text{O}$ (5 mmol) was ground together in a mortar with a pestle. The reaction occurred immediately, and the mixture was washed with CCl_4 ($4 \times 15 \text{ mL}$) (**CAUTION: toxic**) and dried (Na_2SO_4). The solvent was removed to give the crude product. The pure product **9** was obtained by vacuum distillation; yield: 90–96%.

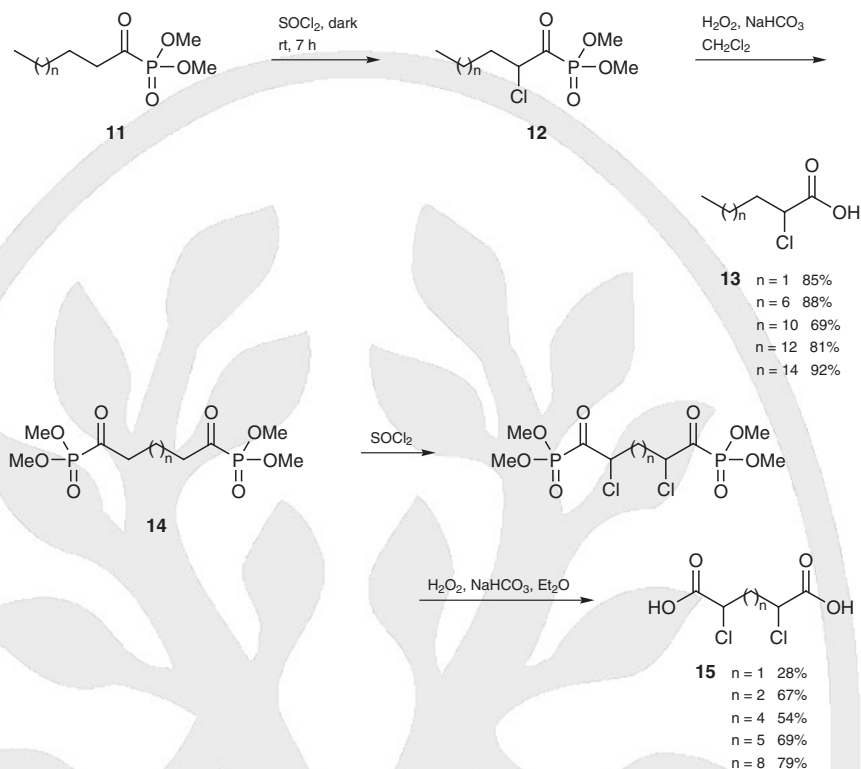
21.14.1.2 Applications of Product Subclass 1 in Organic Synthesis

21.14.1.2.1 Method 1: Halogenation Reactions of Acylphosphonates

Halogenated acylphosphonates are of relative importance in agrochemistry^[15,16] and flotation chemistry.^[17] Methods for the chlorination of fatty acids have included UV light mediated chlorination with thionyl chloride in the presence of benzoyl peroxide and pyridine, and chlorination with gaseous chlorine at high temperatures in the presence of various additives to either promote or inhibit radical formation. A problem associated with many of these methods is that the alkyl chain is indiscriminately chlorinated. Therefore, attempts have been made to selectively chlorinate such entities. A successful approach uses in situ chlorination of acylphosphonates as the key step.

21.14.1.2.1.1 Variation 1: Formation of α -Chloro Carboxylic Acids

An efficient method for the monochlorination of fatty acids has been developed,^[18] where α -chlorinated fatty acids are prepared via in situ chlorination of acylphosphonates **11** using thionyl chloride (Scheme 5). The resulting chloro product **12** can be cleaved to the corresponding α -chlorinated fatty acid **13** using hydrogen peroxide and sodium hydrogen carbonate. Reactions are typically contaminated with more than 5% of the α,α -dichlorinated acid, with overall yields of 55–92% for monochlorination. The advantage of this method is that only very mild conditions are required to generate the α -chloro carboxylic acids, with limited amounts of byproducts.

Scheme 5 α -Chloro Carboxylic Acids via the Chlorination of Acylphosphonates^[18,19]

Similarly, bis(acylphosphonates) **14** can be successfully bis(α -monochlorinated) before being converted into the diacids **15**. In addition to the generation of α -chlorinated fatty acids, dichlorinated acids, as well as α -mono- and α,α' -dichlorinated amides, can be generated using similar strategies.^[19]

α,α' -Dichloroalkanedicarboxylic Acids **15**; General Procedure:^[19]

CAUTION: Trimethyl phosphite is flammable and has a powerful, obnoxious odor. It can induce headaches and is a severe skin and eye irritant. It is also corrosive, and irritating to the respiratory tract.

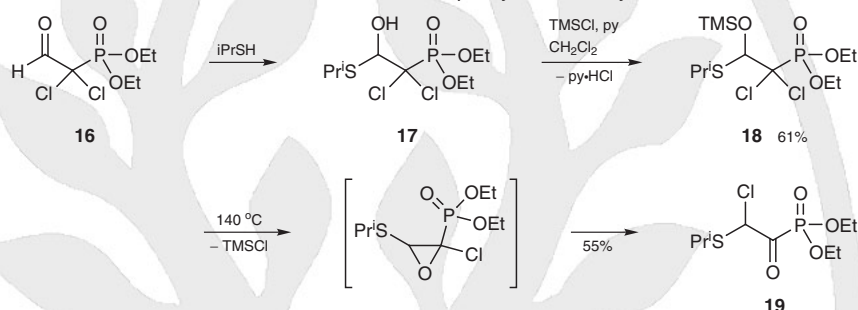
CAUTION: Thionyl chloride reacts violently with water producing large volumes of corrosive gases. It is extremely destructive to all tissues.

In a round-bottomed flask, $\text{P}(\text{OMe})_3$ (32.3 mmol) was added to the diacid dichloride (15 mmol) under a N_2 atmosphere at 0°C . After stirring the mixture for 4 h at rt, excess phosphite and the remaining CH_2Cl_2 were removed under reduced pressure. The flask was covered with Al foil and SOCl_2 (39 mmol) was added by syringe at 0°C . The mixture was stirred for 14 h at rt. The chlorination was stopped by adding dry CH_2Cl_2 (5 mL) and bubbling N_2 through the soln to expel excess SOCl_2 with the remaining HCl and SO_2 . The soln was then added to a mixture of 35% H_2O_2 in H_2O (39 mmol), NaHCO_3 (39 mmol), and Et_2O (10 mL) in a 50-mL round-bottomed flask at 0°C . After stirring for 16 h at rt, the mixture was poured into 0.1 M HCl (20 mL) and extracted with Et_2O (20 mL). The organic layer was dried (MgSO_4), filtered, and the Et_2O was evaporated. Purification of the mixture was performed by crystallization (CH_2Cl_2 and EtOAc) to give pure **15**; yield: 28–79%.

21.14.1.2.1.2

Variation 2:**Selective Chlorination of α -Phosphorylated Aldehydes**

α -Phosphorylated aldehydes are important because of their applications in the preparation of α -monohalogenated acylphosphonates. A method for selectively chlorinating α -phosphorylated aldehydes has been reported (Scheme 6).^[20] Starting with diethyl 1,1-dichloro-2-oxoethylphosphonate (**16**) and subjecting it to propane-2-thiol produces thiohemiacetal **17**, which is further transformed to silyl ether **18** in the presence of chlorotrimethylsilane and pyridine. When heated to 140 °C, α -oxo phosphonate **19** is formed. It is believed that an unstable oxirane intermediate is formed which undergoes rearrangement to generate the acylphosphonate.

Scheme 6 Selective Chlorination of an α -Phosphorylated Aldehyde^[20]**Diethyl Chloro(isopropylsulfanyl)acetylphosphonate (**19**):^[20]**

Propane-2-thiol (1.5 g, 19.7 mmol) was added dropwise while mixing at 0–5 °C to diethyl 1,1-dichloro-2-oxoethylphosphonate (**16**; 5 g, 20.1 mmol). The mixture was stirred for 2 h at rt. Thiohemiacetal **17** was obtained. Following the addition of pyridine (1.6 g, 20.2 mmol) and anhyd CH_2Cl_2 (25 mL), the mixture was cooled to 0 °C and TMSCl (2.3 g, 21.2 mmol) was added dropwise while mixing. The mixture was kept overnight and the residue was separated. Fractional distillation of the residue gave silyl ether **18** as a colorless oil; yield: 4.8 g (61%); bp 124–125 °C/1 Torr.

Silyl ether **18** (4 g, 10 mmol) in *o*-xylene (15 mL) was refluxed for 8 h. The solvent was removed under reduced pressure. Product **19** was obtained as a pale yellow liquid by fractional distillation of the residue; yield: 55%; bp 104–105 °C/0.08 Torr.

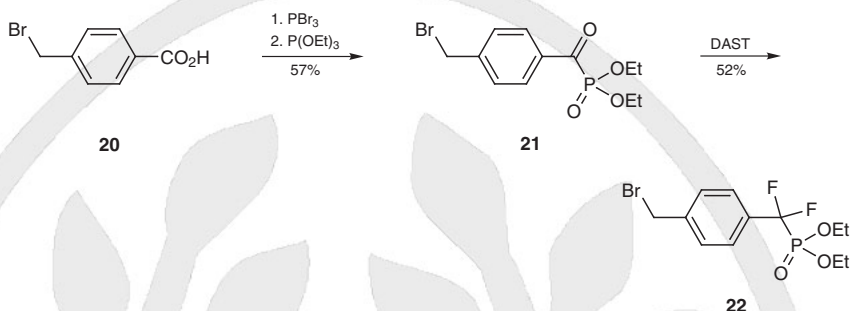
21.14.1.2.1.3

Variation 3:**Fluorination of Acylphosphonates**

Fluorination of acylphosphonates has been used for the study of biological phosphate mimics and other therapeutic applications.^[21,22] Generation of such (fluoroalkyl)phosphonates is shown in Scheme 7. α,α -Difluorination of an acylphosphonate is achieved through the use of a large excess of *N,N*-diethylaminosulfur trifluoride en route to 4-[(dihydroxyphosphoryl)difluoromethyl]-*N* $^\alpha$ -(9-fluorenylmethoxycarbonyl)-L-phenylalanine as analogues of nonhydrolyzable *O*-(dihydroxyphosphoryl)tyrosine for use in peptide synthesis.^[23] Starting with a carboxylic acid such as **20**, treatment with phosphorus tribromide provides an acid bromide which is converted into the α -oxo phosphonate **21** via the Arbuzov reaction (see Section 21.14.1.1.1). Due to the unstable nature of the phosphonate, it is immediately treated with a large excess of *N,N*-diethylaminosulfur trifluoride to give the desired difluorinated phosphonate **22**. Subsequent alkylation at the benzyl bromide position with an imino lactone produces a 4-[(dihydroxyphosphoryl)difluoromethyl]-*N* $^\alpha$ -(9-fluorenylmethoxycarbonyl)-L-phenylalanine analogue. α -Fluorinated propargyl-

phosphonates can be generated in a similar manner using *N,N*-diethylaminosulfur trifluoride.^[24]

Scheme 7 Formation and Fluorination of an Acylphosphonate^[24]



Diethyl [4-(Bromomethyl)phenyl]difluoromethylphosphonate (22**):**^[24]

DAST (10 mL, 0.08 mol) was added to ice-cold diethyl [4-(bromomethyl)benzoyl]phosphonate (**21**; 1.8 g, 5.4 mmol). After stirring at rt overnight, the mixture was diluted with CH_2Cl_2 (40 mL) and then added dropwise to an ice-cold soln of Na_2CO_3 (100 mL). The CH_2Cl_2 layer was separated and dried (Na_2SO_4), and the solvent was removed by rotary evaporation to give **22**; yield: 1 g (52%).

21.14.1.2.2

Method 2:

Condensation of Acylphosphonates with Amines and Hydrazines, and Subsequent Reactions

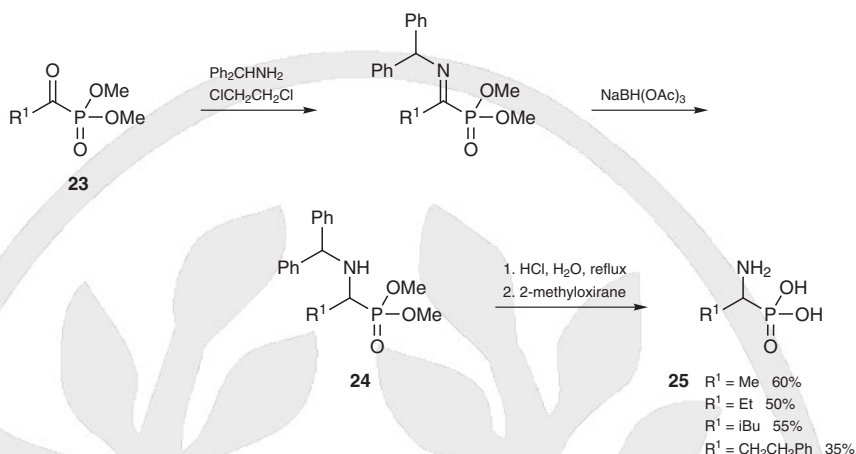
Condensation of amines and hydrazines with the carbonyl of α -oxo phosphonates allows access to pyrazolylphosphonates as well as α -amino-substituted phosphonic acids. The significance of these compounds is exemplified by their wide range of uses as medicinal and agricultural therapeutics.^[25]

21.14.1.2.2.1

Variation 1:

Reductive Amination

Condensation of acylphosphonates **23** with diphenylmethanamine, followed by sodium triacetoxyborohydride-mediated reduction, provides α -amino phosphonates **24** (Scheme 8). Subsequent phosphonate/amine deprotection leads to the formation of α -amino phosphonic acids **25**.^[26] These reactions are compatible with a number of polar, aprotic solvents including dichloromethane, tetrahydrofuran, and chloroform. When performed with benzylamine and α -methylbenzylamine, phosphate elimination provides the corresponding amides as the sole product.

Scheme 8 Reductive Amination of Acylphosphonates^[26]**(1-Aminoalkyl)phosphonic Acids 25; General Procedure:**^[26]

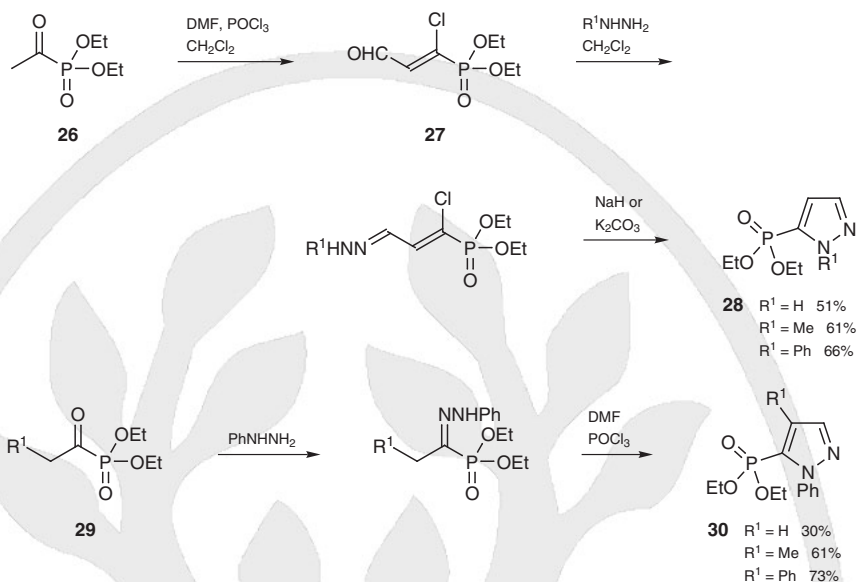
To a soln of an acylphosphonate **23** (4 mmol) in 1,2-dichloroethane (20 mL) was added Ph_2CHNH_2 (4 mmol), which was followed by stirring at rt for 1 h. $\text{NaBH}(\text{OAc})_3$ (8 mmol) was added and the mixture was left overnight. The soln was washed with sat. Na_2HPO_4 soln, dried (MgSO_4), and the solvent was removed under reduced pressure. The obtained oil was purified by column chromatography (silica gel, Et_2O then $\text{Et}_2\text{O}/\text{MeOH}$ 19:1) to give the diethyl 1-(diphenylmethanamino)alkylphosphonates **24**.

The crude diethyl 1-(diphenylmethanamino)alkylphosphonate **24** was dissolved in concd HCl and the mixture was refluxed for 4 h. After filtration, the solvent was removed and the resulting dense oil was dissolved in MeOH . The final product was precipitated by the addition of 2-methyloxirane and then a fivefold amount of acetone. The product was recrystallized ($\text{H}_2\text{O}/\text{MeOH}$ or $\text{H}_2\text{O}/\text{MeOH}/\text{acetone}$) to give acid **25**; overall yield: 35–60%.

21.14.1.2.2.2

Variation 2:**Pyrazoles via the Vilsmeier–Haack Reaction**

Treatment of an acylphosphonate, e.g. diethyl acetylphosphonate (**26**), with the Vilsmeier–Haack reagent (DMF/POCl_3) stereospecifically provides (*Z*)-1-chloro-3-oxoprop-1-enylphosphonate **27** (Scheme 9). Small amounts of tautomerization could be achieved upon refluxing in ethyl acetate to provide a 93:7 ratio of *Z/E*-isomers.^[27] Subsequent condensation of **27** with hydrazines in the presence of either sodium hydride or potassium carbonate provides substituted pyrazolylphosphonates **28**. Alternatively, treatment of acylphosphonates with hydroxylamines and guanidines provides isoxazolylphosphonates and pyrimidinylphosphonates, respectively. Condensation of acylphosphonates **29** with hydrazine prior to treatment with dimethylformamide/phosphoryl chloride also successfully affords pyrazole products **30** (Scheme 9).^[28,29]

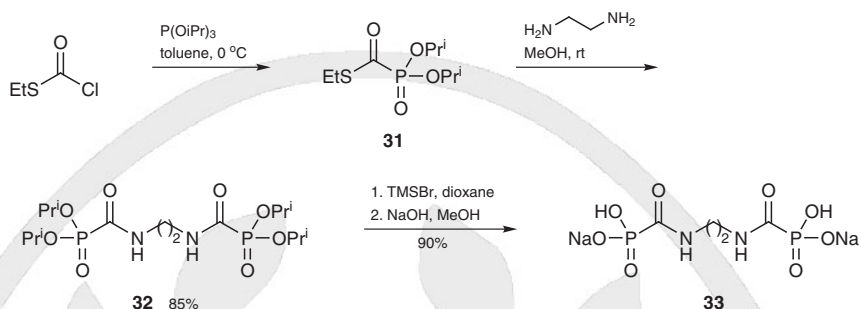
Scheme 9 Pyrazoles via the Vilsmeier–Haack Reaction of Acylphosphonates^[27–29]**Diethyl 1H-Pyrazol-5-ylphosphonates 28; General Procedure:**^[27]

DMF (0.12 mol) in CH_2Cl_2 (5 mL) was added dropwise to POCl_3 (0.12 mol) in CH_2Cl_2 (15 mL) at 5–10 °C under a N_2 atmosphere. The mixture was then stirred at 30 °C for 30 min. Diethyl acetylphosphonate (**26**; 0.02 mol) in CH_2Cl_2 (5 mL) was added dropwise at 15 °C. The mixture was stirred at 35 °C for 30 h. The mixture was poured onto crushed ice (150 g) and stirred at rt for 3 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with sat. brine (50 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography or preparative chromatography (silica gel, EtOAc/petroleum ether 1:6 or 3:1) to give isolat-*E*- and *Z*-isomers of 1-chloro-3-oxoprop-1-enylphosphonate **27**; yield: not reported.

R^1NHNH_2 (0.5 mmol) in CH_2Cl_2 (0.5 mL) was added to diethyl 1-chloro-3-oxoprop-1-enylphosphonate (**27**; 0.5 mmol) in CH_2Cl_2 (0.5 mL) at 20 °C. The mixture was kept at 30 °C for 2 h and subjected to preparative chromatography (EtOAc/petroleum ether 3:1) to give both the hydrazone and pyrazole products. The mixture (0.25 mmol) was treated with NaH (0.25 mmol), stirred at 30 °C for 2 h, and subjected to preparative chromatography (EtOAc/petroleum ether 3:1) to give the pyrazolylphosphonate **28**.

21.14.1.2.2.3**Variation 3:
Synthesis of Bis(acylphosphonates)**

Bis(acylphosphonates) are of great interest as effective anticalcification^[30] and antiresorption^[31] agents both in vitro and in vivo. In an attempt to study the biological effect of chain length of such bis(acylphosphonates), a synthesis was reported^[32] utilizing *S*-ethyl (diisopropoxyphosphoryl)thioformate (**31**), which is easily obtained from the corresponding chlorothioformate (Scheme 10). Tetraester **32** is obtained by the reaction of ethane-1,2-diamine with thioformate **31**. Subsequent dealkylation with bromotrimethylsilane produces the disodium salt of the *N,N'*-bis[(dihydroxyphosphoryl)carbonyl]ethylenediamine species. After recrystallization (MeOH), diacid **33** is obtained in 90% yield. Longer chain bis(acylphosphonates) were synthesized in a similar fashion.

Scheme 10 Synthesis of a Bis(acylphosphonate)^[32]***N,N'*-Bis[(diisopropoxyphosphoryl)carbonyl]ethylenediamine (32); Typical Procedure:**^[32]

S-Ethyl chlorothioformate (0.5 g, 0.004 mol) was added dropwise to a magnetically stirred soln of P(OiPr)_3 (0.83 g, 0.004 mol) in dry toluene (3 mL) under N_2 at 0°C . After 3 h the solvent was removed under reduced pressure and the residue was dissolved in MeOH. A soln of ethane-1,2-diamine (0.12 g, 0.002 mol) in MeOH (3 mL) was added dropwise, and the mixture was stirred for 72 h. The solvent was removed and the product was recrystallized (EtOAc) to give **32**; yield: 0.75 g (85%); mp $83\text{--}85^\circ\text{C}$.

21.14.1.2.3

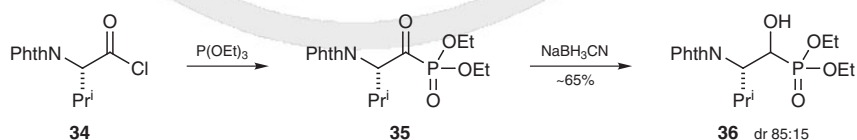
**Method 3:
Reduction of Acylphosphonates**

It is known that α -hydroxy phosphonates serve as important functional groups in a number of biologically active systems.^[33–35] Since the discovery of amino α -hydroxy phosphonic acids,^[36] there has been continued interest in the development of phosphorus-containing analogues of amino acids. One approach for stereocontrolled access to this class of compounds has been through the use of substrate- as well as reagent-controlled reductions of α -oxo phosphonates.

21.14.1.2.3.1

**Variation 1:
Diastereoselective Reductions**

Diastereoselective reductions of acylphosphonates occur with moderate selectivity to generate the corresponding α -hydroxy phosphonates. For example, reduction of acylphosphonate **35** (which is obtained from the acid chloride **34**) with sodium cyanoborohydride gives diethyl (2*S*)-1-hydroxy-3-methyl-2-(phthalimido)butylphosphonate (**36**) as an 85:15 diastereomeric mixture (Scheme 11).^[37] Similarly, in the case of acylphosphonate derivatives of cytidine arabinoside, sodium cyanoborohydride reduction leads to a 5:1 mixture of α -hydroxy phosphonate epimers.^[38] Reduction of α -oxo- β -phthalimido phosphonates with borane–methyl sulfide complex provides products with diastereomeric ratios as high as 10:1.^[39] When catecholborane and catalytic amounts of an oxazaborolidine are employed, a single diastereomer for the reduced product is observed.

Scheme 11 Diastereoselective Reduction of an Acylphosphonate Using Sodium Cyanoborohydride^[37]

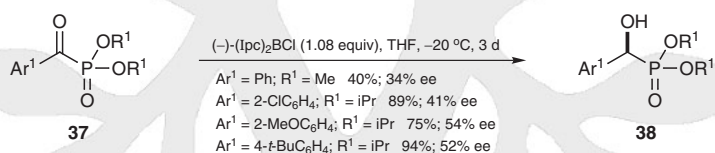
Diethyl (2*S*)-1-Hydroxy-3-methyl-2-(phthalimido)butylphosphonate (36):^[37]

Diethyl (2*S*)-3-methyl-2-(phthalimido)butanoylphosphonate (**35**; 0.64 g, 1.7 mmol) was dissolved in anhyd THF, which was followed by the addition of NaBH₃CN (0.33 g, 5.2 mmol). The mixture was stirred at rt for 24 h, then H₂O (30 mL) was added and the soln was neutralized by the addition of AcOH. The aqueous phase was extracted with CHCl₃ (3 × 20 mL) and the extracts were dried (MgSO₄). The crude product contained the α-hydroxy phosphonate **36** as a nonequimolar mixture of isomers (85:15); yield: ca. 65%; ³¹P NMR (CDCl₃, δ): 22.2, 24.9. After chromatography (silica gel, EtOAc/CH₂Cl₂ 1:1), a colorless, oily product was obtained as a single diastereomer with ca. 20% of *N*-phthaloyl-L-valine contaminant.

**21.14.1.2.3.2 Variation 2:
Enantioselective Reductions**

In addition to Pudovik reactions with chiral catalysts,^[40] enzymatic resolution,^[41] and phosphorus additions to aldehydes,^[42] asymmetric reduction of acylphosphonates provides an enantioselective route to α-hydroxy phosphonates. Thus, a stoichiometric amount of chiral (–)-*B*-chlorodiisopinocampheylborane [(–)-(Ipc)₂BCl] can be used for the asymmetric reduction of aroylphosphonates **37** to yield dialkyl aryl(hydroxy)methylphosphonates **38** (Scheme 12).^[43] The products are formed in moderate to good enantiomeric excesses and with predictable stereochemistry.

Scheme 12 Enantioselective Reductions of Aroylphosphonates Using (–)-*B*-Chlorodiisopinocampheylborane^[43]


Dialkyl Aryl(hydroxy)methylphosphonates 38; General Procedure for Asymmetric Reduction:^[43]

To a soln of (–)-Ipc₂BCl (0.35 g, 1.08 mmol) in dry THF (0.75 mL) at –20 °C under an argon atmosphere, was added the aroylphosphonate **37** (1.0 mmol). The mixture was stored at –20 °C for 3 d and then dried at 10^{–2} Torr for 6 h. The residue was dissolved in Et₂O (3.8 mL) and bis(2-hydroxyethyl)amine (0.23 g, 2.2 mmol) was added. The precipitate was removed by filtration and the filtrate was dried under reduced pressure. The residue was subjected to preparative TLC (0–5% MeOH/CH₂Cl₂) to give the α-hydroxy phosphonate **38**.

**21.14.1.2.4 Method 4:
Organometallic Additions to Acylphosphonates**

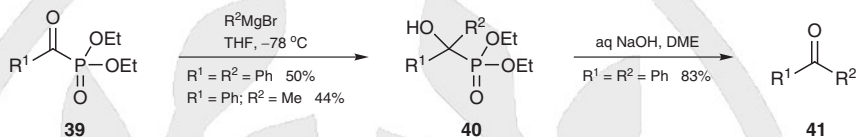
Nucleophilic addition to carbonyl groups has provided an effective way to generate new C–C bonds. Acylphosphonates possess a carbonyl group that is activated for nucleophilic attack. When Grignard reagents or indium-mediated reactions are employed, there is preference for nucleophilic attack at the carbonyl position over the phosphoryl position.

**21.14.1.2.4.1 Variation 1:
Grignard Additions**

The addition of Grignard or other organometallic reagents to acylphosphonates received little attention before 1998, when it was demonstrated that a single equivalent of Grig-

nard reagent can be added to an acylphosphonate **39** to generate a variety of α -hydroxy phosphonates **40** (Scheme 13).^[44] Starting from an acid chloride, the acylphosphonate can be generated by typical Michaelis–Arbuzov procedures (see Section 21.14.1.1.1). Subsequent addition of the Grignard reagent to the phosphonate results in the α -hydroxy phosphonate **40** in moderate to good yield. Upon dephosphorylation with aqueous sodium hydroxide in 1,2-dimethoxyethane, the corresponding ketone **41** is obtained in good yield.

Scheme 13 Grignard Additions to Acylphosphonates, Followed by Dephosphorylation^[44]



α -Hydroxy Phosphonates **40**; General Procedure for Grignard Addition to Acylphosphonates:^[44]

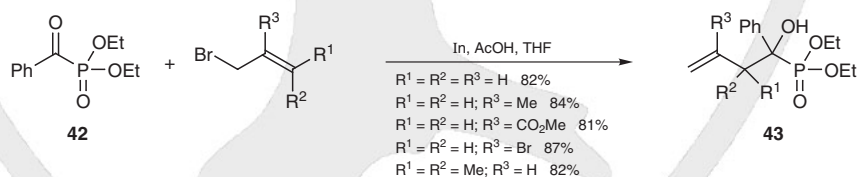
A THF soln of a Grignard reagent (3.3 mmol) was added gradually via a syringe to a THF soln of an acylphosphonate **39** (3.0 mmol), cooled to $-78^\circ C$ in an acetone/dry ice bath. The resulting mixture was stirred for 10 min at the same temperature. The reaction was quenched by the addition of sat. aq NH_4Cl (5 mL). The mixture was poured into sat. aq NH_4Cl (100 mL) and extracted with CH_2Cl_2 (2×100 mL). The combined organic layer was washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/EtOAc or CH_2Cl_2 /acetone/AcOH) to give the product, or analyzed by GLC to determine the yield of **40**.

21.14.1.2.4.2

Variation 2: Indium-Mediated Additions

Indium-mediated additions to acylphosphonates allows for the generation of tertiary α -hydroxy phosphonates such as **43** under mild conditions (Scheme 14).^[45] Diethyl benzoylphosphonate (**42**) is prepared by the reaction of benzoyl chloride with triethyl phosphite. Treatment of phosphonate **42** with an array of allylic bromides, with indium metal in tetrahydrofuran in the presence of acetic acid, gives the tertiary α -hydroxy phosphonates **43** in high yield (>80%).

Scheme 14 Indium-Mediated Additions to Diethyl Benzoylphosphonate^[45]



Diethyl 1-Hydroxy-1-phenylbut-3-enylphosphonate (**43**, $R^1 = R^2 = R^3 = H$); Typical Procedure:^[45]

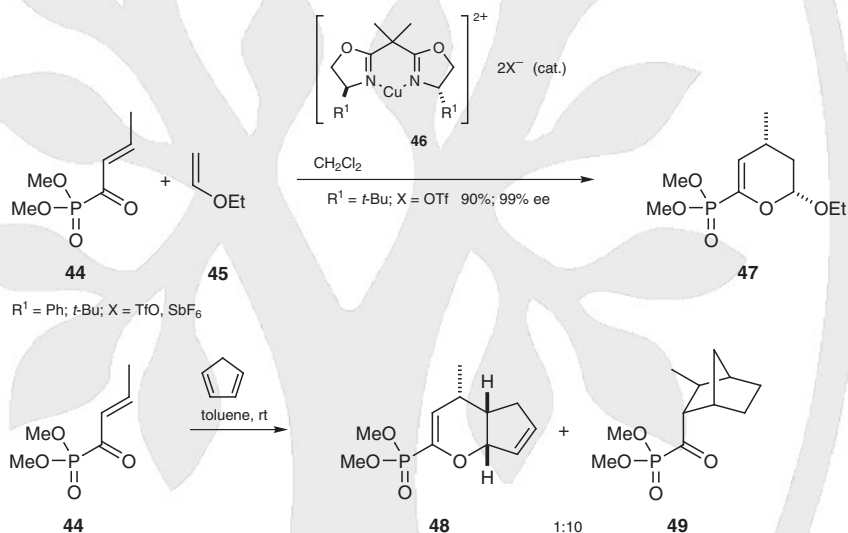
To a stirred suspension of indium (41 mg, 0.36 mmol) and allyl bromide (44 mg, 0.36 mmol) in THF (1 mL), were added successively a soln of diethyl benzoylphosphonate (**42**; 73 mg, 0.3 mmol) in THF (0.5 mL) and $AcOH$ (17.2 μL , 0.3 mmol) at rt. The reaction was stirred for 1 h, quenched by the addition of sat. aq NH_4Cl (0.5 mL), and extracted with Et_2O (2×20 mL). The combined organic layers were washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was purified by

column chromatography (silica gel, EtOAc/hexane 1:1) to give the α -hydroxy phosphonate as a white solid; yield: 82%; mp 72–74 °C.

21.14.1.2.5

Method 5:**Diels–Alder Reactions of Acylphosphonates**

Acylphosphonates can undergo inverse-electron-demand hetero-Diels–Alder reactions. For example, catalytic amounts of the cationic copper(II) complexes **46** of 2,2'-isopropylidenebis(4,5-dihydrooxazole) ligands (box ligands) promote cyclization of acylphosphonates, e.g. **44**, with ethyl vinyl ether (**45**) to give substituted pyrans, e.g. **47** (Scheme 15). These reactions proceed in high yield (84–100%) and with excellent ee (89–99%).^[7,46] It was suggested that the high enantiomeric excesses are due in large part to a rigid transition state in which both the phosphoryl and carbonyl moieties of the acylphosphonate are coordinated to the copper(II) complex. In addition to vinyl ethers, alkylidenedithianes also undergo cyclization with conjugated unsaturated acylphosphonates (the heterodiene) to produce substituted pyrans, i.e. oxadithiaspiro[5.5]undecylphosphonate derivatives.^[47]

Scheme 15 Diels–Alder Reactions of Dimethyl (2*E*)-But-2-enoylphosphonate^[7,48]

Another examination of acylphosphonates in the Diels–Alder reaction found that such phosphonates can react as both the heterodiene and the dienophile.^[48] When dimethyl (2*E*)-but-2-enoylphosphonate (**44**) is reacted at room temperature with cyclopentadiene, a 10:1 mixture of the adduct **49** to the hetero-Diels–Alder adduct **48** is observed, with adduct **49** showing a 7:1 *endo/exo* selectivity [according to the (dimethoxyphosphoryl)carbonyl substituent]. Furthermore, the use of a catalytic amount of tin(IV) chloride favors the alternative reaction pathway to provide the hetero-Diels–Alder adduct **48** in a 30:1 ratio with adduct **49**, in 74% yield.

Dimethyl (2*R*,4*R*)-2-Ethoxy-4-methyl-3,4-dihydro-2*H*-pyran-6-ylphosphonate (47**):^[7]**

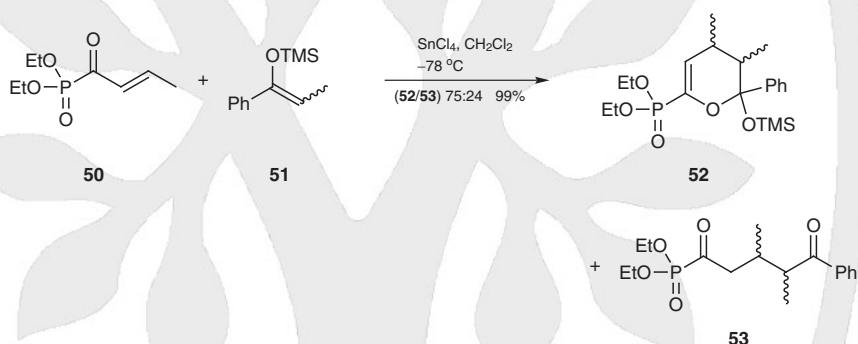
A dry round-bottomed flask with a magnetic stirrer was charged with 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-4,5-dihydrooxazole] or 2,2'-isopropylidenebis[(4*S*)-4-phenyl-4,5-dihydrooxazole] (0.1 equiv) and $\text{Cu}(\text{OTf})_2$ (0.1 equiv) in an inert atmosphere (N_2) glovebox. The flask was removed from the glovebox and a volume of CH_2Cl_2 was added via syringe to form a 0.02 M soln. The mixture was stirred for 2–3 h to produce a homogeneous blue-green soln that was cooled to –78 °C and treated sequentially with dimethyl (2*E*)-but-2-enoylphosphonate (**44**; 46 μL , 53 mg, 0.30 mmol) and ethyl vinyl ether (86 μL , 65 mg,

0.90 mmol). After 48 h, the reaction soln was applied to a silica gel column; elution (EtOAc/hexanes 2:1) gave **47** as a clear oil; yield: 67 mg (90%); 99% ee.

21.14.1.2.6

Method 6:**Mukaiyama–Michael Reactions of β,γ -Unsaturated Acylphosphonates**

β,γ -Unsaturated acylphosphonates present an alternative moiety to typically employed electrophiles for Michael addition reactions. Acylphosphonates provide unique substrates for Mukaiyama–Michael reactions due to the ability of the phosphoryl and carbonyl functionalities to bind with a Lewis acid. This coordination provides the potential for conformational rigidity, as well as increased substrate electrophilicity, compared to the α,β -unsaturated carbonyl analogues. Treatment of acylphosphonate **50** with both *E*- and *Z*-silyl enol ethers **51** in the presence of catalytic amounts of tin(IV) chloride provides a quantitative yield of the cyclic substituted pyrans **52** and the noncyclized adducts **53** (Scheme 16).^[49] Diastereoselectivities are low to moderate (14–52% de), favoring the formation of the *anti*-diastereomer in most cases. While the products resemble hetero-Diels–Alder cycloadducts (see Section 21.14.1.2.5), it was concluded that the mechanistic pathway proceeds via a Mukaiyama–Michael reaction with subsequent cyclization, based on the stereochemical assignment of products.

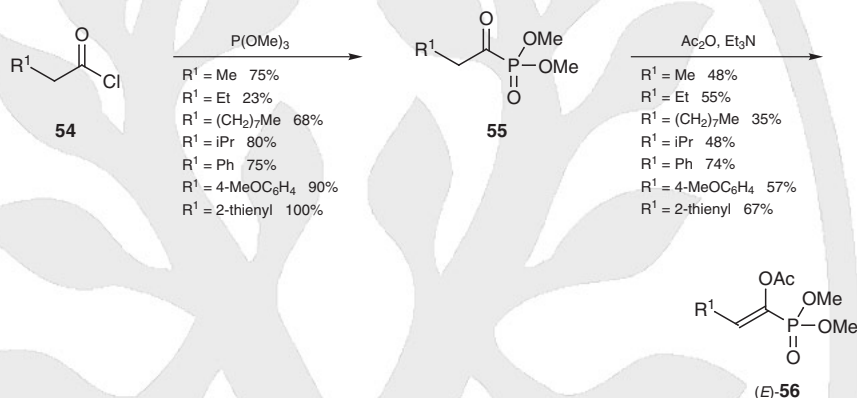
Scheme 16 Mukaiyama–Michael Addition to Diethyl (2*E*)-But-2-enoylphosphonate^[49]**Diethyl 3,4-Dimethyl-2-phenyl-2-(trimethylsiloxy)-3,4-dihydro-2*H*-pyran-6-ylphosphonate (**52**):^[49]**

Diethyl (2*E*)-but-2-enoylphosphonate (**50**; 200 mg, 0.97 mmol), *Z*-silyl enol ether (*Z*)-**51** (200 mg, 0.97 mmol), and CH_2Cl_2 were placed in a 100-mL, round-bottomed flask under a N_2 atmosphere. The flask was cooled to -78°C and SnCl_4 (130 mg, 0.49 mmol) was added. The mixture was stirred for 5 min and then the reaction was quenched with cold H_2O (200 mL) at -78°C . The product was extracted with Et_2O , and the extracts were washed with sat. NaCl soln, H_2O , and dried (MgSO_4). The solvent was removed under reduced pressure, and the crude oil was purified by flash column chromatography (anhyd Et_2O , R_f 0.35) to give homogeneous material as a mixture of *trans,cis*-, *trans,trans*-, and *cis,trans*-isomers **52**; yield: 300 mg (75%).

21.14.1.2.7

Method 7:**Enolization and Subsequent Reactions of Acylphosphonates**

Little was known about the enolization properties of α -oxo phosphonates until 1997 when the first transformation of acylphosphonates into their enol tautomers was reported (Scheme 17).^[50] The starting acylphosphonates **55** are available from the corresponding acid chlorides **54** and trimethyl phosphite. Using mild bases such as triethylamine and treatment with acetic anhydride, the acetyl enol ethers **56** are formed with exclusive *E* configuration. This process is sensitive to the substituents at phosphorus and the alkyl side chain. If R^1 is substituted with aromatic groups, good yields are reported (57–74%); modest yields (35–55%) are reported when R^1 is nonaromatic. Subsequent work in the area has been directed to the application of enolates derived from acylphosphonates.

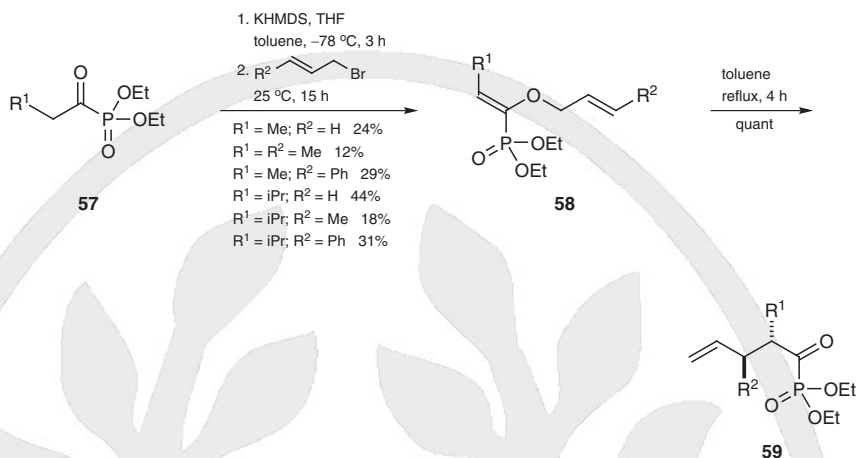
Scheme 17 Formation and Enolization of Acylphosphonates^[50]**Dimethyl (E)-1-Acetoxyprop-1-enylphosphonate (56, $R^1 = Me$); Typical Procedure:**^[50]

Ac₂O (0.93 mL, 9.86 mmol) was added to a stirred soln of dimethyl propanoylphosphonate (**55**, $R^1 = Me$; 1.368 g, 8.24 mmol) and Et₃N (1.29 mL, 9.27 mmol) in CH₂Cl₂ (20 mL) maintained under an atmosphere of dry N₂ at 0 °C. After 8 h, the mixture was washed with ice-cold H₂O and then dried (MgSO₄). Chromatography (Et₂O, *R_f* 0.18) gave **56** ($R^1 = Me$) as an oil; yield: 0.823 g (48%).

21.14.1.2.7.1

Variation 1:**C-Alkylation of Acylphosphonates**

C-Alkylation of acylphosphonates **57** can be achieved via a [3,3]-sigmatropic shift of the corresponding allyl enol ethers **58**, as shown in Scheme 18.^[51] Thus, O-alkylation of acylphosphonates **57** by treatment with potassium hexamethyldisilazide, followed by addition of excess electrophile such as allyl bromide, crotyl chloride, or cinnamyl bromide, gives allyl enol ethers **58** in 12–44% yield. When refluxed in toluene, facile [3,3]-sigmatropic rearrangement of enolates **58** occurs to give the corresponding C-alkylated acylphosphonates **59**. Compounds **59** are obtained in quantitative yield and as a single diastereomer.

Scheme 18 C-Alkylation of Acylphosphonates^[51]

Diethyl (1E)-1-[(2E)-3-Phenylprop-2-enyloxy]prop-1-enylphosphonate (58, $\text{R}^1 = \text{Me}; \text{R}^2 = \text{Ph}$) and Diethyl 2-Methyl-3-phenylpent-4-enoylphosphonate (59, $\text{R}^1 = \text{Me}; \text{R}^2 = \text{Ph}$); Typical Procedure:^[51]

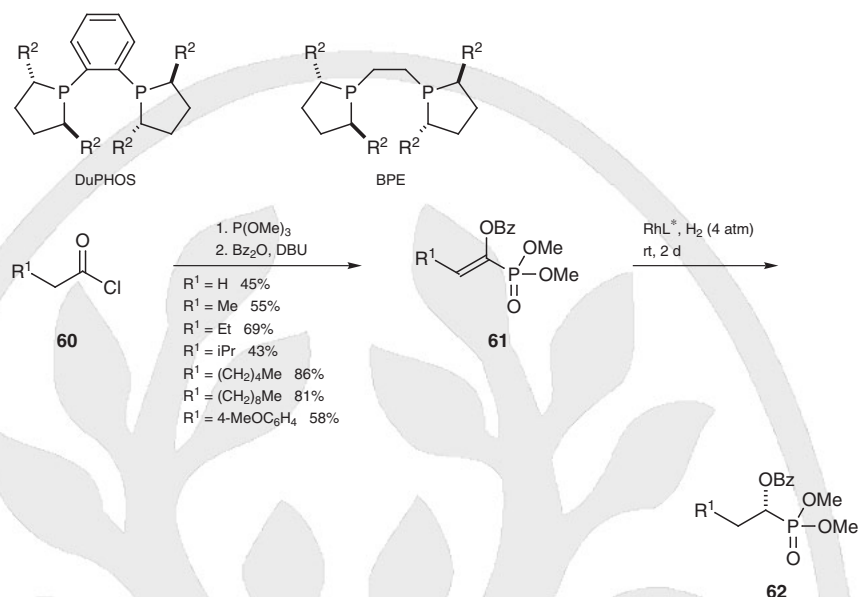
Cinnamyl bromide [3-bromo-1-phenylprop-1-ene; 7.9 g, 40 mmol] was added to a stirred soln of diethyl propanoylphosphonate (**57**, $\text{R}^1 = \text{Me}$; 1.94 g, 10 mmol) in THF (25 mL) maintained under an argon atmosphere at -78°C . A 0.5 M soln of KHMDS in toluene (40 mL, 20 mmol) was added and the resulting soln was stirred at -78°C for 3 h. The mixture was allowed to warm to rt and stirred overnight. The reaction was quenched by addition of 10% aq NH_4OAc (10 mL) and the organic products were extracted with Et_2O (3×20 mL). The combined organic extracts were washed with brine (20 mL) and H_2O (20 mL), and dried (MgSO_4). The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography (EtOAc /petroleum ether 2:3) to give **58** ($\text{R}^1 = \text{Me}; \text{R}^2 = \text{Ph}$) as a colorless oil; yield: 0.89 g (29%).

A soln of the phosphonate **58** ($\text{R}^1 = \text{Me}; \text{R}^2 = \text{Ph}$) in toluene (5 mL) was refluxed for 4 h under an argon atmosphere. The solvent was removed under reduced pressure to give **59** ($\text{R}^1 = \text{Me}; \text{R}^2 = \text{Ph}$) as a colorless oil; yield: quant.

21.14.1.2.7.2

Variation 2:
Asymmetric Hydrogenation

Cationic rhodium catalysts have been used for the asymmetric hydrogenation of enamido^[52] and enol esters.^[53] These catalysts, in conjunction with C_2 -symmetric diphosphine ligands (DuPHOS and BPE, see Scheme 19), can also asymmetrically hydrogenate acylphosphonate enolates in good ee and yield of the resulting α -hydroxy phosphonates.^[54] O-Alkylation of acylphosphonates, formed from acid chlorides **60** and trimethyl phosphite, with benzoic anhydride and 1,8-diazabicyclo[5.4.0]undec-7-ene affords a number of benzoyl enol ethers **61** exclusively as the *E*-isomer in 43–86% yield (Scheme 19). Treatment of a benzoyl enol ether **61** with a rhodium catalyst under hydrogen pressure (4 atm) gives the desired product **62**. Enantiomeric excess ranges from 60–96% and either enantiomer can be obtained depending on the configuration of the chiral rhodium ligand.

Scheme 19 Formation and Asymmetric Hydrogenation of Acylphosphonate Enolates^[54]

R ¹	Ligand (L*)	Config of 62	ee (%) of 62	Conversion (%) of 61 to 62	Ref
H	(<i>R,R</i>)-Me-BPE	(-)-(<i>S</i>)	64	27	[54]
H	(<i>S,S</i>)-Me-DuPHOS	(+)-(<i>R</i>)	84	100	[54]
H	(<i>R,R</i>)-Et-DuPHOS	(-)-(<i>S</i>)	96	100	[54]
H	(<i>R,R</i>)-Pr-DuPHOS	(-)-(<i>S</i>)	92	100	[54]
H	(<i>R,R</i>)-iPr-DuPHOS	(+)-(<i>R</i>)	85	40	[54]
Me	(<i>R,R</i>)-Me-BPE	(+)-(<i>S</i>)	60	45	[54]
Me	(<i>S,S</i>)-Me-DuPHOS	(-)-(<i>R</i>)	86	100	[54]
Me	(<i>R,R</i>)-Et-DuPHOS	— ^a	— ^a	100	[54]

^a Stereochemistry not determined.**α-Benzoyloxy Phosphonates 62; General Procedure for Asymmetric Hydrogenation:**^[54]

Under a N₂ atmosphere, a Fisher–Porter tube was charged with the benzoyl enol ether **61** (ca. 0.050 g), anhyd, degassed MeOH, and a rhodium catalyst (0.001 g). After five vacuum/H₂ cycles, the tube was pressurized to an initial pressure of 4–6 atm of H₂. The mixture was stirred at rt. Conversion was determined by ¹H or ³¹P NMR analysis. The mixture was concentrated, then passed through a silica gel plug (EtOAc) to remove catalyst. The ee was determined with an aliquot of the crude product, without further purification, by a comparison of this enantiomerically enriched benzoyl-protected α-hydroxy phosphonate with the corresponding racemic mixture using chiral HPLC (Daicel column, UV detection at 230 nm). Racemates were prepared by hydrogenation of the corresponding benzoyl enol ethers using 10% Pd/C.

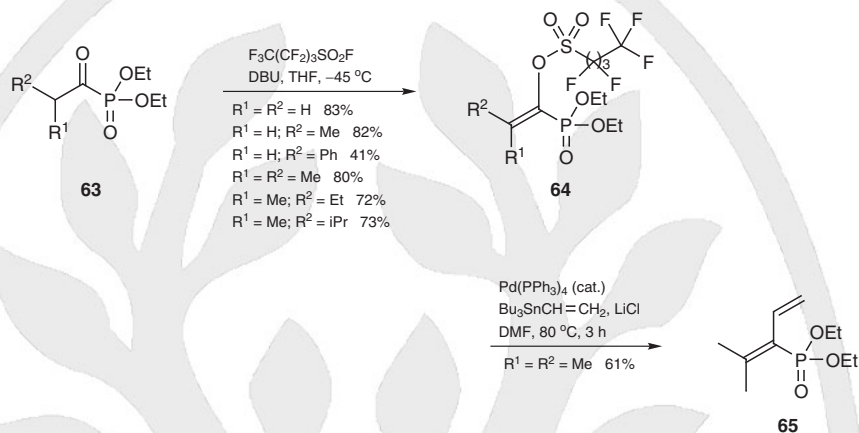
21.14.1.2.7.3

**Variation 3:
Cross-Coupling Reactions**

Vinylphosphonates can be prepared via perfluoroalkylsulfonyl enol ethers from an array of acylphosphonates.^[55] For example, acylphosphonates **63** can be treated with nonafluoro-

robutane-1-sulfonyl fluoride and a base in tetrahydrofuran to generate enolates **64** (Scheme 20); it was established that the use of 1,8-diazabicyclo[5.4.0]undec-7-ene at -45°C gives optimal yields. Subsequent palladium-catalyzed coupling reactions with acetylenes or vinylstannanes were performed to generate diethoxyphosphoryl-containing enynes, as well as dienes, e.g. **65**, in good yields.^[56]

Scheme 20 Formation and Cross-Coupling Reaction of Acylphosphonate Enolates^[55]



Diethyl 1-(Nonafluorobutylsulfonyloxy)vinylphosphonate (64, $\text{R}^1 = \text{R}^2 = \text{H}$); Typical Procedure:^[55]

CAUTION: Nonafluorobutane-1-sulfonyl fluoride is corrosive and irritating to the skin and eyes.

To a soln of diethyl acetylphosphonate (**63**, $\text{R}^1 = \text{R}^2 = \text{H}$; 53 mg, 0.30 mmol) and nonafluorobutane-1-sulfonyl fluoride (58 μL , 0.33 mmol) in THF (2 mL) was added DBU (49 μL , 0.33 mmol) at -45°C . The mixture was stirred at -45°C for 4 h then pH 4 aq buffer was added to quench the reaction. The crude product was purified by preparative TLC (silica gel) to give **64** ($\text{R}^1 = \text{R}^2 = \text{H}$); yield: 113 mg (83%).

21.14.1.2.8

Method 8:

Reaction of Acylphosphonates with Phosphorus(III) Compounds

Acylphosphonates can undergo nucleophilic addition with trialkyl phosphites. As noted in Section 21.14.1.2.4, nucleophilic attack occurs preferentially at the carbonyl position of acylphosphonates. After initial nucleophilic attack, a number of intermediates can be formed depending on the method and type of acylphosphonate system used. These intermediates include anionic and carbene-like intermediates that subsequently undergo cyclization.

21.14.1.2.8.1

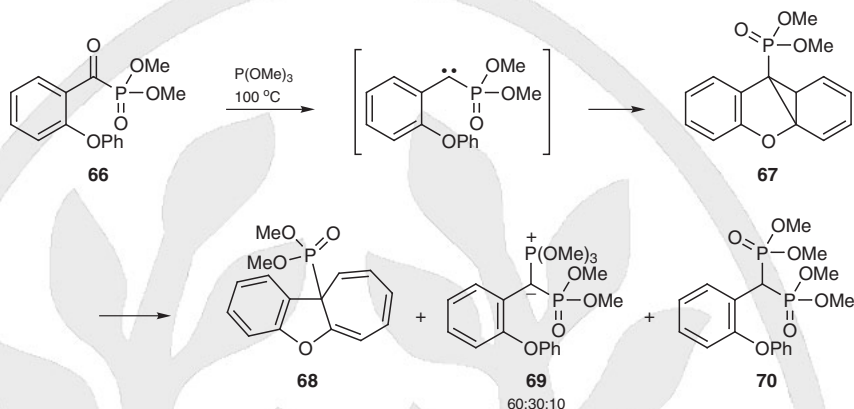
Variation 1:

Reaction with Trialkyl Phosphites

When dialkyl benzoylphosphonates react with trialkyl phosphites a carbene intermediate is formed via anionic intermediates.^[57] Thus, dimethyl 2-phenoxybenzoylphosphonate (**66**) reacts with trimethyl phosphite to facilitate the formation of a carbene intermediate (Scheme 21). Initially the carbene inserts into the π -system of the aromatic ring to generate **67**. Subsequent rearrangement produces tricyclic **68** as the major product in a

mixture of **68**, **69**, and **70**. Similarly, it was demonstrated that this process works for carbene insertion into nonaromatic substituents.^[58]

Scheme 21 Reaction of an Arylphosphonate with Trimethyl Phosphite^[57]



Dimethyl 10aH-Benzo[b]cyclohepta[d]furan-10a-ylphosphonate (68); Typical Procedure:^[57]

CAUTION: Trimethyl phosphite is flammable and has a powerful, obnoxious odor. Induces headache. Severe skin and eye irritant. Corrosive and irritating to the respiratory tract.

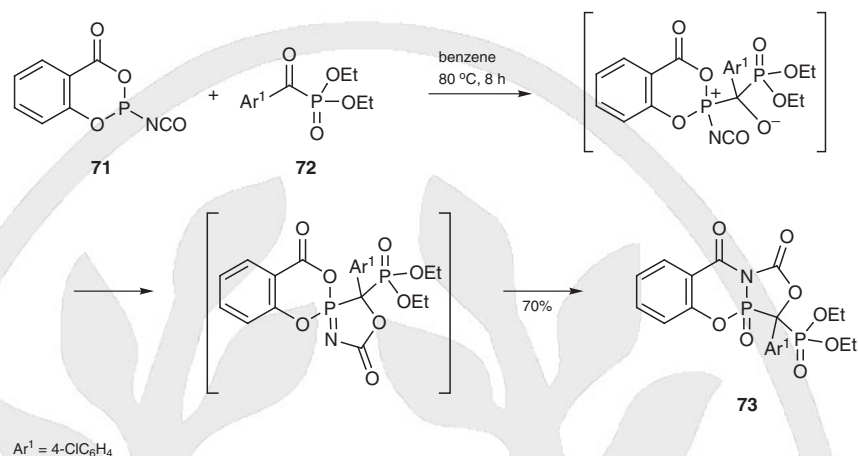
Dimethyl 2-phenoxybenzoylphosphonate (**66**; 3.0 g, 10 mmol) was heated under a N₂ atmosphere with P(OMe)₃ (2.48 g, 20 mmol) at 100 °C for 1.5 h. Analysis of the resulting mixture by ³¹P NMR spectroscopy indicated that the major products, other than trimethyl phosphate, were the phosphonate **68** (60%), and the ylidic phosphonate **69** and its decomposition product (30%). A small quantity of the bisphosphonate **70** (10%) was also formed. The mixture was heated (60 °C) under reduced pressure (0.3 Torr) to remove the volatile components and the residue was subjected to reverse-phase HPLC (Dynamax C₁₈ column, 60% aq MeOH) to give **68** as a yellow solid; mp 78 °C.

21.14.1.2.8.2

Variation 2:

Reaction with 2-Isocyanato-4H-1,3,2-benzodioxaphosphin-4-one

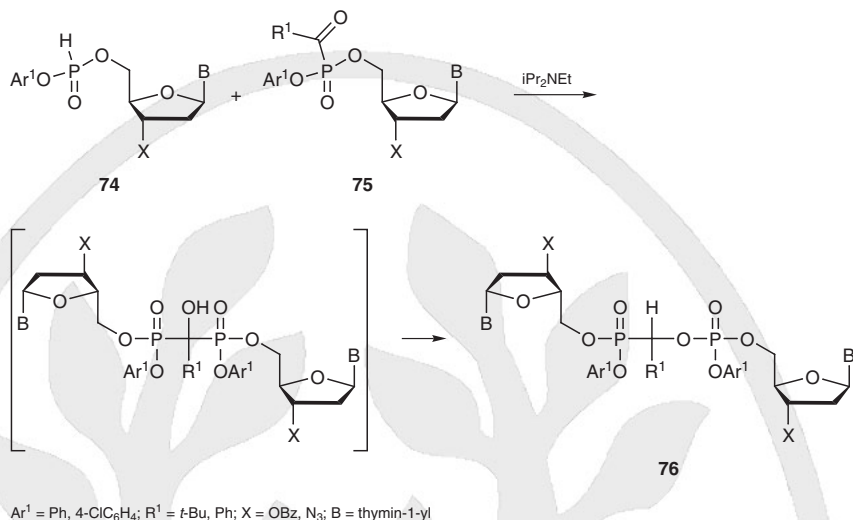
A phosphabicyclo[4.3.0]nonane derivative can be generated by the reaction of a phosphite derivative with an acylphosphonate.^[59] Thus, subjecting 2-isocyanato-4H-1,3,2-benzodioxaphosphin-4-one (**71**) to diethyl 4-chlorobenzoylphosphonate (**72**) in benzene at 80 °C for 8 hours produces the substituted phosphabicyclo[4.3.0]nonane **73** via the cyclization pathway shown in Scheme 22. This reaction exhibits good diastereoselectivity (9:1), with good yield (60–70%).

Scheme 22 Reaction of an Arylphosphonate with 2-Isocyanato-4*H*-1,3,2-benzodioxaphosphin-4-one^[59]**Diethyl 3-(4-Chlorophenyl)-4-oxido-1,10-dioxo-1*H*,3*H*,10*H*-[1,3,4]oxazaphospholo[4,3-*b*][1,3,2]benzoxazaphosphin-3-ylphosphonate (73):^[59]**

A mixture of 2-isocyanato-4*H*-1,3,2-benzodioxaphosphin-4-one (**71**; 4.26 g, 20.4 mmol), diethyl (4-chlorobenzoyl)phosphonate (**72**; 5.64 g, 20.4 mmol), and benzene (10 mL) (**CAUTION: carcinogen**) was heated at 80 °C for 8 h under dry argon. The mixture was precipitated into pentane to isolate compound **73**; yield: 6.93 g (70%); mp 164–166 °C.

21.14.1.2.8.3**Variation 3:****Coupling Reactions of Aryl Acylphosphonates with Aryl Phosphonates**

Simple tetraalkyl phosphonate–phosphate compounds have several therapeutic applications.^[60] The corresponding nucleotide derivatives, such as **76**, had not been investigated until the development of a synthetic protocol to generate these species.^[61] In this 2003 report, coupling of phosphonates with acylphosphonate monoester nucleotides, **74** and **75**, formed in situ, was found to occur readily to generate new nucleotide analogues **76** with a phosphonate–phosphate internucleoside linkage (Scheme 23). When equimolar amounts of an aryl phosphonate and an aryl acylphosphonate are used, generation of **76** occurs quickly (5 min) in the presence of *N,N*-diisopropylethylamine in a mixture of dichloromethane and pyridine.

Scheme 23 Coupling Reactions of Aryl Acylphosphonates with Aryl Phosphonates^[61]**Linked Dinucleoside Phosphonate-Phosphates 76; General Procedure:**^[61]

A nucleoside phosphonate (1 equiv), an acylphosphonate (1 equiv), and the appropriate phenol (2.5 equiv) were rendered anhydrous by repeated evaporation of added pyridine ($3 \times 20 \text{ mL} \cdot \text{mmol}^{-1}$), and then dissolved in $\text{CH}_2\text{Cl}_2/\text{pyridine}$ (9:1, $10 \text{ mL} \cdot \text{mmol}^{-1}$). To the soln was added diphenyl chlorophosphate (2.5 equiv). When the formation of aryl phosphonate esters **74** and **75** was complete (ca. 2 h), $i\text{Pr}_2\text{NEt}$ (10 equiv) was added. After 5 min the mixture was diluted with CH_2Cl_2 (10 times the initial volume) and washed with 5% aq NaHCO_3 . The organic layer was dried (Na_2SO_4) and concentrated, and the oily residue was applied to a silica gel column pre-equilibrated with CH_2Cl_2 . Product **76** was isolated using a stepwise gradient (0–10% $i\text{PrOH}$ in CH_2Cl_2). Fractions containing pure product were concentrated and the residue was precipitated with an excess of petroleum ether. After collection by filtration and drying under reduced pressure, compound **76** was obtained as an amorphous white powder in >98% purity.

21.14.1.2.9

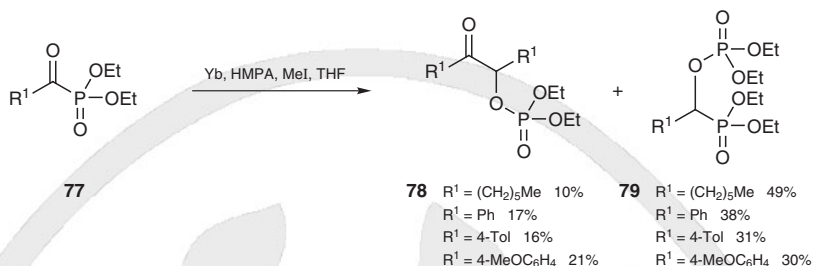
Method 9:**Metal-Mediated Reactions of Acylphosphonates**

Metal-mediated reactions with acylphosphonate functionalities in the presence of low-valent metal species have been found to capitalize on the labile C—P bond linkage. This is exemplified in products resulting from ytterbium and samarium insertion into the C—P bond, as well as the ability of phosphonates to act as leaving groups in metal-promoted radical reactions.

21.14.1.2.9.1

Variation 1:**Ytterbium-Promoted Rearrangements**

Acylphosphonates **77** may be used to form rearranged products **78** and **79** in the presence of low-valent ytterbium metal (Scheme 24).^[62] This process is believed to occur via an acyl-ytterbium intermediate formed from the two-electron transfer of ytterbium into the labile C—P bond of the acylphosphonate. From the acyl-ytterbium intermediate, subsequent reaction with a second equivalent of the starting material via either the phosphoryl anion or the acylcarbanion leads to products **78** and **79** in modest to good yields, but with poor product selectivity.

Scheme 24 Ytterbium-Promoted Rearrangement of Acylphosphonates^[62]

Diethyl 2-Oxoalkyl Phosphates 78 and 1-(Diethoxyphosphoryl)alkyl Diethyl Phosphates 79; General Procedure for Ytterbium-Promoted Rearrangement:^[62]

CAUTION: Hexamethylphosphoric triamide is a possible human carcinogen and an eye and skin irritant.

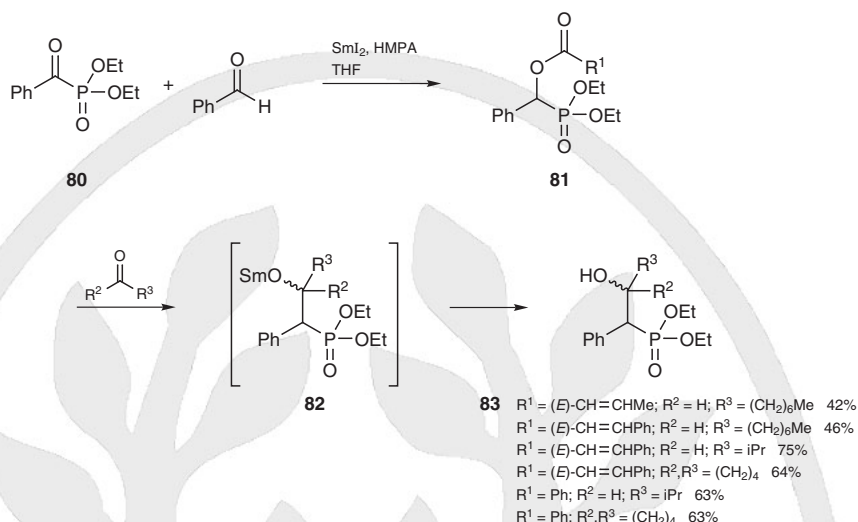
CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

Yb metal (173 mg, 1 mmol) was placed in a 30-mL, two-necked, round-bottomed flask. The flask was flame-dried under reduced pressure. To the flask, THF (4 mL), HMPA (1 mL), and MeI (3 μL) were successively added at rt. The diethyl acylphosphonate **77** (1 mmol) was added at -35°C . The mixture was stirred at the same temperature for several hours. After the reaction was completed, H_2O was added to the mixture. The mixture was extracted with Et_2O ($3 \times 20\text{ mL}$). The combined ethereal extracts were washed with brine (20 mL), dried (MgSO_4), and filtered. After the removal of solvents, the residue was purified by MPLC (silica gel, hexanes/ EtOAc / EtOH) to give the corresponding adducts **78** and **79** as pale yellow oils.

21.14.1.2.9.2

Variation 2:
Samarium(II) Iodide Promoted Three-Component Couplings

As an extension to the ytterbium insertion reactions (see Section 21.14.1.2.9.1), it has been demonstrated that low-valent samarium(II) iodide also undergoes two-electron-transfer reactions with the C—P bond of acylphosphonates.^[63] Thus, treatment of acylphosphonates **80** with samarium(II) iodide in the presence of an aldehyde such as benzaldehyde yields α -acyloxy phosphonates **81** (Scheme 25). Following the elimination of carboxylic acid, subsequent reaction with an aldehyde or ketone gives samarium intermediates **82**, that upon quenching lead to the formation of β -hydroxy phosphonate products **83** in moderate to good yield. The reaction proved problematic for aromatic and α,β -unsaturated aldehydes, and was sensitive to substitution at the phosphorus, with electron-withdrawing groups providing optimal yields.

Scheme 25 Samarium(II) Iodide Promoted Three-Component Couplings^[63] **β -Hydroxy Phosphonates **83**; General Procedure for Samarium(II) Iodide Promoted Three-Component Coupling:**^[63]

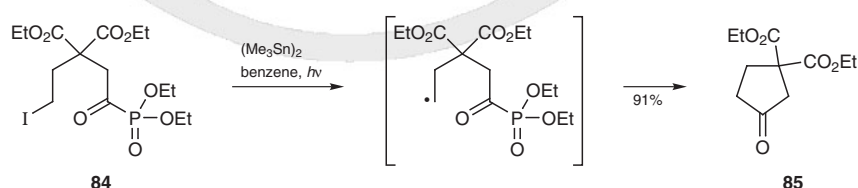
CAUTION: Hexamethylphosphoric triamide is a possible human carcinogen and an eye and skin irritant.

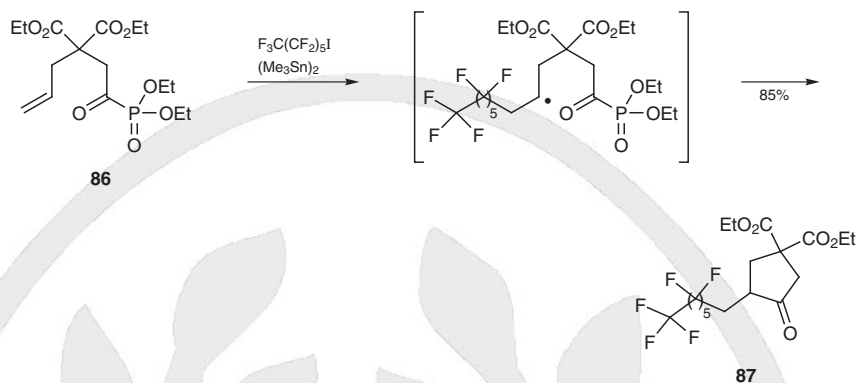
A 0.1 M soln of SmI_2 in THF (20 mL) was slowly added to a soln of an acylphosphonate **80** (0.5 mmol), an aldehyde (1 mmol), and a second aldehyde or ketone (0.4 mmol) in THF (3 mL) and HMPA (1 mL) over 1 h at 0°C, with stirring continued for an additional 1 h at 0°C. The reaction was quenched with 2 M HCl (10 mL) and an internal standard such as tridecane was added to the mixture. The mixture was extracted with Et_2O , washed with NaHSO_3 soln and brine, dried (MgSO_4), and concentrated under reduced pressure. The product **83** was isolated by column chromatography (silica gel, hexanes/ EtOAc); yield: 42–75%.

21.14.1.2.9.3

Variation 3:
Tin-Catalyzed Intramolecular Acylations

Acylphosphonates act as carbonyl radical acceptors capable of undergoing elimination of the phosphonate group via alkoxy radical intermediates.^[64] For example, excitation of hexamethyldistannane promotes radical cyclization of halogenated acylphosphonates such as **84** to generate intramolecular acylated products **85** in good to excellent yield (Scheme 26). In addition, this methodology has been extended to alkenes such as **86**, as well as alkynes, to provide functionalized cyclopentanones, e.g. **87**, in good yield (Scheme 26).

Scheme 26 Tin-Catalyzed Intramolecular Acylations^[64]



Diethyl 3-Oxocyclopentane-1,1-dicarboxylate (85); Typical Procedure:^[64]

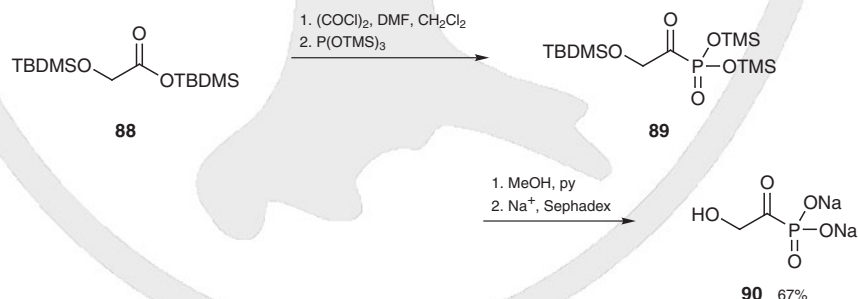
A dry benzene soln (2.0 mL) (**CAUTION: carcinogen**) of diethyl acylphosphonate **84** (98.5 mg, 0.2 mmol) and hexamethyldistannane (65.5 mg, 0.2 mmol) in a quartz tube was degassed with N₂ for 10 min and then irradiated at 300 nm in a Rayonet photochemical reactor for 2 h. The solvent was removed under reduced pressure and the residue was separated by column chromatography (silica gel, EtOAc/hexane 1:3) to give **85**; yield: 41.5 mg (91%).

21.14.1.2.10

Method 10: Deprotection of Acylphosphonates

A variety of functionalized acylphosphonates have been generated as (dihydroxyphosphoryl)formate analogues are potent inhibitors of reverse transcriptase HIV-1.^[65] One such compound of interest is the hydroxyacetylphosphonate **90**. Due to the inability to generate **90** through a standard Arbuzov reaction (see Section 21.14.1.1.1), a strategy shown in Scheme 27 was developed where acylphosphonates can be exhaustively deprotected.^[66] Treating the fully protected glycolic acid **88** with oxalyl chloride, and subsequent addition of a phosphite, yields the appropriate phosphonate, e.g. **89**. Deesterification of the silyl groups with a methanol/pyridine mixture results in the final fully deprotected compound.

Scheme 27 Exhaustive Deprotection To Give an Acylphosphonic Acid^[66]



Disodium Hydroxyacetylphosphonate (90):^[66]

tert-Butyldimethylsilyl (*tert*-butyldimethylsiloxy)acetate (**88**; 2.01 g, 6.6 mmol) was dissolved in dry CH₂Cl₂ (10 mL) containing DMF (4 drops). A 2 M soln of oxalyl chloride in CH₂Cl₂ (4.09 mL, 8.2 mmol) and dry CH₂Cl₂ (5.0 mL) were added dropwise under N₂ over a 40-min period. After stirring the soln at rt for 1 h, the volatiles (unreacted oxalyl chloride)

were removed under reduced pressure to yield a yellow oily residue. The residue was mixed with dry benzene (8.0 mL) (**CAUTION: carcinogen**) and cooled to $<0^{\circ}\text{C}$ before the dropwise addition of tris(trimethylsilyl) phosphite (2.2 mL, 6.6 mmol). After 15 min, the ice bath was removed and the mixture was stirred for a total of 1 h. The mixture was concentrated under reduced pressure, and then a soln of pyridine (0.53 mL, 6.6 mmol) and MeOH (1.34 mL, 33 mmol) was added dropwise to form a sticky white precipitate. This material was passed through a column of DOWEX (H^+) using cold deionized H_2O as the eluent. The resultant hydroxyacetylphosphonic acid was neutralized with pyridine before chromatography on a Sephadex Na^+ column (deionized H_2O). The eluent was lyophilized to give **90**; yield: 67%.

21.14.2

**Product Subclass 2:
Tricoordinate Acylphosphorus Compounds**

Tricoordinate acylphosphorus derivatives are interesting compounds, exhibiting extensive chemical diversity and broad utility. Low-valent acylphosphorus compounds bear the same oxidation state as amides, and therefore exhibit similar reactivity. Work subsequent to prior reviews has focused mainly on secondary and tertiary acylphosphine chemistry. Examples in this section revolve around the preparation of acylphosphines via di- and tricoordinate phosphines, and alkylations of secondary acylphosphines, and subsequent application reactions of tertiary acylphosphines.

Tertiary acylphosphines can be prepared through alkylation or acylation of secondary acylphosphines or phosphines, respectively. This can be achieved through the generation of delocalized anions via deprotonation of a P-H precursor. While being the most general approach, specifically for alkylation reactions, milder conditions have been described for acylation reactions under nonbasic conditions. Advantages of this approach include increased functional group compatibility, and the replacement of the potentially hazardous organolithium bases.

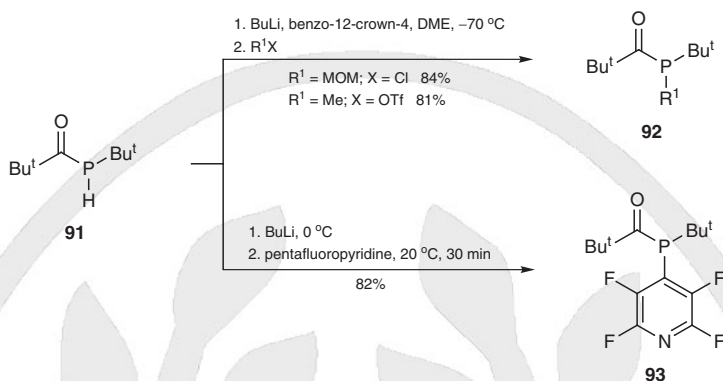
21.14.2.1

Synthesis of Product Subclass 2

21.14.2.1.1

**Method 1:
Alkylation of Secondary Acylphosphines**

Alkylation reactions of the delocalized anions of acylphosphines occur through both the oxygen and phosphorus atoms,^[67] depending on solvent polarities and the use of chelating additives. Alkylation reactions conducted in 1,2-dimethoxyethane with one equivalent of benzo-12-crown-4 result in alkylation at phosphorus, even in the presence of bulky substituents. Thus, treatment of acylphosphines, e.g. *tert*-butyl(2,2-dimethylpropanoyl)-phosphine (**91**), with a variety of electrophiles (halogenated aliphatic systems as well as sulfonium and oxonium salts) under basic conditions gives the corresponding tricoordinate acylphosphorus compounds **92** in good to excellent yield (Scheme 28).^[68] Additional examples of P-alkylations are known in which acylphosphine **91**, upon treatment with base, undergoes nucleophilic aromatic substitution with pentafluoropyridine to give the 4-substituted tetrafluoropyridine **93** in 82% yield.^[69]

Scheme 28 Alkylations of a Secondary Acylphosphine under Basic Conditions^[68,69]

***tert*-Butyl(2,2-dimethylpropanoyl)(methoxymethyl)phosphine (92, $\text{R}^1 = \text{MOM}$); Typical Procedure:**^[68]

CAUTION: Technical grade chloromethyl methyl ether is classified as a human carcinogen, and is an eye and respiratory tract irritant.

To a soln of *tert*-butyl(2,2-dimethylpropanoyl)phosphine (**91**; 3.48 g, 0.02 mol) in Et_2O (10 mL) at $0\text{ }^{\circ}\text{C}$ with stirring, was added dropwise a soln of BuLi in hexane (0.02 mol) over 10 min. The temperature was allowed to rise to rt and the solvents were removed under reduced pressure. To the solid residue was added benzo-12-crown-4 (4.48 g, 0.02 mol), and the mixture was dissolved in DME (15 mL), cooled to $-70\text{ }^{\circ}\text{C}$, and chloromethyl methyl ether (1.61 g, 0.02 mol) in DME (5 mL) was added dropwise. The temperature was gradually (30 min) raised to rt, and the LiCl precipitate was separated in a centrifuge and washed with Et_2O . The organic phase was concentrated under reduced pressure and the residue was fractionated to give **92** ($\text{R}^1 = \text{MOM}$); yield: 3.66 g (84%); bp $95\text{--}96\text{ }^{\circ}\text{C}/10\text{ Torr}$.

21.14.2.1.2

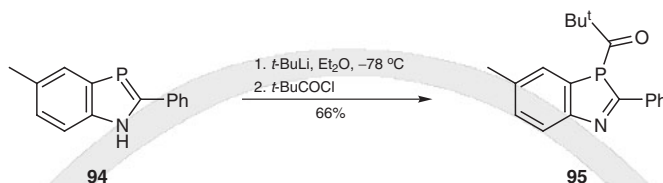
Method 2:**Acylation of Di- and Tricoordinate Phosphines**

Despite continued success in the area of secondary acylphosphine alkylations (see Section 21.14.2.1.1), treatment of di- and tricoordinate phosphines with an acid chloride remains the most general synthetic route to secondary and tertiary acylphosphines. In addition to condensation with acid chlorides in the presence of neutral and anionic phosphines, conditions for utilizing mild to neutral coupling procedures have been developed.

21.14.2.1.2.1

Variation 1:**Under Basic Conditions**

Acylation of 5-methyl-2-phenyl-1*H*-1,3-benzazaphosphole (**94**) with pivaloyl chloride occurs at phosphorus under strongly basic conditions, giving the P-acylated product **95** in 66% yield (Scheme 29).^[70] When acylation was attempted with less bulky acid chlorides (acetyl chloride), hydrolysis products were observed.

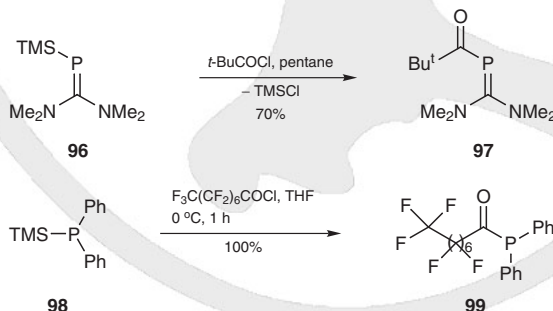
Scheme 29 Base-Promoted Acylation of a 1*H*-1,3-Benzazaphosphole^[70]**3-(2,2-Dimethylpropanoyl)-5-methyl-2-phenyl-3*H*-1,3-benzazaphosphole (**95**):^[70]**

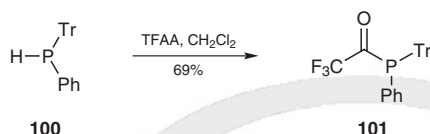
CAUTION: *tert*-Butyllithium ignites in moist air and reacts explosively with water.

5-Methyl-2-phenyl-1*H*-1,3-benzazaphosphole (**94**; 226 mg, 1.0 mmol) dissolved in Et₂O (15 mL) was lithiated with 1.7 M *t*-BuLi in pentane (0.59 mL, 1.0 mmol) at -78 °C. After 1 h at 20 °C, the soln was cooled again to -78 °C and *t*-BuCOC(=O)Cl (0.123 mL, 1.0 mmol) was added with stirring. After warming to rt (3 h), the orange-red color changed to pale yellow. The mixture was allowed to stir overnight and then filtered. Removal of the solvent under reduced pressure (10⁻² Torr) gave a yellow oil, which was extracted with warm hexane to afford a pale yellow powder (100 mg) slightly contaminated with starting material. Upon cooling the filtrate to -78 °C, pure **95** (130 mg; mp 68–70 °C) was collected; total yield: ca. 66%.

21.14.2.1.2.2**Variation 2:
Under Nonbasic Conditions**

Numerous examples of nonbasic coupling of di- and tricoordinate phosphines with acid chlorides have been reported. The majority of neutral cases rely on the use of labile silicon groups. Reaction of *N,N,N',N'*-tetramethyl-1-[(trimethylsilyl)phosphinidene]methanediamine (**96**) with pivaloyl chloride or benzoyl chloride yields the corresponding acylated phosphasalkenes, e.g. **97**, in good yield (Scheme 30).^[71] (Perfluorooctanoyl)diphenylphosphine (**99**) can also be prepared in quantitative yield from the reaction of diphenyl(trimethylsilyl)phosphine (**98**) with perfluorooctanoyl chloride.^[72] Alternatively, acidic conditions can be employed for the coupling of secondary phosphines. Thus, phenyl(trityl)phosphine (**100**) reacts readily with trifluoroacetic anhydride to produce the (trifluoroacetyl)phosphine **101** (Scheme 30).^[73]

Scheme 30 Acylation of Phosphines under Nonbasic Conditions^[71–73]



1-[(2,2-Dimethylpropanoyl)phosphinidene]-N,N,N',N'-tetramethylmethanediamine (97):^[71]

A soln of *t*-BuCOCl (0.14 g, 1.13 mmol) in pentane (10 mL) was added dropwise to a chilled soln (−30 °C) of *N,N,N',N'*-tetramethyl-1-[(trimethylsilyl)phosphinidene]methanediamine (**96**; 0.23 g, 1.13 mmol) in pentane (40 mL), whereupon a light yellow precipitate separated. The chilled slurry was filtered and the filter cake was washed with cold pentane (50 mL) at −30 °C. After drying under reduced pressure, **97** was obtained as a light yellow, analytically pure powder; yield: 0.17 g (70%).

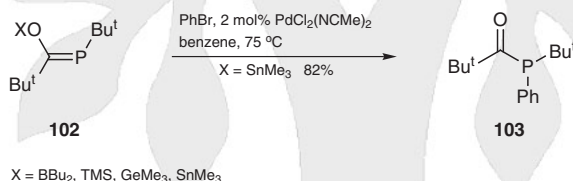
21.14.2.1.3

Method 3:

Palladium-Mediated Cross-Coupling Reactions

Arylation of metal-substituted phosphines can be achieved by palladium-mediated cross-coupling reactions. In the presence of 2 mol% palladium catalyst, bromobenzene arylates phosphalkenes **102** (X = BBU₂, TMS) of low nucleophilicity to give the corresponding phosphine, albeit in poor yield (ca. 10%) (Scheme 31).^[68] In contrast, reaction of bromobenzene with more sterically shielded (more nucleophilic) phosphines (X = GeMe₃, SnMe₃) produces coupled products in moderate to good yield (X = GeMe₃ 25–30% conversion, as determined by ³¹P NMR spectroscopy; X = SnMe₃ 82%).

Scheme 31 Palladium-Mediated Cross-Coupling Reactions^[68]



***tert*-Butyl(2,2-dimethylpropanoyl)phenylphosphine (103); Typical Procedure:**^[68]

A mixture of phosphalkene **102** (X = SnMe₃; 3.37 g, 0.01 mol), PhBr (1.57 g, 0.01 mol), and PdCl₂(NCMe)₂ (50 mg, 0.2 mmol, 2 mol%) in benzene (10 mL) (**CAUTION: carcinogen**) was heated at 75 °C for 16 h in a sealed ampule. The low-boiling products were removed under reduced pressure; distillation of the residue gave phosphine **103**; yield: 2.05 g (82%); bp 104–105 °C/1 Torr; mp 52–53 °C.

21.14.2.2

Applications of Product Subclass 2 in Organic Synthesis

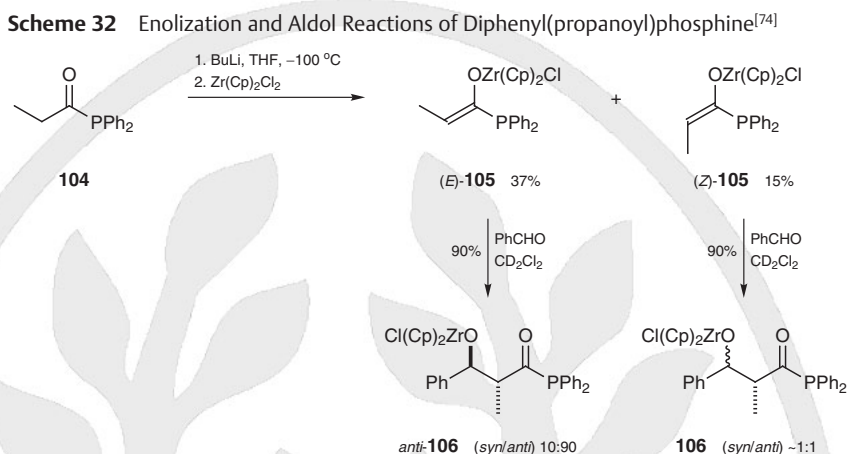
21.14.2.2.1

Method 1:

Enolization and Aldol Reactions of Acylphosphines

Deprotonation at the β -position of acylphosphines requires the use of a strong base under optimal reaction conditions. Best results are obtained when acylphosphines are treated with butyllithium, at $-100\text{ }^{\circ}\text{C}$, yielding the lithium enolate salts as crystalline solids.^[74] Reaction of the lithium α -phosphino enolate derived from diphenyl(propanoyl)phosphine (**104**) with dichlorobis(η^5 -cyclopentadienyl)zirconium(IV) gives the corresponding zircon-

mium *E*- and *Z*-enolates **105** in 52% overall yield (Scheme 32). At low temperatures, the reaction favors the formation of the *E*-isomer as the major product (37% yield).



The zirconium-derived enolates prepared from acylphosphines can undergo aldol reactions.^[74] Thus, the isolated *E*- and *Z*-isomers **105** were both reacted with benzaldehyde to give the aldol products **106** (Scheme 32).^[74] Monitoring by ^1H NMR spectroscopy indicated that the *Z*-isomer reacts with benzaldehyde to give *anti*-diastereomer, *anti-106*, as the major product, while reaction of the *E*-isomer affords a 1:1 mixture of *syn*- and *anti*-diastereomeric products.

Chlorobis(η^5 -cyclopentadienyl)[(*E*)- and -(*Z*)-1-(diphenylphosphino)prop-1-en-1-olato]zirconium(IV) (105**):^[74]**

Diphenyl(propanoyl)phosphine (**104**; 5.00 g, 20.64 mmol) was dissolved in THF (100 mL) and added dropwise via syringe at $-100\text{ }^{\circ}\text{C}$ to 1.6 M BuLi (13.0 mL, 20.8 mmol). The mixture was stirred for 1 h, then $\text{Zr}(\text{Cp})_2\text{Cl}_2$ (5.87 g, 20.08 mmol) was added; the color initially turned orange and then violet. The mixture was stirred overnight, while the temperature was allowed to rise slowly to rt. After the THF was removed, CH_2Cl_2 (50 mL) was added to the residue, and LiCl was removed by filtration. The solvent was evaporated to dryness to leave an oil, which was dissolved in Et_2O (50 mL). A white crystalline solid was collected (yield: 15%); large crystals of the *Z*-isomer, (*Z*)-**105**, suitable for X-ray analysis, were obtained by Et_2O extraction. Hexane (50 mL) was added to the initial Et_2O soln (from which the *Z*-isomer had already been isolated), and the soln was cooled to $-25\text{ }^{\circ}\text{C}$ for a few hours, producing the *E*-isomer, (*E*)-**105** (yield: 37%); overall yield (*E* + *Z*): 52%.

(*R,*S**)-Chlorobis(η^5 -cyclopentadienyl)[3-(diphenylphosphino)-2-methyl-3-oxo-1-phenylpropan-1-olato]zirconium(IV) (**106**); Typical Procedure:^[74]**

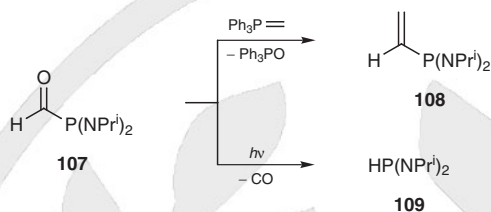
E-Enolate (*E*)-**105** (45 mg, 0.091 mmol), distilled PhCHO (9.2 μL , 0.091 mmol), and CD_2Cl_2 were combined in an NMR tube. Product observation was by ^1H NMR analysis (CD_2Cl_2), which showed the formation of two isomers; dr (*syn/anti*) 10:90.

**21.14.2.2.2 Method 2:
Reactions of Formylphosphines**

The reactivity and remarkable stability of formylphosphines has been probed.^[75] Thus, when formylphosphine **107** is refluxed in toluene for 3 days, no decomposition of the starting material is observed. Formylphosphines do react with Wittig reagents such as methylene(triphenyl)phosphorane to give the corresponding alkenes, e.g. **108**, in good

yield (Scheme 33). Additionally, similar to classical aldehydes, formylphosphine **107** decarbonylates under photolysis (254 nm), affording the diaminophosphine **109** in almost quantitative yield.

Scheme 33 Reactions of a Formylphosphine Derivative^[75]



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