Synthetic Approaches toward Monocyclic 3-Amino-β-lactams

Sari Deketelaere,[a] Tuyen Van Nguyen,[b] Christian V. Stevens,[a] and Matthias D’hooghe*[a]

Due to the emerging resistance against classical β-lactam-based antibiotics, a growing number of bacterial infections has become harder to treat. This alarming tendency necessitates continued research on novel antibacterial agents. Many classes of β-lactam antibiotics are characterized by the presence of the 3-aminoazetidin-2-one core, which resembles the natural substrate of the target penicillin-binding proteins. In that respect, this Review summarizes the different synthetic pathways toward this key structure for the development of new antibacterial agents. The most extensively applied methods for 3-amino-β-lactam ring formation are discussed, in addition to a few less common strategies. Moreover, approaches to introduce the 3-amino substituent after ring formation are also covered.

1. Introduction

β-Lactams, or azetidin-2-ones, are of utmost importance in medicine owing to their broad range of bioactivities.[1] Since the discovery of the antibacterial properties of penicillin G (1, Figure 1) by Alexander Fleming almost 90 years ago,[2] there has been an ongoing interest in the synthesis of β-lactams.

![Figure 1. Different classes of β-lactam antibiotics.](image)

This has led to the design and synthesis of various classes of β-lactam antibiotics (Figure 1). However, the onset of bacterial resistance necessitates ongoing research and development of innovative target compounds by exploring the chemical space around the β-lactam scaffold. Apart from their pharmacological purposes, β-lactams are also valuable from a synthetic point of view as they can function as building blocks for the synthesis of several classes of acyclic and heterocyclic target compounds, a methodology known as the “β-lactam synthon method”.[3] For example, 3-amino-β-lactams can be transformed into a broad variety of β-lactam and non-β-lactam products through selective side-chain modifications and/or manipulation of the ring system (Figure 2).

β-Lactam antibiotics interfere in the biosynthesis of the bacterial cell wall by inhibiting the penicillin-binding proteins (PBPs) that catalyze the synthesis of peptidoglycan, the main component of the bacterial cell wall. An important structural characteristic of these molecules is the presence of a 3-aminoazetidin-2-one core in which the amino substituent is a key ele-

![Figure 2. Synthetic applications of 3-amino-β-lactams to produce a broad variety of β-lactam and non-β-lactam products.](image)
ment in the resemblance of d-alanyl-d-alanine, the natural substrate of the PBPs. Although many literature reviews are available on β-lactam chemistry, 3-amino-β-lactams are often only briefly mentioned in these papers. Hence, this Review provides a resource for the synthesis of this key structure as an important building block. Typically, these compounds are obtained by modification of intermediates produced by biosynthesis. This method, however, is not included here, but can be studied in detail in the appropriate literature. Furthermore, only monocyclic β-lactams are considered here, even though most methods can be applied to the synthesis of bicyclic lactams by using cyclic starting materials or a later cyclization step. The different synthetic methods are organized according to the type of reaction. In the first part of our discussion, the Staudinger ketene-imine and enolate-imine cyclocondensations, two very popular methods for the synthesis of 3-amino-β-lactams are described, followed by the less frequently applied Kikugasa cycloaddition. The different cyclization reactions using open-chain precursors are then reviewed and are classified according to the atoms involved. The 3-amino group can be in-

Matthias D’hooghe was born in Kortrijk (Belgium) in 1978. He received a Masters degree in 2001 (Master of Science in Bioscience Engineering: Chemistry) and a PhD degree in 2006 (Doctor in Applied Biological Sciences: Chemistry), both from Ghent University (Belgium) with Prof. N. De Kimpe. In 2007, he became a Postdoctoral Assistant at the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, and then undertook a short postdoctoral stay with Prof. D. Vogt at Eindhoven University of Technology (The Netherlands) in the field of homogeneous catalysis. He was later promoted to Professor (Research Professor) at the Department of Sustainable Organic Chemistry and Technology (Ghent University), and he was granted tenure in 2015. His main research interests include the chemistry of small-ring azaheterocycles, with a special focus on aziridines, azetidines and β-lactams, and the synthesis of different classes of bioactive heterocyclic compounds.

Sari Deketelaere was born in 1993 in Ghent (Belgium). She obtained a Masters degree in Bioscience Engineering: Chemistry and Bioprocess Technology at Ghent University (Belgium) in 2016. For her Masters thesis, she worked on the synthesis of novel monocyclic β-lactams as potential inhibitors of the penicillin-binding proteins of resistant bacteria. Currently, she is a PhD student working at the Department of Sustainable Organic Chemistry and Technology at Ghent University under the guidance of Prof. Matthias D’hooghe. Her research interests are focused on the synthesis and deployment of functionalized β-lactams for the construction of biologically relevant mono-, poly-, and spirocyclic azaheterocycles.

Tuyen Nguyen Van was born in Thanh Hoa province (Vietnam) in 1961. He received his PhD under the supervision of Professor Dr. P. F. Vlad in 1991, Kishinev (Moldavia). He then worked as a Postdoctoral Fellow at the Department of Pharmacognosy, College of Pharmacy, University of Illinois at Chicago (USA) under the supervision of Prof. Dr. H. S. H. Fong. He performed postdoctoral research at the Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University (Belgium), under the guidance of Prof. N. De Kimpe. Since 1993, he has been head of the Laboratory of Medicinal Chemistry at the Institute of Chemistry, Vietnamese Academy of Science and Technology in Hanoi (Vietnam) and, since 2010, he has been Director of the Institute of Chemistry. He is Full Professor at the Institute of Chemistry-Vietnam Academy of Science and Technology, established in 2013. His interests are in the synthesis of small-ring azaheterocycles, such as aziridines, azetidines, and β-lactams, and the synthesis of biologically active compounds used in medicine.

Christian V. Stevens (1965) is currently Senior Full Professor and Chair of the Department of Sustainable Organic Chemistry and Technology at the Faculty of Bioscience Engineering at Ghent University (Belgium). He graduated from the same department as a Bioengineer in Chemistry in 1988 and obtained a PhD in 1992, working with Prof. Norbert De Kimpe. He then performed postdoctoral work at the University of Florida (USA) with the late Prof. Alan Katritzky as a NATO Research Fellow. He performed a short postdoctoral stay at the University of Alicante (Spain) with Prof. Miguel Yus and then became Research Leader of the FWO-Flanders (Fund for Scientific Research). He became Associate Professor at the Faculty of Bioscience Engineering and started the research group SynBioC (Synthesis, Bioresources and Bio-organic Chemistry). He later became Full Professor and then 2016 Chair of the Department. His research interest is focussed on the use of renewable resources for industry and on synthetic heterocyclic chemistry related to agrochemical and medicinal applications.
duced after β-lactam ring formation as well, and this approach will be covered in the final section of this Review.

2. Preparation of 3-Amino-β-lactams by Cyclocondensation Reactions

In the first part of this section, the synthesis of 3-amino-β-lactams by cyclocondensation reactions is documented. These methods, involving reaction of a ketene or enolate with an imine, are well known and have been applied extensively. In 1991, van der Steen and van Koten published a comprehensive literature survey for the specific synthesis of 3-amino-β-lactams by these approaches.[6]

2.1. Staudinger Ketene–Imine Cyclocondensation

2.1.1. General Mechanism

The first synthesis of the β-lactam ring structure was reported in 1907 by Hermann Staudinger.[7] The Staudinger synthesis is still one of the most popular methods in β-lactam chemistry and involves a [2+2] cyclocondensation between ketenes 5, generated in situ by treatment of acid chlorides 4 with a mild base, and imines 6 (Scheme 1). Instead of acid chlorides, carboxylic acids can also be used as ketene precursors by treatment with an appropriate activator and subsequent addition of a mild base.[8] The initial step of the reaction, a nucleophilic addition of the imine nitrogen across the electrophilic carbon of the ketene at the less-hindered side, results in zwitterionic intermediates 7/8 which, whether or not after isomerization, undergo conrotatory electrocyclic ring closure to afford azetidin-2-ones 9/10.

![Scheme 1. Staudinger [2+2] cyclocondensation between ketenes 5 and imines 6.](image_url)

An important aspect in the Staudinger synthesis concerns the relative stereoselectivity of the products, which is the result of competition between direct ring closure and isomerization of the imine bond in the zwitterionic intermediate 7 as concluded by Xu and co-workers.[8] This competition is regulated by electronic effects induced by the substituents of the ketene 5 and imine 6 on the ring-closure step and the steric hindrance exerted by the N-substituent of the imine. An increased size of the N-substituent results in an increased formation of the cis isomer 9. The presence of electron-donating ketene substituents and electron-withdrawing imine substituents preferentially leads to cis-β-lactams 9 by accelerating the direct ring closure. Electron-withdrawing ketene substituents and electron-donating imine substituents slow down the direct ring closure and afford thermodynamically more stable trans-β-lactams 10 after isomerization. Ketenes are divided into three groups according to their electron-donating ability. Bose–Evens ketenes possess strong electron-donating substituents, such as O-alkyl/aryl or N-alkyl/aryl groups, and formation of cis-β-lactams 9 will thus be preferred. With Sheehan ketenes, such as phthalimidoketene, the stereocchemical outcome is more complex. Moore ketenes, possessing weak electron-donating substituents such as 5-alkyl/aryl, alkyl and aryl groups, favor the formation of trans-β-lactams 10. The same group of researchers has investigated the effect of the reaction conditions on the stereoselectivity.[9] They observed the formation of increased amounts of the cis isomers 9 in nonpolar solvents. These observations indicate that a nonpolar solvent cannot stabilize the zwitterionic intermediates 7 and thus facilitates the direct ring closure toward cis-β-lactams 9. From that point of view, the use of polar solvents can increase the half-life of the intermediate 7 through stabilization and therefore facilitates isomerization. The application of different additives did not lead to any change in stereoselectivity.

In case ketenes 5 need to be generated in the presence of a base, the order of addition can play an important role. Two different approaches are often applied, the acid chloride can be added dropwise to the solution of the imine and base, or the base can be added to the mixture of acid chloride and imine. The experiments indicate that, in general, the latter approach results in a decrease of the stereoselectivity. Furthermore, the interval between the addition of the acid chloride and base also affects the stereochemical outcome. If the base is added after a longer period of time, the β-lactams are obtained in low yields and the selectivity is generally small. Another important factor influencing the outcome of the Staudinger reaction is the reaction temperature.[10] With increasing temperature, the cis selectivity generally decreases. The effect is substantial in case of the phthalimidoketene-participating reaction. At 40 °C the cis/trans-ratio is 87:13, and this reverses to 4:96 at 150 °C for the reaction of this ketene with N-isopropyl-1-(4-methoxyphenyl)methanimine. It should be noted that in the higher temperature range this influence is more pronounced.

In addition to the use of classic ketene precursors, ketenes can be generated through photolysis of metal–carbene complexes, so-called Fischer carbenes.[11] Mechanistic studies have shown that by irradiation ofaminocarbene complexes 11, carbon monoxide insertion results in ketene complexes 13 (Scheme 2).[12] Alternatively, the mesionic münchnones 14 can be used for the synthesis of 3-amido-β-lactams (Scheme 2).[13] The strategy involving 14 can also be thought of as a multiple component reaction. In that respect, Arndtsen and co-workers have reported the Pd-catalyzed formation of these β-lactams from carbon monoxide, an acid chloride, and two equivalents of an imine via the münchnone intermediates.[14] The required
2.1.2. Staudinger Reaction toward 3-Amino-β-lactams

The group of Sheehan was the first to report the direct synthesis of α-amino-β-lactams.[15] 1,4-Diphenyl-3-phthalimidoazetidin-2-one (18a) was prepared by addition of phthalimidoacetyl chloride (16a) to a solution of triethylamine and N-(benzylidene)aniline (17) and was easily deprotected to the free 3-amino-β-lactam 19 by hydrazinolysis (Scheme 3). The reaction could be further extended to imidates as imine equivalents, as reported by Paul and co-workers.[17] Bose et al. used azidoacetyl chloride (16b) to introduce the amino group, resulting in a mixture of cis- and trans-β-lactams 18b, catalytically reduced to 19 using the Adams’ catalyst.[18] The ratio depended on the sequence of addition, varying from 75:25 to 25:75, respectively, for addition of acid chloride 16b to a solution of imine 17 and triethylamine or addition of triethylamine to the acid chloride 16b and imine 17.

The same group of researchers has reported the application of benzoylcarbonylglycyl chloride, resulting in an carbamate group at C3.[19] After treatment with hydrogen bromide in acetic acid, the amino group can then be provided bearing the desired substituent. Sharma and Gupta have described the use of a protecting group that was initially developed by Dane et al. for peptide synthesis.[20] The “Dane salt” 20, generated by treatment of the potassium salt of an amino acid with a β-dicarbonyl compound, is an enaminoine derivative stabilized by hydrogen bonding (Figure 3). Reaction of this salt with phosphoryl chloride and imines in the presence of triethylamine and subsequent deprotection by a mixture of ethanol and hydrochloric acid (2:1) has been described to give 3-amino-β-lactams. Ozonolysis, instead of acid deprotection, finally resulted in 3-amido-β-lactams.[21] An important feature of this protecting group strategy is the exclusive cis stereoellectivity, except for thioimidates, for which only the trans isomers are afforded.[22] Other activating agents reported for Dane salts in β-lactam formation are phosphorochloridate esters or haloformate esters,[21] cyanuric chloride,[23] propane phosphonic acid anhydride[24] and triphosgene.[25] Some less common precursors for the 3-amino group (such as alkylarylamine, tetraclorophthalimido, and N-fluorenylmethyloxycarbonyl-N-methyamino groups, and saccharin) have been investigated.[26]

Over the years, many activating agents have been evaluated for the synthesis of β-lactams by means of utilizing imines and carboxylic acids for the Staudinger synthesis. In addition to those mentioned for Dane salts, inter alia, triphenylphosphine dibromide,[27] the Vilsmeier reagent (21),[28] the Mukaiyama reagent (22),[29] cyanuric chloride–dimethylformamide complex,[30] and dimethylsulfoxide–acetic anhydride complex[31] have been applied (Figure 4).

![Figure 3. Dane salt 20.](image)

![Figure 4. Reagents for activating carboxylic acids in β-lactam synthesis.](image)
The stereoselective approach with chiral ketenes is limited to imines derived from non-enolizable aldehydes. With enolizable imines, low yields of 3-amino-β-lactams are obtained as a result of isomerization to enamines. In that respect, Palomo et al. have discovered a way to circumvent this limitation by applying N-[bis(trimethylsilyl)methylidene]amines.

Reaction of acid chlorides and imines gave predominantly cis-β-lactams with complete asymmetric induction at C3 (Scheme 5). In most cases, a desirable selectivity was obtained, with only small amounts of the trans isomer (epimeric at C4) formed. Methoxycarbonyl-substituted imine (R_2 = CO_2Me) resulted in an almost equimolar mixture of the two cis-β-lactams. Deprotection of the oxazolidinone moiety occurred following the method of Evans and Sjogren, except for the diphenyl-substituted derivative (R_1 = Ph), which could be easily liberated by palladium-catalyzed hydrogenation. The β-lactam N-substituent can be removed by treatment with cerium ammonium nitrate (CAN) in acetonitrile/water mixture (3:1), which effectively cleaves the C-Si bond, followed by N-deformylation under slightly basic conditions. By prolonged exposure of the β-lactam to CAN in methanol, the azetidin-2-one nitrogen atom can be deprotected directly, without the need for an extra deformylation step, which sometimes results in epimerization at C3.

The utility of camphorsultam as a chiral auxiliary has been demonstrated in a wide range of organic reactions and has therefore been investigated for the asymmetric synthesis of 3-amino-β-lactams. Treatment of camphorsultam-derived acid chlorides and carboxylic acids with imines resulted in the formation of single cis isomers of β-lactams in moderate to good yields (Scheme 6). However, attempts to remove the camphorsultam moiety by acid or base hydrolysis or by using reductive techniques were unsuccessful.

2.1.3.2. Chiral Induction by the Imine

Chiral induction by the imine component originates from the imino carbon or imino nitrogen substituent, depending on whether the imine is derived from a chiral aldehyde and an achiral amine or from an achiral aldehyde and a chiral amine, respectively. In general, low levels of diastereoselectivity are obtained in the latter case. For example, imines derived from (1R)-1-phenylethylamine reacted with phthalimido acid chlorides to produce a diastereomeric mixture (d.r. = 81:19) of the two cis-4-fluoromethyl-β-lactams (Scheme 7).
Georg et al. used the same amine, in addition to \((1R)-1-(1\text{-}naphthyl)\)ethylamine for the enantioselective synthesis of 4-styryl- and 4-chloromethyl-\(\beta\)-lactams.\(^{37/38}\) The same level of diastereoselectivity was obtained (d.r. = 80:20 to 85:15), with the asymmetric induction of \((1R)-1-(1\text{-}naphthyl)\)ethylamine being only slightly higher.

Preparation of \((3S)\)-phthalimido-\(\beta\)-lactam as a single isomer has been accomplished by application of imine 39 derived from \(\alpha\)-glucosamine (Figure 5).\(^{40}\) The application of \(O\)-silylated imines (with two chiral centers) as chiral auxiliaries for the enantioselective synthesis of \(cis\)-azetidin-2-ones has independently been reported by Gunda and Bose. Replacement of the trimethylsilyl (TMS) protecting group in imine 40 by the more bulky tert-butyldimethylsilyl (TBDMS) group, resulted in a shift in diastereomeric ratio from 66:34 to 89:11.\(^{41}\) If the hydroxyl group in \(\alpha\)-threonine-derived imine 41 is unprotected (\(R = H\)), hydrogen bonding occurs with the carbonyl of the ester group, resulting in an almost planar structure and as a consequence no diastereoselectivity.\(^{42}\) If imine 41 is derived from phenylserine instead of threonine, two diastereomeric \(cis\)-\(\beta\)-lactams were formed in an 80:20 ratio. With \(O\)-silylated imines 41, a slight increase (from 80 to 90\%) in diastereoselectivity was observed by exchanging the TBDMS moiety for the triphenylsilyl (TPS) group.

Asymmetric induction by the imino-carbon substituent has known to be more successful over the years. \(\alpha\)-Glyceraldehyde acetonide-derived imines 43 reacted with potassium azidoacetate (42), in the presence of cyanuric chloride as activating agent, giving rise to \(cis\)-(3\(R\))-3-azidoazetidin-2-ones 44 as single isomers (Scheme 8).\(^{45}\) Many asymmetric Staudinger syntheses with protected aminoketones show \(cis\)-selectivity. Panunzio and co-workers, however, have reported the exclusive formation of \(trans\)-\(\beta\)-lactams 47 with \(N\)-(trimethylsilyl)imines 45 derived from chiral \(O\)-silyl-protected \(\alpha\)-hydroxy aldehydes (Scheme 9).\(^{46}\) The reaction with phthalimido acid chlorides resulted in \(N\)-unsubstituted \(trans\)-\(\beta\)-lactams 47, due to loss of the TMS group during workup and purification. To explain the \(trans\) selectivity, intermediate 46 was proposed. The obtained \(\beta\)-lactams, however, consisted of two diastereomers in equal amounts. If a more sterically demanding imine side chain (\(R\)), such as isopropyl, was used, the diastereomeric ratio increased to 85:15.

As reported by Palomo et al., the nitrogen analogues 48 and 49 can also be used for the enantioselective synthesis of \(3\)-amino-\(\beta\)-lactams (Figure 6).\(^{47}\) Due to the opposite stereochemistry of the chiral auxiliary of imine 48 with respect to imine 43, the \((3S)\)-\(\beta\)-lactam is formed. In addition to these chiral aldehydes, other examples have been investigated by other research groups. In that respect, the application of chiral \(\alpha,\beta\)-epoxyimines 50 has been shown to lead to the formation of \(cis\)-3-phthalimido-\(\beta\)-lactams with a diastereomeric excess between 80\% and 94\%.\(^{48}\)

### 2.1.3.3. Double Asymmetric Induction

The double asymmetric induction approach utilizing Evans–Sjogren ketenes and imines bearing chiral N-substituents was
With amino-ester-derived iminedithiocarbonates [48], after the cyclocondensation of the iminedithiocarbonates, tert-butyl glyceraldehyde acetonide and O-silylated α-hydroxy aldehydes, have thoroughly proven their utility in the asymmetric synthesis of 3-amino-β-lactams. The next question that arises, is how the combination of both influences the stereogenic outcome. Palomo et al. have published their observations in terms of “matched” and “mismatched” cycloadditions.[45, 48] An x,y-matched pair means that the chiral substituents at positions x and y exhibit the same induction sense, whereas for a x,y-mismatched pair the opposite is observed. As could be expected, only one isomer of the β-lactams 56 was obtained, as acid chlorides 54 and imines 55 formed 3,4-matched pairs (Scheme 11). [46] However, reaction with imines 57 resulted in a mixture of the two cis isomers 58/59 because both chiral templates were mismatched. By increasing the 3D size of the ketene substituent, changing from a phenyl group in 54a to an isopropyl group in 54b, the influence became more evident, leading to β-lactam 58b as the major stereoisomer, the so-called Evans-product. However, the results have to be interpreted with care because, surprisingly, if the oxazolidinone is substituted with a bulky tert-butyl group, only the anti-Evans adduct is formed.[46] To obtain β-lactam 58 in a stereoselective manner, an alternative approach can be followed, starting from the 3,4-matched template-derived β-lactams 56. In that respect, the hydroxyl group can, after desilylation, be converted into a ketone by Swern oxidation. Subsequent stereoselective reduction of the keto group by treatment with l-selectride resulted in the desilylated form of β-lactam 58 as a single isomer.

In the same report, the application of three chiral templates was investigated, whereby three combinations were taken into account: 1,3,4-matched, 1,4-matched–3,4-mismatched, and 1,3-matched–3,4-mismatched. In the first case, only one β-lactam isomer was formed, as expected. In the latter two cases, mixtures of the Evans and anti-Evans products were observed. Nevertheless, the chiral N-substituent seems to reinforce the chiral induction sense of the matched partner.

Most asymmetric syntheses are chiral auxiliary based and thus require additional steps to introduce and remove these auxiliaries. The group of Lectka has investigated the catalytic asymmetric synthesis of β-lactams.[49] This method involved a chiral nucleophilic catalyst, such as benzoylquinine (63), that reacted with the ketene derived from acid chloride 60 to produce the zwiterionic enolate 64 (Scheme 12). Proton Sponge (62) was chosen as non-nucleophilic, stoichiometric base to produce the ketene from the acid chloride. By formation of the enolate, the ketene polarity was changed, affording the possibility to synthesize β-lactam 65 with the electron-deficient imine 61. Owing to the distinctive mechanism, this method cannot be referred to as a standard Staudinger synthesis and is often described as the “umpolung” Staudinger approach. The mechanism is probably more comparable with the enolate-imine cyclocondensation, in which the imine acts as the electrophile. This is discussed in more detail in the next section.

### 2.1.4. Obstacles Associated with Aliphatic Imines and Formaldime

For the synthesis of 4-unsubstituted derivatives, the instability of the required formaldehyde imines presents a problem. Therefore, formaldime precursors need to be deployed that mostly appear as trimers such as hexahydro-s-hydrazines [50]. Treatment of these trimers with a Lewis acid generates in situ the monomeric formaldimes 67 (Scheme 13). Alternatively, iminodithiocarbonates can be deployed as formaldehyde imine equivalents.[51] After the cyclocondensation of the iminodithio-
carbonate with a ketene, generated by photolysis of a chromium-carbene complex, a nickel boride desulfurization leads to the 4-unsubstituted 3-aminoazetidin-2-one system.

The issue of the instability of formaldimines can also be circumvented by the use of dialkyl hydrazones, which show greater stability. Fernández, Lassaletta and co-workers have extensively investigated the application of hydrazones in this cyclocondensation reaction with a mechanism comparable to the classical Staudinger synthesis.\[52\] If the N-benzyl-N-(benzylloxycarbonyl)aminoketene derived from 68 was applied, the best stereoselectivities were obtained with C₂-symmetric dialkyl hydrazones, for example 69b, an inherent property of this type of auxiliary (Scheme 14). With chiral ketenes, such as that derived from (R)-2-(2-oxo-4-phenylloxazolidin-3-yl)acetic acid, a high selectivity was observed with asymmetric chiral hydrazones such as 69a. Both (S)- and (R)-3-amino-β-lactams can be synthesized in enantiomerically pure form by applying α-mannitol- and l-proline-derived hydrazones, respectively. The β-lactam nitrogen was liberated by oxidative N–N bond cleavage with magnesium monoperoxyphthalate. Additionally, the reaction can be extended to higher hydrazones derived from aliphatic, enolizable aldehydes.\[53\] The application of these hydrazones mainly leads to trans-4-alkyl-3-aminoazetidin-2-ones, and not to the expected cis stereoisomers.\[54\] Apparently, due to steric hindrance between the bulky amino substituent of the ketene and the alkyl group of the hydrazone, no direct ring closure occurs. According to the authors’ results, the isomerization of the zwitterionic intermediate is the result of a nucleophilic addition, rotation and elimination effected by nucleophiles present in the reaction mixture.\[55\] The reaction temperature also has a significant influence on the stereochemical outcome. If the reaction is performed at room temperature instead of at 80 °C, the cis isomer is favored.

As mentioned in the previous section, the application of N-[bis(trimethylsilyl)methylidene]amines also provides an answer to the problem of the instability of imines derived from formaldehyde and enolizable aldehydes.

2.2. Enolate–Imine Cyclocondensation

Gilman and Speeter were the first to report the synthesis of β-lactams by an ester–imine cyclocondensation, based on a Reformatsky-type reaction between the zinc enolate of an α-bromo ester and an imine.\[56\] By applying esters of amino acids 71, in which the amino functionality is protected by an acyl or carbamate group, 3-amino-β-lactams can be synthesized. In addition to these amino esters, dialkyl, dibenzyl and N,N-bis-silyl protections are often used, the latter group being easily removed by acid- or base-catalyzed hydrolysis. By adding lithium base, the corresponding anion 72 was formed and reacted with imine 73 via intermediate 75 (Scheme 15). The same difficulty as with the Staudinger synthesis arose, that is, the instability of imines of formaldehyde. In this case, the use of secondary N-(cyanomethyl)amines 74 as precursors provided the synthesis.
of 4-unsubstituted derivatives.\[57\] These precursors can be converted in situ to formal imines by treatment with organolithium or Grignard reagents. The ester enolate-imine cyclocondensation can also be conducted using solid-phase synthesis, as reported by Schunk and Enders.\[58\] Their approach utilized resi-bound esters (R\(^1\) = Me) that, after reaction with imines (R\(^1\) = R\(^2\) = aryl) and subsequent cleavage, produced 3-amido-\(\beta\)-lactams.

In some cases, a transmetallation reaction occurred prior to imine addition, for example, with ZnCl\(_2\), Me\(_3\)AlCl, Ti(OiPr)\(_4\)Cl. The group of van Koten has extensively investigated the application of metal enolates and the diastereoselective outcome associated with this approach. In general, zinc-mediated reactions resulted predominantly in trans-\(\beta\)-lactams because of the chelation-controlled formation of \(Z\)-enolates, whereas lithium enolates afforded cis isomers or cis/trans mixtures.\[59\] The same research group reported the application of aluminum enolates, obtained by transmetallation with an excess of dialkyl aluminum chloride, with even better trans selectivity than zinc enolates.\[60\] During the transmetallation, however, an amide side product was obtained, making the reaction less clean than the zinc-mediated one. It has to be noted that, in some cases, trans selectivity was observed for the reaction of lithium enolates and imines. The treatment of benzoylglycine ethyl ester with lithium disopropylamide generated the dienion that underwent reaction with diialyl imines to give only trans-3-amido-\(\beta\)-lactams instead of the expected cis isomers.\[61\] Trans-selectivity was also observed in the synthesis of a 3-phthalimido-\(\beta\)-lactam by the condensation of an imine and the titanium enolate of a mixed anhydride, formed by treatment of a carboxylic acid with Lawesson's reagent.\[62\]

Cis/trans selectivity is also known to be influenced by the steric and electronic properties of the substituents.\[63\] Bulky and electron-withdrawing substituents on the \(\alpha\)-amino group of the zinc enolate and electron-withdrawing groups attached to the imine nitrogen induce higher trans selectivity. Additionally, C4-functionalization will enhance the selectivity as well. The application of bis-imines results predominantly in trans-4-imidoyl-\(\beta\)-lactams (de > 90\%), whereas the sulfur and oxygen analogues show a lower selectivity (de 0–85\%).\[64\]

Another important factor concerns the solvent polarity. Reactions with zinc enolates afford trans-azetidin-2-ones in weakly polar solvents, whereas in polar solvents, cis isomers are favored.\[65\] The best strategy toward cis selectivity is the use of hexamethylphosphoramide (HMPA) as a co-solvent. In addition to solvent influence, increasing the amount of zinc chloride also enhances formation of cis-\(\beta\)-lactams. These effects are not cumulative, as in polar solvents no effect of using an excess of zinc chloride has been observed. Furthermore, zinc enolates can react with activated as well as with unactivated imines, whereas lithium enolates only react with activated ones.\[66\] In that respect, together with the possible reversal in diastereoselectivity, the zinc-mediated condensation is favored.\[67\]

For the enantioselective synthesis, three strategies can be applied.\[68\] The first approach is the application of chiral esters (\(R^1\)), but initially, little chiral induction was observed.\[69\] Ojima and Habus, however, obtained high enantioselectivity with chiral N,N-bis-silyl-protected glycine esters in a lithium-mediated reaction, specifically with methyl and trans-2-phenyl-1-cyclohexyl esters (ee > 99\%).\[70\] Presumably, in chelation-controlled transition states (zinc- or aluminum-mediated reactions), the chiral center is too remote to cause large energy differences, thus inducing low selectivity.\[71\]

In a second approach, a chiral auxiliary at the imino-carbon (\(R^1\)) was expected to show high chiral induction because of the proximity to the newly formed chiral centers. This method has been applied by Cainelli et al. with silyl imines of lactic aldehyde.\[72\] It was shown that high enantioselectivities can be obtained via these substrates if the proper protection of the \(\alpha\)-hydroxyl group is chosen. It was also noticed that cations present in the reaction mixture can affect the stereoselectivity. For example, the presence of Na\(^+\) instead of Li\(^+\) resulted in lower selectivity. This research group also investigated the reaction of \(\beta\)-hydroxy-substituted silyl imines, which resulted, however, in the four possible isomers in a different ratio that depended on the substituents and reaction conditions.\[72\] Also, in zinc-mediated reactions, desirable results in terms of selectivity were obtained.\[66\]

The last approach involved a chiral imine N-substituent (\(R^1\)) and has been applied to the synthesis of 4-unsubstituted \(\beta\)-lactams, resulting in a 11:1 mixture of diastereomers.\[73\] For the zinc-mediated reaction with N-(\(R\))-\(\alpha\)-methylbenzyl-substituted 1-aza-4-hetero-1,3-butadienes, the nitrogen analogue induced a higher selectivity than the oxygen analogue.\[64\] If ethyl-substituted imines were applied, the four isomers were obtained in good selectivities by changing the polarity of the solvent. The use of amino esters to generate chiral imines not only resulted in chiral induction, but also provided a carboxyl or ester functionality, which is present in many \(\beta\)-lactam antibiotics, without the need for extra steps.\[69\] \(\beta\)-Lactam formation with these imines necessitates double activation, implying the need for complexation of the imine with zinc chloride prior to addition to the zinc enolate. The reaction of the STABASE-protected ethyl ester of glycine with N-benzylidine-2-phenylglycine methyl ester provided the 35,43,\(\alpha\)-R isomer in a diastereomeric excess of 97\%. Other imino esters were also used, with a good overall selectivity depending on the substituents.\[72\] It was also observed that the \(\alpha\)-center of the phenylglycine methyl ester could epimerize after \(\beta\)-lactam formation upon treatment with triethylamine, whereas no epimerization was detected for the other esters under alkaline conditions.

It was already clear that the metal counter ion controls the cis/trans selectivity, which is determined in the C–C bond formation step. Presumably, it can also influence the outcome in asymmetric synthesis. Fujisawa et al. have reported a complete reversal of the selectivity from 35,4R to 3R,4S after transmetalation with chlorotitanium(IV) triisopropoxide instead of zinc chloride.\[71\] It is likely that any stereoisomer can thus be synthesized by the enolate-imine condensation if the proper set of parameters (substituents, counter ion, reaction conditions) is chosen.
3. Kinugasa Alkyne–Nitrone Cycloaddition toward 3-Oxazolidinone- and 3-Phthalimido-β-lactams

In 1972, Kinugasa and Hashimoto reported the formation of β-lactams by reaction of copper(I) phenylacetylide and nitrones with pyridine as both base and solvent.[72] This method is still used for the stereoselective synthesis of 3-amino-β-lactams starting from the chiral ynamides 77.[73] The initial step, a 1,3-dipolar cycloaddition of the copper acetylide with nitrones 78, provides metalated isoxazoline intermediates 79, which form β-lactam rings after rearrangement (Scheme 16). The stereochemistry is defined during the cycloaddition step and the final protonation, as revealed by the proposed model of Hsung and co-workers.[73] In the preferred pathway, the nitrone approaches the copper acetylide in such a way that steric interactions are minimized. Due to allylic strain, an isomerization step takes place and subsequently a facially selective protonation occurs to give the cis-(3R)-3-oxazolidinone-β-lactam as the major isomer.

Chmielewski and co-workers have reported on the Kinugasa reaction of phthalimido acetylene (83) with cyclic chiral nitrones 84, resulting in bicyclic β-lactams 85 with moderate selectivity (Scheme 17).[74] The six-membered ring can be opened by reduction with lithium borohydride, thus providing an alternative route toward the monocyclic β-lactam 88.

4. Preparation of 3-Amino-β-lactams by Cyclization Reactions

4.1. N1–C4 Cyclization

Another frequently used strategy for the synthesis of 3-amino-β-lactams is N1–C4 ring closure, which is known as a biomimetic process, via a variety of intermediates. N1–C4 cyclization of substituted hydroxamates, formed by coupling of an amino acid and an O-substituted hydroxylamine, has been described in detail by Miller and co-workers.[75] The use of β-halo-hydroxamates requires a base to induce ring closure to the corresponding 3-amino-β-lactams. To avoid the halogenation step, cyclization of β-hydroxy hydroxamates 89 (Scheme 18), readily accessible from the amino acids serine and threonine, seemed to be more convenient. In that respect, the hydroxyl functionality needs to be transformed into a good leaving group and

Scheme 16. The Kinugasa cycloaddition between 3-ethynyloxazolidin-2-ones 77 and nitrones 78.

Scheme 17. The copper-catalyzed conversion of phthalimido acetylene (83) and cyclic nitrones 84 to monocyclic β-lactam 88.

Scheme 18. N1–C4 cyclization of α-amino-β-hydroxy hydroxamates 89.
simultaneous formation of the nitrogen anion is required. Conversion of β-hydroxy hydroxamates 89 to N-Cbz- and N-Boc-protected 3-aminoazetidin-2-ones 90 occurred efficiently by the combined use of triphenylphosphine (PPh₃) and diethyl azodicarboxylate (DEAD) (Scheme 18). This N-alkylation under Mitsunobu conditions required that the acidic component has a pKₐ below 13, which is the case for O-alkylhydroxamates (the N–H bonds have pKₐ values of 9–10). A major advantage of this method is the predictability of the stereochemical outcome: retention of configuration at C3 and inversion at C4, implying the possibility to synthesize any chiral β-lactam starting from the corresponding amino acids. The by-products of the Mitsunobu cyclization (PPh₂O and diethyl hydrazidocarboxylate) however, are difficult to remove from the reaction mixture. As a possible solution, solid-phase synthesis with the hydrazinocarbonyl chloride, with sodium acetate as chloride scavenger and acetic acid as a catalyst. In this case, however, the ring opening appeared to be somewhat slow and TFA had to be added as a stronger catalyst. Subsequent cleavage of the benzoyl group in 93 failed. Therefore, this group had to be removed prior to triphenylphosphine ring opening.

In addition to hydroxamates, some less common intermediates can be cyclized under Mitsunobu conditions as well, although initially unexpectedly, according to Miller et al. because of the less acidic character of the amine proton in these intermediates. Treatment of dipeptides 96, for example, resulted, after hydrolysis of the terminal ester functionality within the formed β-lactam, directly in the desired N-substituent, that is, a carboxymethyl group present in several known β-lactam antibiotics (Figure 7). However, at first, epimerization occurred in the α-position of the carboxymethyl group, and a small amount of the elimination product 97, due to deprotonation at the C3 carbon, was observed. By adaptation and optimization of the cyclization conditions, implying a shift from 2.5 equivalents of PPh₂/DEAD to one equivalent of P(OEt)₂/DEAD, the diastereomeric ratio increased from 66:34 to >98:2, but formation of side product 98 was detected. Switching from the phthalimido toward an oxazolinone protecting group resulted in the formation of only one diastereomer, which could be deprotected without loss of optical purity. Varying the phosphorus reagent can influence the reaction outcome, as is clear from the observations described above. The azodicarboxylate reagent can be varied as well; in some cases more hindered ones are required to avoid the formation of azodicarboxylate adducts, which was observed with serylaminomalonates 96 \([R^2=CO_2R']\) [80]. These phthalimido- and also oxazolone-protected serylaminomalonates, as well as their phosphorous analogues \([R^2=PO(Oalkyl)]\), could be converted in good yields to the corresponding β-lactams if the appropriate Mitsunobu reagents were applied.

Other syntheses utilized intermediates such as N-arylamides and hydrazide derivatives 99 (Figure 7) [84]. During cyclization of
the carboxybenzyl-protected N-aryl amides 99 under Mitsuno-
bu conditions, the formation of aziridine 100 was ob-
served.[84a,b] This side product can also be formed with carboxy-
benzyl- or tert-butyloxycarbonyl-protected dipeptides.[86] To cir-
cumvent the formation of these aziridines, phthalimido or oxaz-
olinone derivatives can be used. Furthermore, the hydroxyl
group of N-aryl amides, as well as peptide analogues, can be
activated by conversion to an imidazolyl sulfonate.[83] Subse-
quent base-induced ring closure delivers the desired β-lactams
in good yields (63–85%).

Kita and co-workers have reported the synthesis of 3-amino-
β-lactams 102 by a Pummerer-type rearrangement.[80] Ac-
countingly, sulfoxide 101 was treated with ketene methyl tert-
dimethylsilyl acetal in the presence of catalytic amount of
zinc iodide (Scheme 20). The cis/trans-selectivity depended on
the stereochemistry of the sulfoxide; (R)-sulfoxides resulted
preferentially in cis-β-lactams.[87] More dilute conditions favored
the formation of cis-β-lactams, but also decreased the overall
reaction rate.

In the synthesis of α,α-disubstituted amino acid derivatives
by ring opening of cyclic sulfamidate 105, the unexpected 3-
amino-β-lactam 108 was observed if the lithium salt of 3-meth-
ylbutyramine 106 was used as a nucleophile.[88] Presumably,
the ester functionality in 105 was initially attacked by the nu-
cleophile 106, resulting in amide 107 which subsequently un-
derwent cyclization to β-lactam 108 in 60% yield (Scheme 21).

More recently, the synthesis of chiral α-amino-β-lactams 110
through palladium(II)-catalyzed amidation of C(sp^3)-H bonds
has been reported by Shi and co-workers.[89] By optimization of
the reaction conditions, NaO{sub}3 was identified as the best overall
oxidant in terms of reactivity and chemoselectivity, with acetic
anhydride as an additive in acetonitrile. Using the conditions
optimized for the conversion of amide 109, only a single di-
 stereoisomer of 110, with a small amount of the β-acetoxylat-
ed side-product 111, was observed (Scheme 22). This method
provides the possibility to prepare functionalized 3-amino-β-
lactams from simple alanine derivatives as the second step of
a two-step C(sp^3)-H monoarylation/amidation sequence in

moderate yields, in which the PIP directing group controls the
selectivity in the arylation step and enhances the reactivity in
the subsequent amidation step. By the same principles, 4-un-substituted derivatives can be synthesized via a cobalt-cata-
lyzed amidation with 8-quinoline as a directing group.[90]

4.2. N1–C2 Cyclization
To achieve N1–C2 ring closure, also known as Salzmann’s pro-
cedure, trimethylsilyl chloride and alkyl magnesium chloride
can be applied.[91] Using dichloromethane as the solvent in-
stead of diethyl ether, α,β-diamino esters 112 (R = alkyl) have
been converted into 3-amino-β-lactams 113 (Scheme 23, meth-
ood a).[92] In some cases, the cyclization of these esters with

![Scheme 20. A Pummerer-type rearrangement of tripeptide 101.](image)

![Scheme 21. The ring-closure-induced ring opening of cyclic sulfamidate 105.](image)

![Scheme 22. The Pd-catalyzed amidation of amide 109.](image)

![Scheme 23. N1–C2 cyclization of α,β-diamino carboxylic acids and esters 112.](image)
Grignard reagents was conducted without β-amino silylation, resulting in a cis/trans-mixture accompanied by a tertiary alcohol as a consequence of the attack of the Grignard reagent to the ester functionality (method b). A strong base, such as lithium bis(trimethylsilyl)amide (HMDS), can induce cyclization as well, provided that the β-lactam nitrogen group (R) is non-enolizable (method c). To introduce the desired carboxymethyl substituent at the β-lactam nitrogen, α,α-disubstituted esters 112 (R2 = CR’R”CO2Me) or silyl ethers 112 (R2 = CH2CH2OTMS) can be chosen as precursors which, after β-lactam formation, can be deprotected and oxidized toward the corresponding carboxyl group.

In addition to esters, the α,β-diamo acids 112 (R = H) can be applied by in situ activation of the carboxylic acid and subsequent base-induced cyclization (Scheme 23, methods d-f). In the literature, different dehydrating condensation reagents are mentioned, such as 2,2'-dipyridyl disulfide [(PyS)2] in combination with triphenylphosphine [94], 3,3'-phenolphosphoryl-bis(1,3-thiazolidine-2-thione) (PPTT), [95] methanesulfonyl chloride, [96] 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) [97] and the Mukaiyama reagent. [98] The stereochemistry is determined by the starting products, whereby retention of configuration is observed.

4.3. C3–C4 Cyclization

The intramolecular oxidative coupling of dianions provides an example of a C3–C4 bond formation method for the synthesis of 3-amino-β-lactams. The initial step comprised the generation of dianions 115 from acyclic tertiary amines 114, synthesized through alkylation and acylation of amines, by adding a base and a coordinative reagent (Scheme 24). The dianions 115 can be transformed into the corresponding β-lactams 116 by means of an oxidant. Copper(II) as an oxidant is very effective, yet is nonselective in ring closure. On the contrary, if Niodosuccinimide (NIS) is used, selectivity toward cis-β-lactams is observed. The (R)-1-phenylethyl substituent has been used as a chiral auxiliary for asymmetric synthesis, giving rise to (3S,4S)-β-lactam 116 as the major stereoisomer (90%).

5. Introduction of the 3-Amino Group after β-Lactam Formation

Contrary to the previously mentioned methods, the introduction of the amino substituent can occur after β-lactam ring formation through, inter alia, rearrangement, substitution and addition reactions. In this section, the different approaches are classified according to the C3-substituent of the starting β-lactam.

5.1. 3-Carboxy-β-lactams

The transformation of a carboxylic acid into an amine equivalent can be achieved by the Curtius rearrangement. Accordingly, treatment of 3-carboxy-β-lactam 117 with diphenylphosphoryl azide (DPPA) resulted in an isocyanate intermediate that, in the presence of benzyl alcohol, furnished benzyl carbamate 118 in 65% yield (Scheme 25).

5.2. 3-Hydroxy-β-lactams

Lattrell and Lohaus have reported the conversion of trans-β-lactams 120 bearing different sulfurylxylo substituents at the C3-position to cis-3-azidoazetidin-2-ones 121. [101] This method has been applied by different groups to the synthesis of 3-amino-β-lactams starting from 3-hydroxy-substituted derivatives via intermediates 120 with inversion of configuration at C3 (Scheme 26). It is important to note that this conversion occurred without loss of optical purity, thus affording the possibility to synthesize the desired 3-aminoazetidin-2-one in an enantioselective manner.

5.3. 3-Oxo-β-lactams

A third approach relates to the oxidation of the 3-hydroxyl group into a keto functionality, which, in turn, can serve as a substrate for the synthesis of 3-amino-β-lactams. More specifically, a 3-amino group has been introduced by treatment of 3-oxazetidin-2-ones 122 with hydroxylamine hydrochloride (Scheme 27). The resulting oximes 123 were reduced to 3-(acylamino)azetidin-2-ones 125, and subsequently hydroxylaminated to the free amines 124. The keto group can also be converted to an imino group by reaction with an alkyl amine. Subsequent transamination by the addition of a catalytic or stoichiometric amount of potassium tert-butoxide has been reported to give β-lactam 126 with a cis/trans-ratio of 20:80 or 80:20 respectively, which was transformed into the Cbz-protected 3-amino-β-lactam 127 by reaction with hydroxylamine hydrochloride and subsequent protection of the amino group. Other reductive aminations included the treatment of 3-oxo-β-lactam 128 with secondary amines, resulting in iminium intermediates.
that were reduced with NaBH(OAc)$_3$ to provide 3-amino-$\beta$-lactams 129 (Scheme 26).

Banik and co-workers have reported a bismuth-nitrate-catalyzed reaction for the synthesis of 3-pyrrolyl-$\beta$-lactams 131 (Scheme 29).

The most common method for the conversion of 3-halo-$\beta$-lactams to the corresponding amino-substituted derivatives is based on an $S$_N2 displacement, as is the case for the hydroxyl-substituted analogues mentioned in Section 5.2. Kehle and Jensen converted different trans-3-bromo-$\beta$-lactams to cis-3-azido-$\beta$-lactams with sodium azide in an aprotic solvent, for example:

![Scheme 26. Conversion of 3-hydroxy-$\beta$-lactams to 3-azido derivatives.](image)

![Scheme 27. Different approaches to introduce the 3-amino group starting from 3-oxo-$\beta$-lactams.](image)

![Scheme 28. Treatment of 3-oxo-$\beta$-lactams with secondary amines.](image)

![Scheme 29. Bismuth-nitrate-catalyzed conversion of 3-oxo-$\beta$-lactams toward 3-pyrrolyl-$\beta$-lactams.](image)
ample, DMSO.\cite{108} The same reaction can be realized for a phthalimido substituent at the C3-position by treatment with potassium phthalimide.\cite{109}

Furthermore, an amine equivalent has been introduced at C3 by reaction of 3-bromoazetidin-2-one 132, generated by ring expansion of the corresponding aziridine, with di-tert-butyldiazocarboxylate (DBAD) after lithium–halogen exchange, resulting in β-lactam 133 (Scheme 30).

Furthermore, a n-amine equivalent has been introduced at C3 by reaction of 3-bromoazetidin-2-one 132, generated by ring expansion of the corresponding aziridine, with di-tert-butyldiazocarboxylate (DBAD) after lithium–halogen exchange, resulting in β-lactam 133 (Scheme 30).\cite{109}

**Scheme 30.** Introduction of a 3-amine group after lithium–halogen exchange.

### 5.5. 3-Alkylidene-β-lactams

Addition of N-nucleophiles across the double bond of 3-alkylidene-β-lactams 134 has been reported to deliver an amino group at the C3-position (Scheme 31).\cite{111} At least one electron-withdrawing substituent (R<sup>2</sup>, R<sup>3</sup>) at the double bond is required to effect this reaction.\cite{112c} As an alternative, these 3-alkylidene-β-lactams can be converted into 3-oxo-β-lactams by ozonolysis, which can be transformed further into the desired 3-aminoazetidin-2-ones as described in Section 5.3.\cite{114c}

**Scheme 31.** Addition of N-nucleophiles onto 3-alkylidene-β-lactams 134.

### 5.6. 3-Unsubstituted β-Lactams

3-Amino-β-lactams can also be synthesized from 3-unsubstituted derivatives. The most convenient method for doing so consists of deprotonation and subsequent addition of the appropriate electrophile.\cite{108} Treatment with a lithium base, mostly lithium diisopropylamide, has been shown to result in the lithium enolate of β-lactam 136, which was quenched with an arylsulfonyl azide leading to introduction of a 3-azo substituent in a trans relationship to the C4 substituent, which was readily reduced to the free amine.\cite{5c,112} If a nitrite was applied as the electrophile, the oxime intermediates 137 were formed, and subsequent reduction preferentially gave the cis-β-lactams 138 (Scheme 32).\cite{113}

**Scheme 32.** Conversion of 3-unsubstituted β-lactams 136 to 3-amino-β-lactams 138.

Miller and co-workers serendipitously discovered an azide transfer to the C3-position with simultaneous cleavage of the N–OH bond in the N-hydroxy-β-lactam 139 upon treatment with 4-(azidosulfonyl)benzoic acid in the presence of triethylamine (Scheme 33).\cite{114} Isolation of an intermediate with a sulfonylated hydroxyl group led to the proposal of a plausible mechanism. After sulfonylation, the enolate 142 is formed, which is expected to be facilitated by the electron-withdrawing sulfonyloxy group at nitrogen in 141, allowing the azide to attack at C3, which results in N–O bond cleavage (Scheme 34).

**Scheme 33.** Simultaneous azide transfer and N–O bond cleavage during diazotization of β-keto ester 139.

By testing different conditions, the use of an excess of the nucleophile was preferred, in combination with an on-nucleophilic base to prevent competition.\cite{113c} The substituent at C4 plays an important role in the stereoselectivity. The larger this group, the more the attack is directed to the opposite side, leading to a more pronounced trans selectivity.

To avoid the use of intermediate azides, primary or secondary amine nucleophiles have also been screened, assuming they could also catalyze the enolization step prior to the nucleophilic substitution.\cite{113b} Sterically hindered amines (R<sup>1</sup> = iPr or R<sup>1</sup> = fBu, R<sup>2</sup> = H; Scheme 34) resulted in 3-aminoazetidin-2-
ones (predominantly trans). Less sterically hindered amines, however, afforded β-ketoamides as a side product at the expense of the desired β-lactams as a result of nucleophile-induced ring opening. The basicity of the used amine is a second important factor to promote the enol formation. It was observed that a pKₐ around 11 is optimal, otherwise more basic non-nucleophilic amines need to be added.

6. Other Approaches

β-Lactams can also be formed in the Ugi four-component reaction, in which the amine and carboxylic acid are included in the same substrate. The cyclocondensation of β-amino acid 144, formaldehyde (145) and isocyanides 146 has been reported to result, after rearrangement via an acyl transfer, in 3-azido-β-lactams 148 (Scheme 35).[117] Carboxylic acids containing Cbz- or Boc-protected amino groups at the α-position instead of an azido group, can also be converted.[118]

In addition to the discussed methods for β-lactam synthesis, several other approaches are available for the construction of this four-membered heterocycle, for example, through cycloaddition of vinyl ethers with isocyanates and the carbonylation of aziridines. However, these strategies have not been applied for the synthesis of 3-aminoazetidin-2-ones, and are therefore not mentioned in this Review.

7. Conclusions

3-Aminoazetidin-2-ones are important building blocks in heterocyclic chemistry, not only for the synthesis of the celebrated class of β-lactam antibiotics. Various scaffolds with other pharmacological purposes can be synthesized through the incorporation of this key structure, or it can be utilized for the preparation of other heterocycles and amino acid analogues by the β-lactam synthon method. The range of applications is likely to expand in the future, as β-lactams are expected to attract more and more attention, as for example, enzyme inhibitors (PBP inhibitors, β-lactamase inhibitors, cathepsin inhibitors, and so forth) or due to other important bioactivities (inhibition of cholesterol absorption, vasopressin V1A antagonist activity, anticancer properties, and so forth). Due to their widespread applicability, many efforts have led to the development of various methods to synthesize these 3-amino-β-lactams in parallel with other C3-substituted azetidin-2-ones. The first method, the Staudinger ketene–imine cyclocondensation, is still the most extensively applied approach. Since the proposal of this strategy, much progress has been made in terms of substrate scope and stereoselectivity. Nonetheless, this stereoselectivity often remains difficult to control and achieving the desired stereoselectivity sometimes requires a trial-and-error approach. The main limitation of the Staudinger synthesis—the instability of enolizable imines, with the exception of N-[bis(trimethylsilyl)methylidene]amine—has been eliminated by using the enolate-imine cyclocondensation, in which the imine becomes the electrophile. The stereochemical outcome of this reaction can be fine-tuned by applying a proper set of parameters, including selection of the substituents, the counter ion and the reaction conditions.

Since the discovery of the antibacterial properties of monocyclic β-lactams, several research groups have investigated the synthesis of 4-unsubstituted 3-amino-β-lactams. Accordingly, ketene and enolate-imine cyclocondensations can be applied, however, some amendments have to be made to the classical approaches. A very popular method nowadays concerns the N1–C4 cyclization of hydroxamates. Due to the highly acidic character of the proton of the hydroxamate nitrogen, selective deprotonation and subsequent cyclization is possible. This method has been extended to certain peptides, amides and hydrazides. In those cases, however, a variety of side products can be obtained. The great advantage of this approach rests in the predictability of the stereochemical outcome; retention at C3 and inversion at C4. Cyclizations involving other atoms of the final β-lactam, such as C3–C4 cyclizations, are less frequently applied. The introduction of the amino group at C3 after β-lactam ring formation has been developed starting from both unsubstituted and a range of substituted β-lactams.

In conclusion, the 3-amino-β-lactam scaffold can be obtained with any desired stereochemistry at C3 and C4. The main requirement is the correct choice of starting materials and synthetic approach, however, this is not conclusive. The substrate scope of some methods imposes a prominent limitation as well. The design of general methods for enantioselective β-lactam synthesis remains a major objective for the future, in parallel with the search for catalytic strategies and novel substitution patterns. Ongoing research and further developments in this field are thus highly desirable.

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Conflict of interest
The authors declare no conflict of interest.

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