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Synthetic Approaches toward Monocyclic 3-Amino-β-lactams

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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.

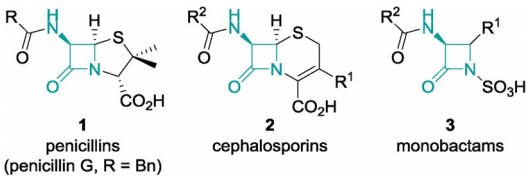

Figure 1. Different classes of β-lactam antibiotics.

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-

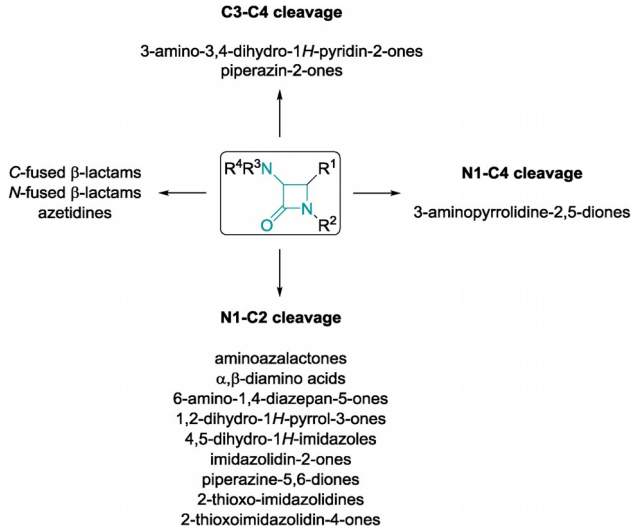

Figure 2. Synthetic applications of 3-amino-β-lactams to produce a broad variety of β-lactam and non-β-lactam products.

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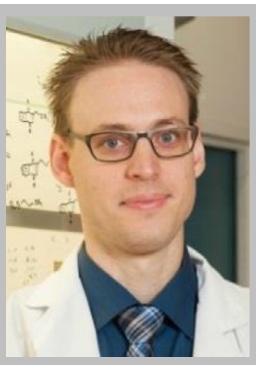
ment in the resemblance of D-alanyl-D-alanine, the natural substrate of the PBPs. Although many literature reviews are available on β-lactam chemistry,[4] 3-amino-β-lactams are often only briefly mentioned in these papers. Hence, this Review provides a resource for the synthesis of this key structure 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.[5] 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 Kinugasa 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-



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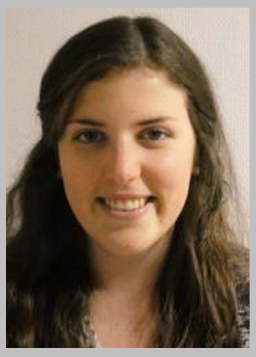

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Christian V. Stevens (1965) is currently Senior Full Professor and Chair of the Department of Sustainable Organic Chemistry and Technology at the Faculty of Bioscience Engineering at Ghent University (Belgium). He graduated from the same department 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.

troduced after β-lactam ring formation as well, and this approach will be covered in the final section of this Review.

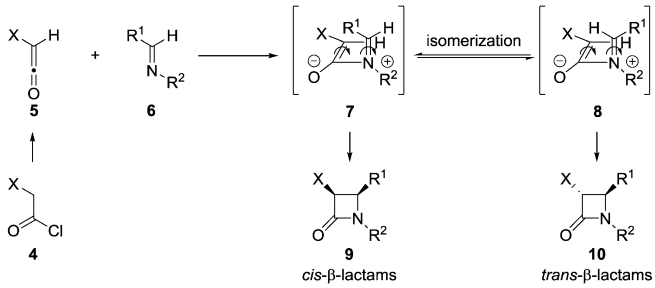
2. Preparation of 3-Amino-β-lactams by Cyclocondensation Reactions

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.[6] 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**.

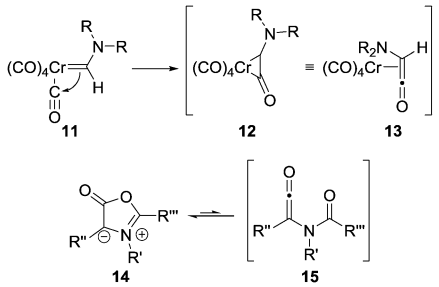


Scheme 1. Staudinger [2+2] cyclocondensation between ketenes **5** and imines **6**.

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–Evans 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 stereochemical outcome is more complex. Moore ketenes, possessing weak electron-donating substituents such as *S*-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 of aminocarbene complexes **11**, carbon monoxide insertion results in ketene complexes **13** (Scheme 2).[12] Alternatively, the mesoionic 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

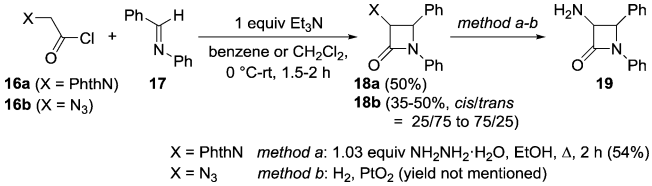


Scheme 2. Ketene generation by photolysis of chromium–carbene complexes **11** and münchnones **14**.

acid halide can also be generated in situ by Pd-catalyzed carbonylation of aryl halides.[15]

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.[16] 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



Scheme 3. Synthesis of 3-amino-β-lactam **19** starting from acetyl chloride **16** and imine **17**.

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 benzyloxycarbonylglycyl 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 enaminone derivative

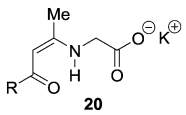


Figure 3. Dane salt **20**.

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* stereoselectivity, 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 alkylarylamino, tetrachlorophthalimido, and *N*-fluorenylmethyloxycarbonyl-*N*-methylamino 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).

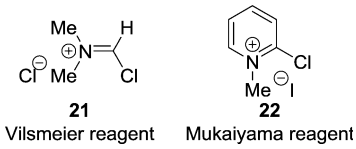


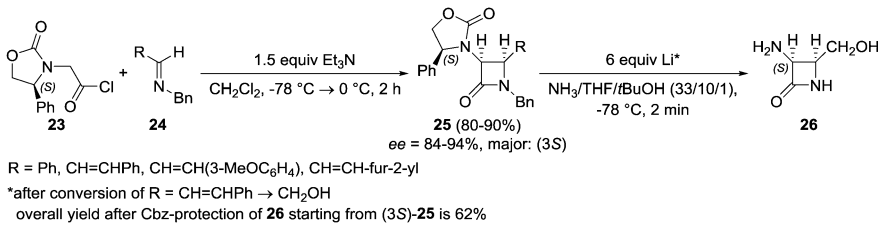
Figure 4. Reagents for activating carboxylic acids in β-lactam synthesis.

2.1.3. Asymmetric Staudinger Synthesis

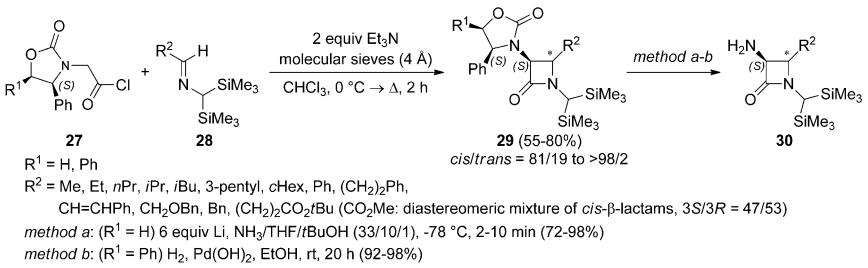
For the asymmetric synthesis of β-lactams, ketenes and/or imines with chiral substituents have to be used. Palomo et al. published a literature survey on this topic in 1999, with a specific section covering 3-amino-β-lactams.[4a,32] In the next section, the main contributions of this area are documented, ordered according to the position from which the asymmetric induction is exerted.

2.1.3.1. Chiral Induction by the Ketene

For ketene-mediated chiral induction, chiral oxazolidinone-protected aminoketenes are most often used. Evans and Sjogren, who were the first to apply this asymmetric approach, obtained *cis*-β-lactams **25** with good selectivities (*ee* 84–94%) through the reaction of (4*S*)-2-oxo-4-phenyloxazolidin-3-ylacetyl chloride (**23**) and *N*-benzylimines **24** (Scheme 4).[33] The oxazolidinone protecting group can be removed by Birch reduction (lithium in liquid ammonia) with simultaneous N-debenzylation. For asymmetric synthesis using chromium–carbene complexes, chiral oxazolidines instead of oxazolidinones have been investigated. However, varying selectivity was observed, with a diastereomeric excess ranging from only 10% to >97%.[34]



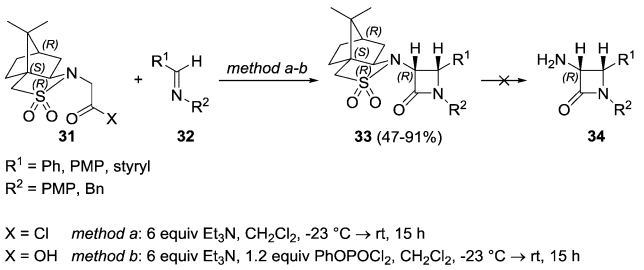
Scheme 4. Asymmetric Staudinger synthesis using (4*S*)-2-oxo-4-phenyloxazolidin-3-ylacetyl chloride (**23**) and imines **24**.



Scheme 5. Asymmetric synthesis using *N*-[bis(trimethylsilyl)methylidene]amines **28**.

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.[35] Reaction of acid chlorides **27** and imines **28** gave predominantly *cis*-β-lactams **29** 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 **28** ($R^2 = CO_2Me$), however, 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 an acetonitrile/water mixture (3:1), which effectively cleaves the C–Si bond, followed by N-deformylation under slightly basic conditions. By prolonged exposure of β-lactam **29** 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 advantage of the *N*-[bis(trimethylsilyl)methylidene]amines is their broader applicability, and non-enolizable as well as enolizable imines, but also the formaldehyde-derived imine, show great stability.[36]

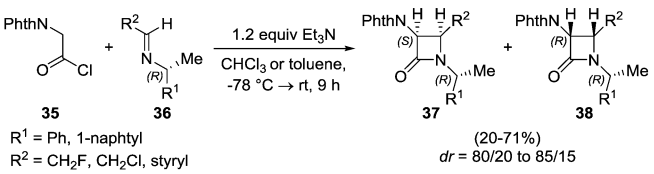
The utility of camphorsultam as a chiral auxiliary has been demonstrated in a wide range of organic reactions and has therefore been investigated for the asymmetric synthesis of 3-amino-β-lactams.[37] Treatment of camphorsultam-derived acid chlorides and carboxylic acids **31** with imines **32** resulted in the formation of single *cis* isomers of β-lactams **33** 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.



Scheme 6. Asymmetric synthesis using camphorsultam-derived ketenes.

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 **36** derived from (1*R*)-1-phenylethylamine reacted with phthalimido acid chlorides **35** to produce a diastereomeric mixture (d.r. = 81:19) of the two *cis*-4-fluoromethyl-β-lactams **37**/**38** (Scheme 7).[38]



Scheme 7. Asymmetric induction by imines **36** derived from (1*R*)-1-phenyl- and (1*R*)-1-(1-naphtyl)ethylamine.

Georg et al. used the same amine, in addition to (1*R*)-1-(1-naphthyl)ethylamine for the enantioselective synthesis of 4-styryl- and 4-chloromethyl-β-lactams **37**/**38**.[39] The same level of diastereoselectivity was obtained (d.r. = 80:20 to 85:15), with the asymmetric induction of (1*R*)-1-(1-naphthyl)ethylamine being only slightly higher.

Preparation of (3*S*)-phthalimido-β-lactam as a single isomer has been accomplished by application of imine **39** derived from D-glucosamine (Figure 5).[40] The application of *O*-silylated

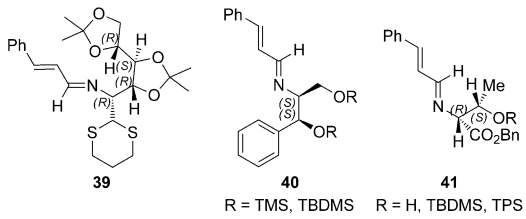
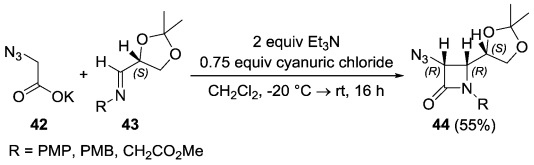


Figure 5. Imines **39**–**41** derived from chiral amines D-glucosamine, 2-amino-1-phenylpropane-1,3-diol and D-threonine.

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 D-threonine-derived imines **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*-β-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.



Scheme 8. Asymmetric induction by imines **43** derived from D-glyceraldehyde acetonide.

Asymmetric induction by the imino-carbon substituent has known to be more successful over the years. D-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).[43] Many asymmetric Staudinger syntheses with protected aminoketenes show *cis*-selectivity. Panunzio and co-workers, however, have reported the exclusive formation of *trans*-β-lactams **47** with *N*-(trimethylsilyl)imines **45** derived from chiral *O*-silyl-protected α-hydroxy aldehydes (Scheme 9).[44] The reaction with phthalimido acid chlorides resulted in N-unsubstituted *trans*-β-lactams **47**, due to loss of the TMS group during workup and purification. To explain the *trans* selectivity, intermediate **46** was proposed. The obtained β-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-β-lactams (Figure 6).[45] Due to the opposite stereochem-

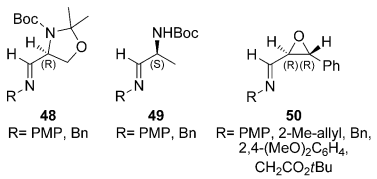
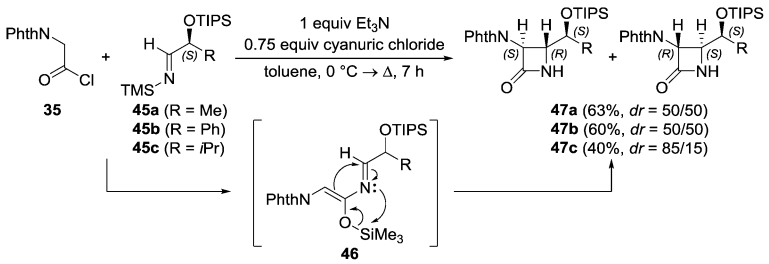


Figure 6. Imines derived from chiral aldehydes: nitrogen analogue **48** of D-glyceraldehyde acetonide, α-amino imines **49** and α,β-epoxyimines **50**.

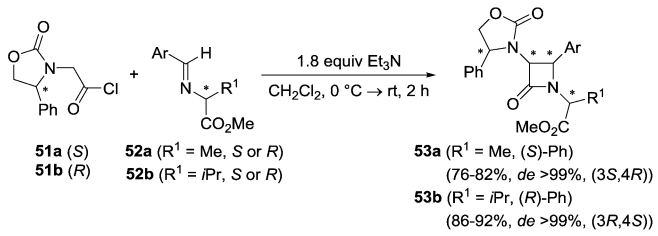
istry of the chiral auxiliary of imine **48** with respect to imine **43**, the (3*S*)-β-lactam is formed. In addition to these chiral aldehydes, other examples have been investigated by other research groups. In that respect, the application of chiral α,β-epoxyimines **50** has been shown to lead to the formation of *cis*-3-phthalimido-β-lactams with a diastereomeric excess between 80% and 94%.[46]

2.1.3.3. Double Asymmetric Induction

The double asymmetric induction approach utilizing Evans–Sjogren ketenes and imines bearing chiral N-substituents was



Scheme 9. Asymmetric induction by imines **45** derived from *O*-silyl-protected α-hydroxy aldehydes.



Scheme 10. Double asymmetric induction approach using chiral ketenes derived from **51** and chiral N-substituted imines **52**.

first applied by Ojima and co-workers.[47] With amino-ester-derived chiral imines **52** (both enantiomers), *cis*-β-lactams **53** were obtained exclusively (Scheme 10). No significant influence of the chiral imine substituent was observed; only the oxazolidinone substituent was shown to determine stereoselectivity.

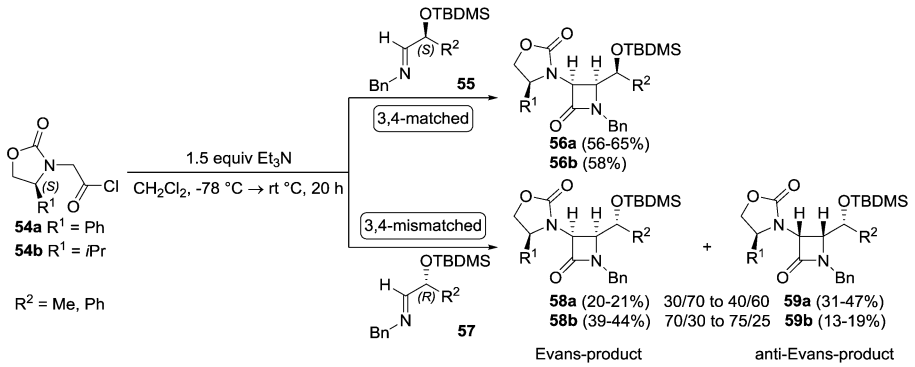
As mentioned in the previous paragraphs, Evans–Sjogren ketenes and imines derived from chiral aldehydes, such as glyceraldehyde acetonide and *O*-silylated α-hydroxy aldehydes, have thoroughly proven their utility in the asymmetric synthesis of 3-amino-β-lactams. The next question that arises, is how 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).[48] 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.[48] 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.

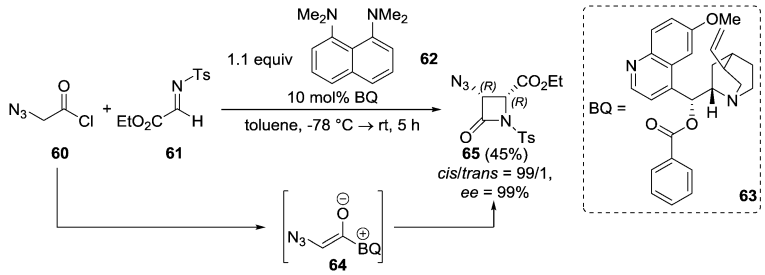
Most asymmetric syntheses are chiral auxiliary based and thus require additional steps to introduce and remove these auxiliaries. The group of Lectka has investigated the catalytic asymmetric synthesis of β-lactams.[49] This method involved a chiral nucleophilic catalyst, such as benzoylquinine (**63**), that reacted with the ketene derived from acid chloride **60** to produce the zwitterionic 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 Formaldimine

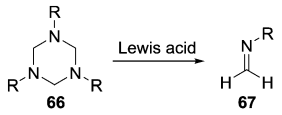
For the synthesis of 4-unsubstituted derivatives, the instability of the required formaldehyde imines presents a problem. Therefore, formaldimine precursors need to be deployed that mostly appear as trimers such as hexahydro-*s*-hydrazines **66**.[50] Treatment of these trimers with a Lewis acid generates in situ the monomeric formaldimines **67** (Scheme 13). Alternatively, iminodithiocarbonates can be deployed as formaldehyde imine equivalents.[51] After the cyclocondensation of the iminedithio-



Scheme 11. Double asymmetric induction approach using "matched" or "mismatched" chiral templates.



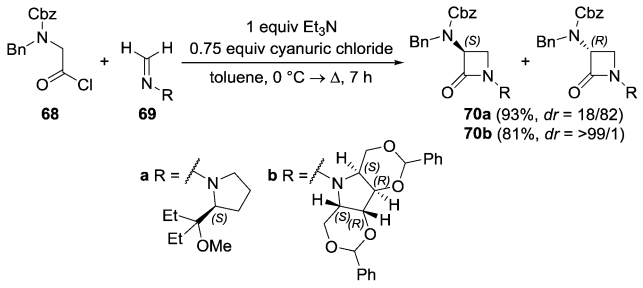
Scheme 12. The catalytic, asymmetric, "umpolung" Staudinger reaction. Ts, *p*-toluenesulfonyl; BQ, benzoylquinine (**63**).



Scheme 13. Conversion of hexahydro-*s*-hydrazines **66** to monomeric formaldimines **67** by treatment with a Lewis acid.

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*-(benzyloxycarbonyl)aminoketene derived from **68** was applied, the best stereoselectivities were obtained with C_2-symmetric dialkyl hydrazones, for example **69b**, an inherent property of this type of auxiliary (Scheme 14). With chiral ketenes, such as that



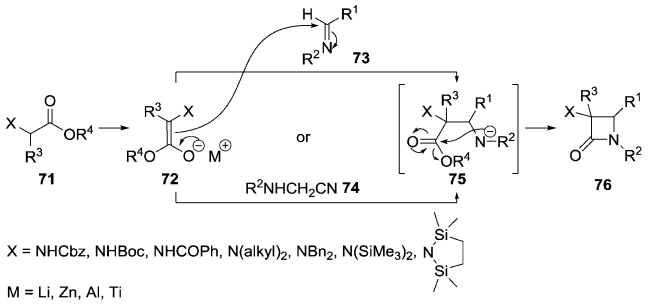
Scheme 14. Staudinger synthesis with dialkylhydrazones **69**.

derived from (*R*)-2-(2-oxo-4-phenyloxazolidin-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 D-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 a 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



Scheme 15. The cyclocondensation between α-amino esters **71** and imines **73** or *N*-(cyanomethyl)amines **74**.

of 4-unsubstituted derivatives.[57] These precursors can be converted in situ to formaldimines 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 resin-bound esters (R^3 = Me) that, after reaction with imines (R^1 = R^2 = aryl) and subsequent cleavage, produced 3-amido-β-lactams.

In some cases, a transmetallation reaction occurred prior to imine addition, for example, with $ZnCl_2$, Me_2AlCl, $Ti(OiPr)_3Cl$. 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*-β-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 diisopropylamide generated the dianion that underwent reaction with diaryl imines to give only *trans*-3-amido-β-lactams instead of the expected *cis* isomers.[61] *Trans*-selectivity was also observed in the synthesis of a 3-phthalimido-β-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 α-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-β-lactams (*de* > 90%), whereas the sulfur and oxygen analogues show a lower selectivity (*de* 0–85%).[64]

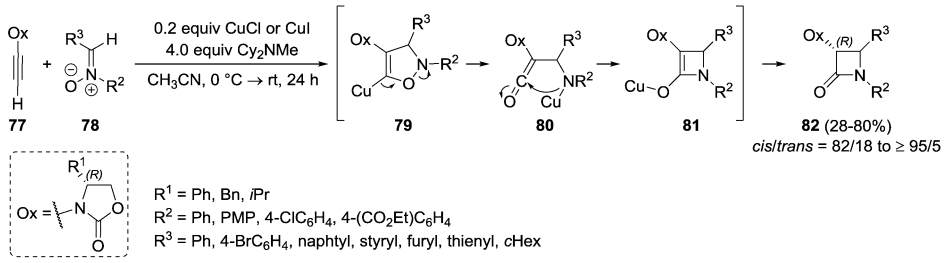
Another important factor concerns the solvent polarity. Reactions with zinc enolates afford *trans*-azetidin-2-ones in weakly polar solvents, whereas in polar solvents, *cis* isomers are favored.[65] The best strategy toward *cis* selectivity is the use of hexamethylphosphoramide (HMPA) as a co-solvent. In addition to solvent influence, increasing the amount of zinc chloride also enhances formation of *cis*-β-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.[63b] In that respect, together with the possible reversal in diastereoselectivity, the zinc-mediated condensation is favored.[65]

For the enantioselective synthesis, three strategies can be applied.[66] The first approach is the application of chiral esters (R^4), but initially, little chiral induction was observed.[61] Ojima and Habus, however, obtained high enantioselectivity with chiral *N*,*N*-bis-silyl-protected glycine esters in a lithium-mediated reaction, specifically with menthyl and *trans*-2-phenyl-1-cyclohexyl esters (*ee* > 99%).[67] 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.[66]

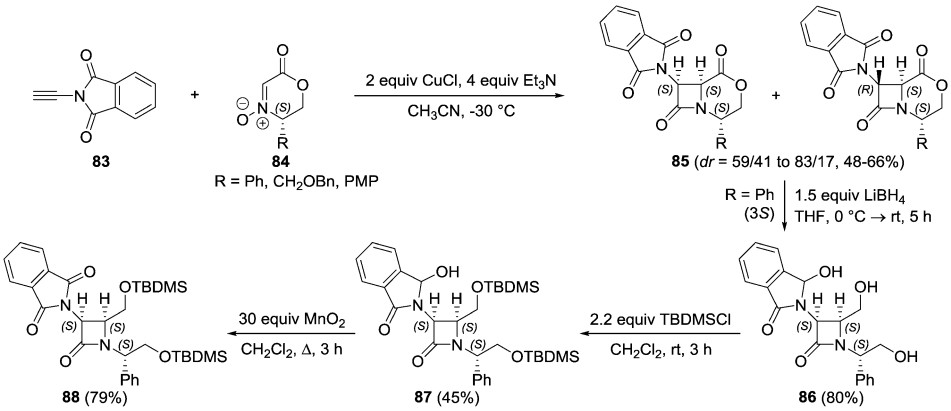
In a second approach, a chiral auxiliary at the imino-carbon (R^1) was expected to show high chiral induction because of the proximity to the newly formed chiral centers. This method has been applied by Cainelli et al. with silyl imines of lactic aldehyde.[68] It was shown that high enantioselectivities can be obtained via these substrates if the proper protection of the α-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 β-hydroxy-substituted silyl imines, which resulted, however, in the four possible isomers in a different ratio that depended on the substituents and reaction conditions.[68c] Also, in zinc-mediated reactions, desirable results in terms of selectivity were obtained.[66]

The last approach involved a chiral imine N-substituent (R^2) and has been applied to the synthesis of 4-unsubstituted β-lactams, resulting in a 11:1 mixture of diastereomers.[57] For the zinc-mediated reaction with *N*-(*R*)-α-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 β-lactam antibiotics, without the need for extra steps.[69] β-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*-benzylidene-2-phenylglycine methyl ester provided the 3*S*,4*S*,α-*R* isomer in a diastereomeric excess of 97%. Other imino esters were also used, with a good overall selectivity depending on the substituents.[70] It was also observed that the α-center of the phenylglycine methyl ester could epimerize after β-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 3*S*,4*R* to 3*R*,4*S* after transmetallation 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.



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**.

3. Kinugasa Alkyne–Nitrone Cycloaddition toward 3-Oxazolidinone- and 3-Phthalimido-β-lactams

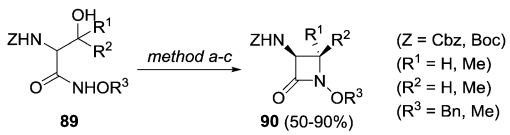
In 1972, Kinugasa and Hashimoto reported the formation of β-lactams by reaction of copper(I) phenylacetylide and nitrones with pyridine as both base and solvent.[72] This method is still used for the stereoselective synthesis of 3-amino-β-lactams starting from the chiral ynamides **77** (Scheme 16).[73] 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*-(3*R*)-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

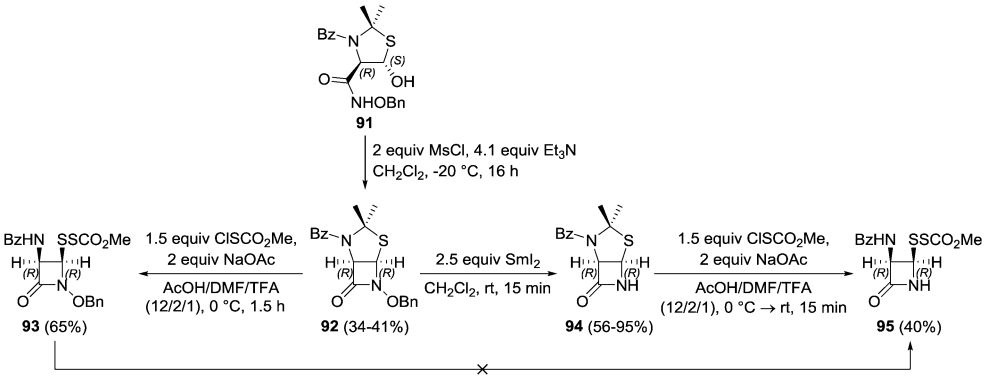
4.1. N1–C4 Cyclization

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-halohydroxamates 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



method a: 1 equiv PPh_3/DEAD or 1 equiv PPh_3/CCl_4/Et_3N, THF, rt-50 °C, 1-20 h
method b: 1) 1.2-1.3 equiv MsCl, pyridine, 0 °C, 1-2 h
2) 3 equiv K_2CO_3, acetone, Δ, 1-3 h
method c: 1) 1.35 equiv pyridine·SO_3, pyridine, 55 °C, 3 h or
1.2 equiv 2-methylpyridine·SO_3, MIBK, rt, 1-2 h
2) 6 equiv K_2CO_3 (aq.), EtOAc, Δ, 2 h or
4 equiv $K_2B_4O_7$, 2 equiv KOH, H_2O, MIBK, 70 °C, 1 h

Scheme 18. N1–C4 cyclization of α-amino-β-hydroxy hydroxamates **89**.



Scheme 19. Conversion of C-fused β-lactam **92** to monocyclic 3-aminoazetidin-2-one **95**.

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 (PPh_3) and diethyl azodicarboxylate (DEAD) (Scheme 18). This N-alkylation under Mitsunobu conditions required that the acidic component has a pK_a below 13, which is the case for *O*-alkylhydroxamates (the N–H bonds have pK_a 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 (PPh_3O and diethyl hydrazodicarboxylate) however, are difficult to remove from the reaction mixture. As a possible solution, solid-phase synthesis with the hydroxamate *O*-trityl bound to the carrier has been proposed, in which the by-products can be easily removed by washing.[76]

An alternative strategy involves the mesylation of the β-hydroxy group and cyclization under basic conditions to afford the 3-amino-β-lactam **90**.[77] This method, however, appeared to be inefficient if cyclization of tertiary hydroxyl amino acids was required due to nonselective mesylation as a result of steric hindrance.[78] Therefore, a sulfonation–cyclization process involving treatment with a pyridine–SO_3 complex was proposed.

Through cyclization of hydroxamate **91**, the C3–C4-fused bicyclic β-lactam **92** has been synthesized (Scheme 19).[79] The thiazolidine ring can be opened by treatment with methoxycarbonylsulfenyl 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 benzyloxy group in **93** failed. Therefore, this group had to be removed prior to thiazolidine 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.[75,80] 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

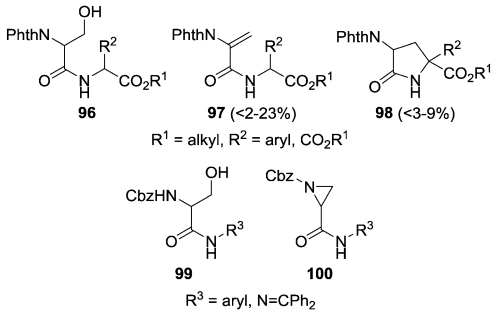
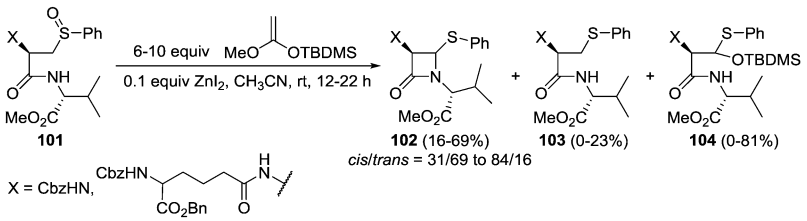


Figure 7. Elimination products **97** and pyrrolidinone side products **98** of the cyclization of dipeptides **96**, and aziridine side products **100** of the cyclization of *N*-arylamides **99**.

amount of the elimination product **97**, due to deprotonation at the C3 carbon, was observed.[81] By adaptation and optimization of the cyclization conditions, implying a shift from 2.5 equivalents of PPh_3/DEAD to one equivalent of $P(OEt)_3$/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.[82] 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** ($R^2 = CO_2R^1$).[80] These phthalimido- and also oxazolinone-protected serylaminomalonates, as well as their phosphorous analogues [$R^2 = PO(Oalkyl)_2$], could be converted in good yields to the corresponding β-lactams if the appropriate Mitsunobu reagents were applied.[83]

Other syntheses utilized intermediates such as *N*-arylamides and hydrazide derivatives **99** (Figure 7).[84] During cyclization of

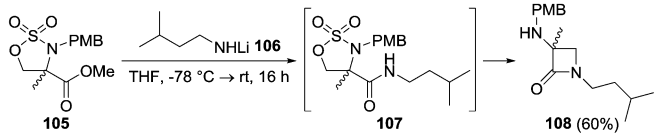


Scheme 20. A Pummerer-type rearrangement of tripeptide **101**.

the carboxybenzyl-protected *N*-arylamides **99** under Mitsunobu conditions, the formation of aziridine **100** was observed.[84a,b] This side product can also be formed with carboxybenzyl- or *tert*-butyloxycarbonyl-protected dipeptides.[80] To circumvent the formation of these aziridines, phthalimido or oxazolinone derivatives can be used. Furthermore, the hydroxyl group of *N*-arylamides, as well as peptide analogues, can be activated by conversion to an imidazolyl sulfonate.[85] Subsequent base-induced ring closure delivers the desired β-lactams in good yields (63–85%).

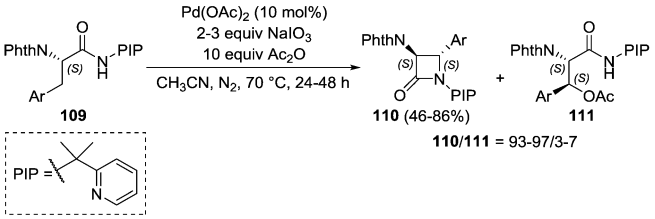
Kita and co-workers have reported the synthesis of 3-amino-β-lactams **102** by a Pummerer-type rearrangement.[86] Accordingly, sulfoxide **101** was treated with ketene methyl *tert*-butyldimethylsilyl acetal in the presence of a catalytic amount of zinc iodide (Scheme 20). The *cis*/*trans*-selectivity 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-methylbutylamine **106** was used as a nucleophile.[88] Presumably, the ester functionality in **105** was initially attacked by the nucleophile **106**, resulting in amide **107** which subsequently underwent cyclization to β-lactam **108** in 60% yield (Scheme 21).



Scheme 21. The ring-closure-induced ring opening of cyclic sulfamidate **105**.

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, $NaIO_3$ 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 diastereoisomer of **110,** with a small quantity of the β-acetoxylated 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

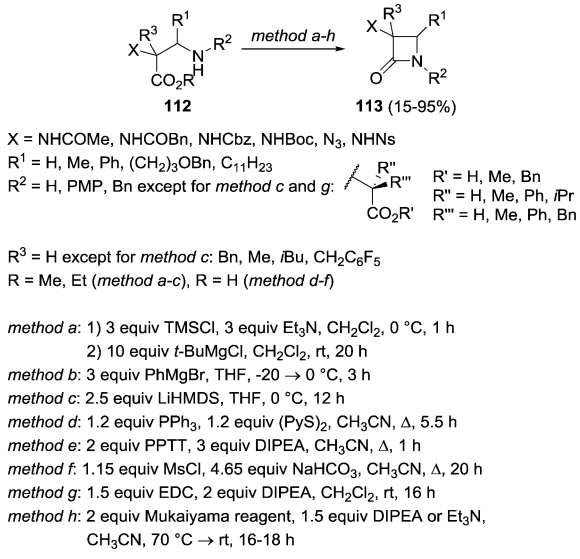


Scheme 22. The Pd-catalyzed amidation of amide **109**.

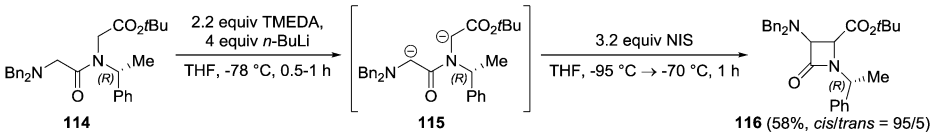
moderate yields, in which the PIP directing group controls the selectivity in the arylation step and enhances the reactivity in the subsequent amidation step. By the same principles, 4-unsubstituted derivatives can be synthesized via a cobalt-catalyzed amidation with 8-quinoline as a directing group.[90]

4.2. N1–C2 Cyclization

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



Scheme 23. N1–C2 cyclization of α,β-diamino carboxylic acids and esters **112**.



Scheme 24. C3–C4 bond formation by oxidative coupling of amide **114**.

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).[93] A strong base, such as lithium bis(trimethylsilyl)amide (HMDS), can induce cyclization as well, provided that the β-lactam nitrogen group (R^2) is non-enolizable (method c). To introduce the desired carboxylmethyl substituent at the β-lactam nitrogen, α,α-disubstituted esters **112** ($R^2 = CR''R'''CO_2Me$) or silylethers **112** ($R^2 = CHRCH_2OTMS$) 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-diamino 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′-dipyridyldisulfide [$(PyS)_2$] in combination with triphenylphosphine,[94] 3,3′-phenylphosphoryl-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

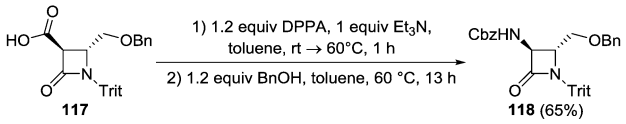
The intramolecular oxidative coupling of dianions provides an example of a C3–C4 bond formation method for the synthesis of 3-amino-β-lactams. The initial step comprised the generation of dianions **115** from acyclic tertiary amides **114**, synthesized through alkylation and acylation of amines, by adding a base and a coordinative reagent (Scheme 24).[99] 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 *N*-iodosuccinimide (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 (3*S*,4*S*)-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.[100] 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).[101]



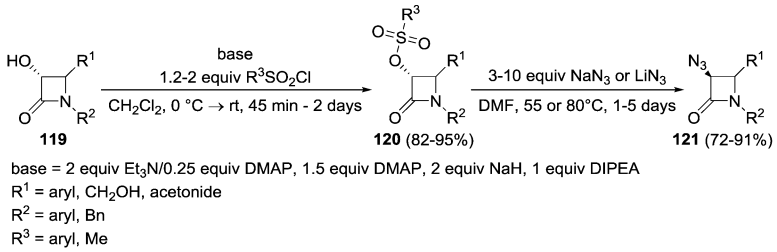
Scheme 25. Conversion of 3-carboxy-β-lactam **117** to 3-amino-β-lactam **118**.

5.2. 3-Hydroxy-β-lactams

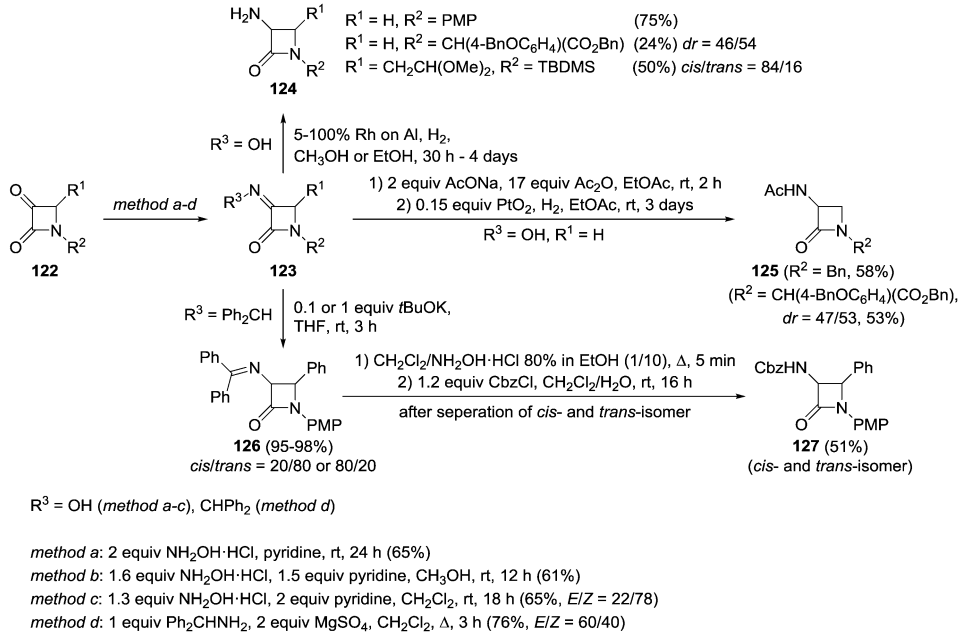
Lattrell and Lohaus have reported the conversion of *trans*-β-lactams **120** bearing different sulfonyloxy substituents at the C3-position to *cis*-3-azidoazetidin-2-ones **121** by S_N2 displacement with sodium azide.[102] This method has been applied by different groups to the synthesis of 3-amino-β-lactams starting from 3-hydroxy-substituted derivatives via intermediates **120** with inversion of configuration at C3 (Scheme 26).[3k,103] 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.[43b]

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-oxoazetidin-2-ones **122** with hydroxylamine hydrochloride (Scheme 27).[104] The resulting oximes **123** ($R^3 = OH$) were reduced to 3-(acylamino)azetidin-2-ones **125** or hydrogenated to the free amines **124**. The keto group can also be converted to an imino group by reaction with an alkyl amine.[105] 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



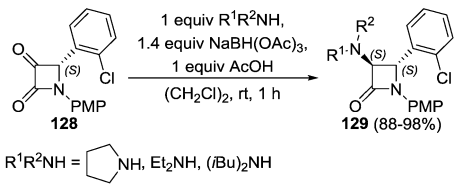
Scheme 26. Conversion of 3-hydroxy-β-lactams **119** to 3-azido derivatives **121**.



Scheme 27. Different approaches to introduce the 3-amino group starting from 3-oxo-β-lactams **122**.

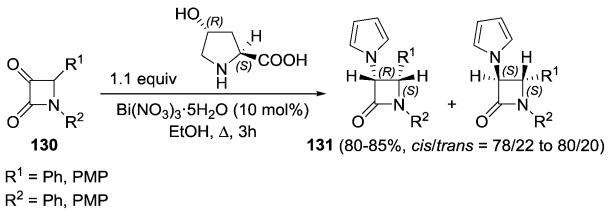
that were reduced with $NaBH(OAc)_3$ to provide 3-amino-β-lactams **129** (Scheme 28).[103b]

Banik and co-workers have reported a bismuth-nitrate-catalyzed reaction for the synthesis of 3-pyrrolyl-β-lactams **131**



Scheme 28. Treatment of 3-oxo-β-lactams **128** with secondary amines.

(Scheme 29).[106] 3-Oxoazetidin-2-ones **130** were treated with 4-hydroxyproline in the presence of bismuth nitrate, resulting in introduction of a pyrrolyl group, the desired substituent, at C3 in a single step. However, Hegedus reported the conversion of the 3-pyrrolyl moiety into the free amino group. In that respect, ozonolysis resulted in a formamido residue that, through



Scheme 29. Bismuth-nitrate-catalyzed conversion of 3-oxo-β-lactams **130** toward 3-pyrrolyl-β-lactams **131**.

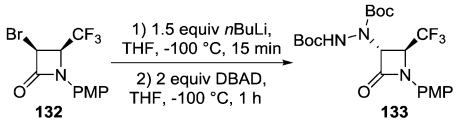
hydrolysis with PBr_3 in methanol, followed by treatment with Et_3N, was converted into the free amino group.[107]

5.4. 3-Halo-β-lactams

The most common method for the conversion of 3-halo-β-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. Kühlein and Jensen converted different *trans*-3-bromo-β-lactams to *cis*-3-azido-β-lactams with sodium azide in an aprotic solvent, for ex-

ample, DMSO.[108] The same reaction can be realized for a phthalimido substituent at the C3-position by treatment with potassium phthalimide.[109]

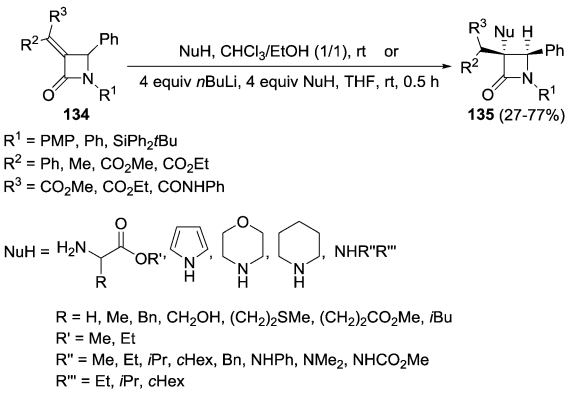
Furthermore, an amine equivalent has been introduced at C3 by reaction of 3-bromoazetidin-2-one **132**, generated by ring expansion of the corresponding aziridine, with di-*tert*-butylazodicarboxylate (DBAD) after lithium–halogen exchange, resulting in β-lactam **133** (Scheme 30).[110]



Scheme 30. Introduction of a 3-amino 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).[111] At least one electron-

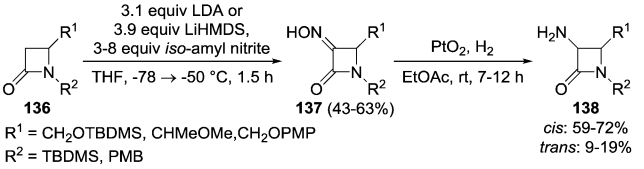


Scheme 31. Addition of N-nucleophiles onto 3-alkylidene-β-lactams **134**.

withdrawing substituent (R^2, R^3) at the double bond is required to effect this reaction.[111c] 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.[104c]

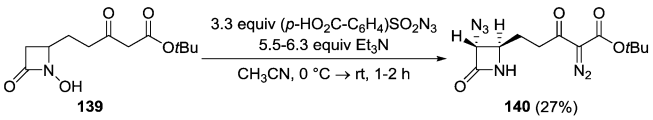
5.6. 3-Unsubstituted β-Lactams

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.[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-azido substituent in a *trans* relationship to the C4 substituent, which was readily reduced to the free amine.[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).[113]



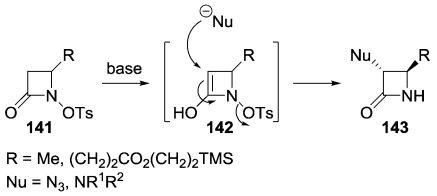
Scheme 32. Conversion of 3-unsubstituted β-lactams **136** to 3-amino-β-lactams **138**.

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).[114] Isolation of an intermediate with a sulfo-



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

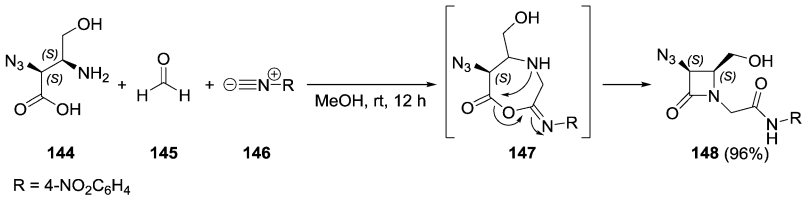
nylated hydroxyl group led to the proposal of a plausible mechanism. After sulfonylation, the enolate **142** is formed, which is expected to be facilitated by the electron-withdrawing sulfonyloxy group at nitrogen in **141**, allowing the azide to attack at C3, which results in N–O bond cleavage (Scheme 34).



Scheme 34. Addition of N-nucleophiles to 3-unsubstituted *N*-tosyloxy-β-lactams **141**.

By testing different conditions, the use of an excess of the nucleophile was preferred, in combination with a non-nucleophilic base to prevent competition.[115] 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 enolizaton step prior to the nucleophilic substitution.[116] Sterically hindered amines (R^1, R^2 = *i*Pr or R^1 = *t*Bu, R^2 = H; Scheme 34) resulted in 3-aminoazetidin-2-



Scheme 35. Ugi reaction of α-azido-β-amino acid **144**, formaldehyde (**145**) and isocyanides **146**.

ones **143** (predominantly *trans*). Less sterically hindered amines, however, afforded β-ketoamides as a side product at the expense of the desired β-lactams **143** 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 pK_a 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 stereochemistry 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.

Keywords: 3-amino-β-lactams · cyclization · cycloaddition · reactivity · Staudinger synthesis

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