Review

Synthesis of 2-Azetidinones via Cycloaddition Approaches: An Update

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Abstract: The present review is a comprehensive update of the synthesis of monocyclic β-lactams via cycloaddition reactions. According to the IUPAC definition of cycloaddition, both elementary and stepwise processes (formal cycloadditions) have been considered. The years 2019–2022 are covered by the cited literature. The focus of the review is on synthetic aspects with emphasis on the structural scope, reaction conditions, mechanistic aspects, and selectivity results. Selected significant data related to biological activities and synthetic applications are also highlighted.

Keywords: 2-azetidinone; β-lactam; cycloaddition; ketene; imine; isocyanate; nitrone

1. Introduction

2-Azetidinones, or monocyclic β-lactams or monobactams, are a highly studied class of compounds [1–5]. In addition to their well-documented antibacterial and anti-β-lactamase activities, β-lactams have attracted interest as promising drugs in other therapeutic areas, including neurodegenerative diseases and coagulation therapy [6–10]. β-Lactams are also useful synthetic intermediates for the synthesis of β-amino alcohols, β-amino acids, and nitrogen-containing compounds in general [11,12].

This review is an update of the CHEC-IV 2.01 Chapter “Azetidines, Azetines and Azetes: Monocyclic” by Andresini, Degennaro and Luisi [1], as well as the Chemical Review article by Pitts and Lectka [3]. The purpose of this review focuses on β-lactam synthesis and, among the numerous synthetic methods reported in the literature, we provide here a comprehensive survey of monocyclic 2-azetidinones synthesized by a cycloaddition approach from 2019 to 2022 (articles that appeared as online publications in the above time interval are cited in this review according to the final publication date). The cycloaddition reactions covered in this review adhere to the IUPAC definition of a cycloaddition: “A reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity. . . Cycloadditions may be pericyclic reactions or non-concerted stepwise reactions.” [13] (pp. 1103–1104).

On this basis, the different types of cycloaddition processes applied in the synthetic assembly of 2-azetidinones are described and discussed, with a focus on structural scope, reaction conditions, mechanistic aspects, and related selectivity outcomes. Significant results related to various biological activities and applications are also highlighted.

Examples of stereoselective synthesis of trans- and cis-3,4-disubstituted-2-azetidinones are reported. In general, the value of the coupling constant between the 3-H and 4-H protons on the β-lactam ring was used to determine the cis- and trans-configurations ($J_{3,4\text{ cis}} = 3.0–5.6 \text{ Hz}, J_{3,4\text{ trans}} = 0–2.7 \text{ Hz}$). In some cases, the structures were confirmed by X-ray analysis.
2. Ketene–Imine Cycloaddition (Staudinger Synthesis)

Ketene–imine cycloaddition, known as Staudinger synthesis and discovered in 1907, still remains the most general method to access variously substituted 2-azetidinones [1–5,14–18]. This reaction, which is quite simple from the practical point of view, has a rather complex mechanism, especially with regard to stereoselectivity. This depends largely on the nature of the reactants (mainly on the electronic and steric effects of the substituents) and the experimental conditions (solvent, temperature) and for these reasons numerous theoretical and experimental studies on this topic are still present in the literature.

The process is a formal [2+2]-cycloaddition able to generate up to two chiral centers in the cyclic product. The concerted thermal approach requires the orbital symmetry allowed [\(\pi 2s+\pi 2a\)] pathway which is, unfortunately, geometrically demanding. Thus, a two-step mechanism involving a sequential formation of the N(1)–C(2) and C(3)–C(4) covalent bonds of the \(\beta\)-lactam ring is commonly accepted. The first step of the reaction likely implies the nucleophilic addition of the imine nitrogen on the sp-hybridized carbon atom of the ketene to form a zwitterionic intermediate. The following four-electron conrotatory electrocyclization (that can be also viewed as an intramolecular Mannich-type reaction of the enolate on the electrophilic iminium moiety) gives rise to the four-membered cycloadduct (Scheme 1) [19,20].

\[ \text{Scheme 1. Ketene–imine cycloaddition (Staudinger synthesis of } \beta\text{-lactams).} \]

The scope of the Staudinger cycloaddition was computationally analyzed by considering a series of substituents placed at the ketene Cα and imine Cα and N positions. The results obtained by means of DFT calculations show that the reaction performance mainly depends on the electrocyclic step (rate-determining step), rather than the initial nucleophilic attack. In particular, the reaction outcomes are scarcely influenced by the substituents on the imine, while they are essentially determined by the steric and electronic nature of the substituents present at the α-position of the ketene. The latter has a dominant effect on the overall feasibility of the reaction [21].

One of the main critical aspects of the process is the cis–trans-diastereoselectivity. In this regard, it is usually assumed that the first step takes place through the less hindered side of the ketene (exo-approach, that is favored with respect to the endo-approach) (Scheme 2). The second step, a conrotatory electrocyclization, is subject to torquoelectronic effects that depend on the relative in/out relationship between the C-3 and C-4 substituents. In general, \((E)\)-imines give cis-\(\beta\)-lactams while \((Z)\)-imines yield trans-\(\beta\)-lactams; however, recent studies have shown that the stereochemical outcome may also depend on isomerization pathways at the level of the starting imine or in the zwitterionic intermediate (Scheme 2) [14].

Recently, the mechanism of the Staudinger synthesis has been studied using electron localization function (ELF) quantum topological analysis as a valuable tool to understand the bonding changes along the ketene–imine reaction. This theoretical study explains the experimental results, including the cis/trans-stereoselectivity, and rejects the analyses based on the FMO theory involving HOMO/LUMO interactions throughout the nucleophilic attack of the imines on the ketenes and a torquoelectronic effect throughout the conrotatory ring closure step leading to azetidine-2-ones [22].

The use of preformed and isolated ketenes as reagents in the Staudinger synthesis is limited by the instability of these compounds. Commonly, ketenes are generated in situ from precursors such as acyl chlorides, carboxylic acids, diazo compounds, haloesters, and enolates.
Ketenes are often generated from acyl chlorides by treatment with a tertiary amine and are trapped in situ by imines to give azetidinones via [2+2]-cycloaddition (Scheme 4, X = Cl; B = R$_3$N). Recently, several monocyclic β-lactams have been prepared using this protocol. This approach is often used to synthesize hybrid molecules [24], that is, compounds containing the β-lactam ring linked to other bioactive heterocycles. The goal is to create new potential drug candidates with improved biological properties due to the synergistic action of the two or more heterocycles.
The contents of this section are organized by type of substituents on the C-2 of the acyl chloride (corresponding to the C-3 position of 2-azetidinones) and then, possibly, by substituents on the nitrogen atom of imine (corresponding to the N-1 position of 2-azetidinones). Schemes and charts show the structures of β-lactams, the conditions used to generate them and the yields by which they were obtained. When β-lactams were designed and tested for a particular bioactivity, the types of tests are also mentioned.

2.2.1. Ketene Generated In Situ from Acetyl Chloride

Staudinger cycloaddition of imines with ketenes generated from acetyl chloride affords 3-unsubstituted β-lactams.

As shown in Scheme 5, 2-azetidinones 3 variously decorated with oxadiazole and indole and quinazolin-3(2H)-one and 11H-indeno-[1,2-b]-quinoxaline moieties, respectively, were prepared in good yield from acetyl chloride and suitable aromatic imines in the presence of triethylamine as a base at low temperature [25–27].

Scheme 5. Synthesis of 3-unsubstituted-2-azetidinones. (Tested activities are in italics).

2.2.2. Ketene Generated In Situ from 2-Alkyl-, 2-Vinyl-, and 2-Arylacetyl Chloride

3-Vinyl-2-azetidinones 4 were prepared by adding crotonyl chloride to a solution of suitable aromatic imines and triethylamine in dichloromethane under reflux conditions (Scheme 6) [28]. The reaction was highly diastereoselective with exclusive formation of trans-adducts, as attested by a characteristic coupling constant between the 3-H and 4-H hydrogens of less than 3 Hz. Furthermore, the stereochemical assignment of 4b (R = Et, OMe, SMe) and 4c (Ar = 4-MeOC₆H₄) was confirmed by X-ray structural analysis.
Derivative 4c (Ar = 4-MeO-3-HOC₆H₃) showed potent activity in MCF-7 breast cancer cells (IC₅₀ = 8 nM) and minimal cytotoxicity against nontumorigenic cells.

Scheme 6. Synthesis of 3-vinyl-2-azetidinones. (Tested activities are in italics.)

Some 3-alkyl- and 3-aryl-2-azetidinones prepared by Staudinger synthesis are shown in Scheme 7. trans-1,4-Diaryl-2-azetidin-2-ones 5a and 5b were synthesized in refluxing toluene (Scheme 7) [29]. Ketenes were generated in situ from the monomethyl ester chloride of succinic, glutaric, suberic, and sebacic acids by treatment with tributylamine.

Hydroxide anion of the ionic liquid 1-methyl-3-methylimidazolium hydroxide [(Bmim)OH] was used as a base to promote the formation of phenyl ketene in the synthesis of 5c and 5d (Scheme 7) [30]. The reaction was conducted under microwave irradiation (mw) at 120 °C and provided the trans-isomer 5c as the main or sole product.

3-Phenyl-, 3-vinyl-, and 3-propenyl-β-lactams 5e were prepared by Staudinger synthesis in toluene at 100 °C with complete trans-stereoselectivity (Scheme 7) [31]. Structure of the 3-phenyl derivative 5e (R = Ph, X = F) was confirmed by X-ray analysis. This β-lactam, which showed remarkable metabolic stability, was found to have high activity against HT-29 colon cancer cells (IC₅₀ = 9 nM) and MCF-7 breast cancer cells (IC₅₀ = 17 nM).

3-Phenyl-2-azetidinone 5f (R¹ = R² = Me) showed good cytotoxicity against MFC-7, A-589, and HeLa cancer cells (IC₅₀ = 0.63-0.85 μM) (Scheme 7) [32].

4-Spiro-fused (2-oxindolin-3-yl)-2-azetidinones 5g and 5h (Scheme 7) [33] were prepared from isatin-derived imines with 2-(4-chlorophenyl)acetyl chloride in the presence of triethylamine in refluxing DMF. Under these reaction conditions, the unwanted isomer trans-5g was mainly formed. Fortunately, the diastereoselectivity was reversed by forming acyl chloride in situ from 2-(4-chlorophenyl)acetic acid and oxalyl chloride and carrying out the reaction at room temperature (see Scheme 53 below).

In a recent review on electrochemically induced synthesis and functionalization of β-lactams, the application of this technique to the Staudinger synthesis was reported. In particular, 1-aryl-3,4-diphenyl-2-azetidinones were prepared via dehydrohalogenation of 2-phenylacetoyl chloride with an electrogenerated N-heterocyclic carbene (NHC) to give the phenylketene, which was trapped in situ by arylimine [34].
Scheme 7. Synthesis of 3-alkyl- and 3-aryl-2-azetidinones 5. (Tested activities are in italics).

1-Aminoindane (IND-NH$_2$) and 1,2,3,4-tetrahydro-1-naphthylamine (THN-NH$_2$) in both enantiomeric forms were used as chiral auxiliaries in the synthesis of 3-benzyl-$
\beta$-lactams 6a and 6b (Scheme 8) [35]. The chiral imines, prepared by grinding amines and aromatic aldehydes, were treated directly with 3-phenylpropionyl chloride and triethylamine in xylene at high temperature (140 °C). Under the reported reaction conditions, trans-diastereoselectivity was complete, while the control of the absolute configuration of the newly generated C-3 and C-4 stereocenters ranged from 59 to 76%. In general, THN-NH$_2$ was a more efficient chiral auxiliary than IND-NH$_2$, and the highest selectivity was obtained with Ar = 3,4,5-(MeO)$_3$C$_6$H$_2$. 

**Conditions:**
- **Et$_3$N, toluene, 100 °C, 5 h, then rt, 15 h**
  - R = Ph: X = F (25%), Cl (42%), Br (43%), I (62%), Me (58%).
  - R = vinyl: X = F (70%), Cl (61%), Br (63%), I (51%), Me (71%).
  - R = propen-2-yl: X = F (32%), Cl (68%), Br (47%), I (45%), Me (64%).
  - *antiproliferative and antiapoptotic activities*

- **Et$_3$N, C$_6$H$_6$, reflux, 3 h**
  - R$^1$, R$^2$ = Cl, Cl (67%); Cl, Me (76%); Cl, H (75%); Me, Cl (65%); Me, Me (68%); Me, H (71%); H, Cl (63%); H, Me (58%); H, H (60%).
  - *antimicrobial, antioxidant, and anticancer activities*
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2.2.3. Ketene Generated In Situ from 2-Amidoacetyl Chloride

N-Propargyl-2-azetidinone 9 was prepared in enantiopure form from (S)-2-(2-oxo-4-phenyloxazolidin-3-yl)acetyl chloride 7, imine 8, and triethylamine at low temperature (Scheme 9) [36]. The reaction was completely cis-stereoselective. The terminal alkyne moiety was exploited to introduce a 1,2,3-triazole ring, which in turn was converted into a triazolium salt. The corresponding Au complex having a 1,2,3-triazolyldene was used as a catalyst in the cycloisomerization of enynes (see also Scheme 10, Scheme 17).

Scheme 8. Synthesis of optically active 3-benzyl-2-azetidinones.


3-Benzamido- and 3-phthalimido-2-azetidinones 10a–10e were prepared by Staudinger synthesis starting from the corresponding 2-amidoacetyl chlorides (Scheme 10) [36–39].

The reaction of propargylimine 8 with phthalimidoacetyl chloride and triethylamine at 80 °C gave trans-2-azetidinone 10b as the only product [36]. Compound 10b was used as a precursor of β-lactam-substituted mesoionic metal carbene complexes, which were tested as catalysts in the cycloisomerization of enynes (Au-carbene complexes) and in the hydrosilylation of phenyl acetylene (Pt-carbene complexes) (see also Scheme 9, Scheme 8).

Orthogonally protected azetidinone 10c was obtained as a cis/trans-mixture [38]. The N-(4-methoxyphenyl) protecting group was selectively removed by treatment with cerium ammonium nitrate (CAN). Then, the 3-N exocyclic nitrogen atom was first deprotected using hydrazine and then acylated with 4-chlorophenyl isocyanate to generate a 3-ureido-2-azetidinone.

β-Lactams 10d and 10e were obtained mainly as cis-isomers and used to study the selective deprotection of N-1 and 3-N nitrogen atoms [39]. Oxidative cleavage with CAN and ammonia-free Birch reduction were effective in removing 2,4-dimethoxybenzyl and benzyl groups from N-1, respectively. Hydrazine easily removed the phthalimido group in 4-alkyl-substituted lactams (R = alkyl), but in the case of 4-aryl derivatives (R = aryl...
and heteroaryl), the addition of HCl was necessary to obtain satisfactory conversions. β-Lactams having a carbamate group on C-3 were also examined (see 96, Figure 6 below).

Scheme 10. Synthesis of 3-amido-2-azetidinones. (Tested activities are in italics).

Chiral imines 12 derived from α-amino acids 11 were reacted with phthalimidoacetyl chloride and a base to obtain dipeptidic 4-phenyl β-lactams 13 (Scheme 11) [40]. The reaction carried out at low temperature (method A) gave low yields. Better results were obtained at 110 °C in toluene in the presence of 2,6-lutidine as the base (method B). Under these reaction conditions, mainly 3,4-trans-disubstituted β-lactams were formed with low control of the absolute configuration of C-3 and C-4 stereocenters. The 3-N nitrogen atom was deprotected with hydrazine and then coupled with 2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetic acid in search of novel inhibitors of penicillin-binding protein (PBP).
A scalable process for the production of the monobactam antibiotic LYS228 on a multi-kilogram scale was described (Scheme 12) [41]. Two approaches to the key intermediate 16 were investigated, both starting from enantiopure (S)-glyceraldehyde acetonide 14. Aldehyde 14 was condensed with 2,4-dimethoxybenzylamine, and imine 15 was reacted directly with phthalimidoacetyl chloride in the presence of triethylamine as a base and SOCl₂ as a trace water scavenger (method A). Then the phthalimido group was removed by treatment with hydrazine, and the free 3-N amino group was protected with benzyl chloroformate to obtain 16 (91.9 Kg, 99.8% ee) with an overall yield of 30.7% from 14. To avoid exchange of protecting groups, N-Cbz glycine was activated as mixed anhydride with isopropyl chloroformate in the presence of triethylamine and reacted with imine 15 directly to obtain 16 with an overall yield of 50.4% (method B).

![Scheme 12. Synthesis of enantiopure 2-azetidinone 16.](image)

2.2.4. Ketene Generated In Situ from 2-Alkoxy-, 2-Aryloxy-, and 2-Acetoxyacetyl Chloride

Enantiopure acyl chlorides or imines have recently been used for the synthesis of optically active β-lactams. trans-Azetidinones 17 were obtained by microwave-promoted cycloaddition of N-(chrysen-6-yl)imines with a ketene derived from naturally occurring (+)-car-3-ene (Scheme 13) [42]. An explanation for the high stereoselectivity of the Staudinger synthesis was proposed. Removal of the chiral auxiliary by treatment with Zn/AcOH gave the corresponding enantiopure 3-hydroxy-2-azetidinones, which were in turn acetylated.

D-Mannitol was used to prepare an enantiopure 1,3-dioxolan-4-yl)methanimine that was reacted with 2-benzyloxy- and 2-methoxyacetyl chloride in the presence of triethylamine at room temperature (Scheme 14) [43]. Under the reported reaction conditions, exclusive formation of the cis-isomer of 4-(1,3-dioxolan-4-yl)azetidin-2-ones 18 was observed. Acetal hydrolysis with p-TsOH in THF/H₂O followed by oxidation of the glycol moiety with NaIO₄ afforded optically active 4-formyl-β-lactams in good yields.
mine and the crude imine was reacted with reactions 2024, 5, FOR PEER REVIEW

Scheme 16. Synthesis of optically active N-(chrysen-6-yl)-2-azetidinones.

(2R,3R)-2-Chloro-3-phenylpent-4-enal (19) was prepared with high enantioselectivity by iridium-catalyzed allylic substitution of chloroacetaldehyde. Aldehyde 19 was condensed with cyclohexylamine and the crude imine was reacted with 2-(benzyloxy)acetyl chloride in the presence of triethylamine in benzene (Scheme 15) [44]. Purification of the crude mixture (dr 5.5:1.5:1) afforded pure cis-β-lactam 20 in 73% overall yield.


3-Methoxy-N-ethyl-tert-butylcarbamate β-lactams 21 were prepared by Staudinger synthesis at −82 °C (Scheme 16) [45]. The reaction was highly stereoselective producing only cis-adducts 21. Treatment of 21 with TFA in CH₂Cl₂ at room temperature afforded the corresponding deprotected N-(2-aminoethyl) derivatives in 70–97% yields. All azetidinones were evaluated for antimicrobial and anticancer activities.


 cis-3-Benzzyloxy-N-propargyl-2-azetidinone 22 was prepared with high stereoselectivity and high yield under similar reaction conditions (Et₃N, CH₂Cl₂, −78 °C then rt) (Scheme 17) [36]. Lactam 22 was used for the preparation of β-lactam-substituted 1,2,3-triazolin mesoionic carbene metal complexes as in the case of the analogues 3-amido-N-propargyl-β-lactams 9 and 10b (see Schemes 9 and 10).
Organocatalytic oxidative condensation of primary amines to unstable imines was applied to the one-pot synthesis of cis-β-lactams 25 and 26 under mild conditions (Schemes 18 and 19) [46]. Imines 24 were generated in situ by homocondensation of benzylamines 23 using 4,6-dihydroxy salicylic acid as an organocatalyst and molecular oxygen as a co-oxidant. Imines 24 were then treated with acyl chlorides and triethylamine in the presence of molecular sieves in acetonitrile at 0°-rt to give cis-azetidinones 25 with high selectivity. Gram-scale syntheses of 25a (Ar = Ph) and 25c were carried out by this method.

Scheme 18. One-pot synthesis of 2-azetidinones by organocatalytic oxidative condensation of primary amines.

Scheme 19. One-pot synthesis of 2-azetidinones by organocatalytic oxidative condensation of primary amines.

cis-Azetidin-2-ones 26 bearing three different substituents were prepared by the 4,6-dihydroxy salicylic acid-catalyzed oxidative cross-condensation of two different amines followed by [2+2]-cycloaddition with ketenes under similar conditions (Scheme 19) [46]. β-Lactams 26a and 26b underwent acid-catalyzed hydrolysis to afford the corresponding β-amino acids as single diastereomers.

The role of imine isomerization in the stereoselectivity of the Staudinger synthesis was investigated both computationally and experimentally. Different reaction conditions were considered, including more polar and less polar solvents (CH2Cl2 and toluene), different reaction temperatures (−78 °C and room temperature), and different orders of reactant addition (acyl chloride first and imine first) (Scheme 20) [20]. The cis- and trans-stereostereochemistry of azetidine-2-ones 29 was determined by analysis of the coupling constants between 3-H and 4-H. The structure of the two isomers cis-31a and trans-31a (R = Ac) derived from N-methyl-isatin was confirmed by X-ray analysis. The N'-unsubstituted
imine 30b was reacted with an excess of acid chloride 27 (2.2 molar equiv). Under these conditions, the isatin nitrogen atom was acylated and azetidinones 31b were obtained as an equimolar mixture of cis- and trans-isomers. On the basis of experimental data and DFT calculations, the isomerization of the starting imine was found to be critical for the stereoselectivity of the cases studied.

**Scheme 20.** Study of the stereoselectivity of the Staudinger synthesis under different reaction conditions.

Bis-4-spiro-fused-β-lactams 32–35 were prepared by double Staudinger synthesis of 2-(2-(allyloxy)phenoxy)acetyl chloride and 2-allyloxyacetyl chloride with various diimines (Schemes 21–24) [47,48]. Diimines were synthesized by condensation of 9-fluorenone and unsubstituted imine [43]. Cycloadditions were carried out under standard conditions and afforded a mixture of syn/anti adducts in high yield. The structures of bis-azetidinones anti-34 [X = −(CH2)2] and anti-35 [X = −(CH2)2] were determined by single-crystal X-ray diffraction. Dienes 32–35 were then cyclized by ring-closing metathesis (RCM) to give macrocycles containing bis-4-spiro-β-lactams moieties in good yields, except for 34 [X = −(CH2)2] and 35 [X = −(CH2)2], which failed to undergo RCM because of the short ethylene linker.

Phenoxy- and p-chlorophenoxy-ketenes were generated by treating 2-aryloxyacetyl chloride with a base and trapped in situ with variously functionalized imines to generate 3-phenoxy- and 3-p-chlorophenoxy-2-azetidinones (Scheme 25) [31,37,43,45,49–52]. Condensation of aromatic aldehydes with 2-amino-1-phenylethanol afforded imines that were reacted with phenoxyketene without protection of the hydroxyl group. The reaction was performed at room temperature and provided N-(2-hydroxy-2-phenylethyl)-β-lactams 36a with complete cis-selectivity. After oxidation of the secondary benzyl alcohol to the corresponding ketone, treatment with phosphorus oxychloride converted the azetidinones into highly strained azetidine-fused oxazolium salts that underwent spontaneous opening to 2-vinylloxazole derivatives [49]. Phenoxyacetyl chloride was also used in the Staudinger synthesis of cis-4-(oxiran-2-yl)-β-lactams 36b [43].
Scheme 21. Synthesis of bis-4-spiro-fused-β-lactams 32.

Scheme 22. Synthesis of bis-4-spiro-fused-β-lactams 33.

Scheme 23. Synthesis of bis-4-spiro-fused-β-lactams 34.

Scheme 24. Synthesis of bis-4-spiro-fused-β-lactams 35.
Scheme 25. Synthesis of 3-aryloxy-2-azetidinones. (Tested activities are in italics).
3-Phenoxy-azetidinones 36c bearing an N-Boc group were synthesized by ketene-imine cycloaddition at −82 °C with complete cis-selectivity [45]. After recrystallization, the pure β-lactams 36c were recovered in moderate to good yields (21–77%). Similarly to the corresponding 3-methoxy derivatives 21 (see Scheme 16), 36c were treated with trifluoroacetic acid (TFA) to obtain the deprotected N-(2-aminooethyl) cis-azetidinones.

The synthesis of β-lactams 36d was performed at high temperature (100 °C) in toluene [31]. Complete trans-stereoselectivity was observed under these conditions, except for derivative 36d (X = F), which was obtained as a mixture of trans- and cis-diastereomers. The structure of the trans-36d (X = F) and cis-36d (X = F) isomers was confirmed by X-ray analysis. The stability of β-lactam 36d (X = Cl) was studied under acidic, neutral, and basic conditions. Its half-life (t1/2) at pH 4, 7.4, and 9 was more than 15 h.

β-Lactams 36e–36h conjugated with 1,3,4-thiadiazole and imidazole nuclei, heterocycles present in various bioactive compounds, were prepared in high yields (75–89%). Ketenes generated in situ from 2-benzoyloxy- or 2-(p-chlorobenzoyloxy)acetyl chloride and triethylamine reacted with imines derived from β-tetralone in dichloromethane at 0 °C–rt [50,51]. All β-lactams 36e–36h were purified by crystallization and were obtained with complete cis-stereoselectivity. X-ray analysis confirmed the structures of the two derivatives 36g (Ar = 4-MeC6H4 and Ar = 4-ClC6H4).

The synthesis of azetidinones 36g was carried out by dropwise addition of 2-(p-chlorobenzoyloxy)acetyl chloride to an imine in the presence of pyridine as a base at 0 °C in dichloroethane (DCE), followed by heating to reflux temperature [37].

β-Lactam 36j was obtained as a mixture of two diastereomers in a 58:42 ratio by reacting a suitable hydrazone with in-situ-generated phenoxyketene [52].

2-Acetoxyacetyl chloride is a useful building block for the synthesis of 3-acectoxy-2-azetidinones. The acetoxy group can be selectively hydrolyzed to 3-hydroxy-2-azetidinones. For example, β-lactams 37 were synthesized by Staudinger synthesis followed by treatment with hydrazine (Scheme 26) [31]. Lactams 37 retained the trans-stereochemistry established in the cycloaddition step carried out at high temperature (100 °C). X-ray crystallographic analysis confirmed the structure of 3-hydroxy-β-lactam 37 (X = F). Azetidinone 37 (X = F) showed potent activity in HT-29 (IC50 3 nM) and MCF-7 (IC50 22 nM) cell lines and strongly inhibited tubulin assembly. It also showed high stability towards hepatic enzymes, analogous to the corresponding 3-phenyl derivative 5e (R = Ph, X = F) (Scheme 7).

Chiral imines 38 derived from d-mannitol were subjected to Staudinger [2+2] cycloaddition with in-situ-generated acetoxyketene at low temperature (0 °C-rt) (Scheme 27) [53]. The reaction afforded cis-β-lactams 39, which were hydrolyzed by treatment with LiOH to 3-hydroxy-2-azetidinones (90–95% yield) and then converted to optically active 2,3-fused β-lactams-1,4-dioxepane.
Scheme 27. Synthesis of optically active 3-acetoxy-2-azetidinones 39.

Scheme 28 shows some 3-acetoxy-2-azetidinones recently synthesized by the Staudinger synthesis using 2-acetoxyacetyl chloride and a base for in situ generation of the corresponding ketene [54–58].


The synthesis of azetidinone 40a under microwave irradiation was investigated using a heterogeneous catalyst such as Mg-Al hydroxide (MAH) instead of an organic base [54]. In this case, both cis-40a and trans-40a were formed in low yields. Better results were observed when halogenated acyl chlorides were used (see below: 47, Scheme 33; 48, Scheme 34; 58a, Scheme 43; and 59b, Scheme 44). Mixtures of diastereomeric β-lactams 40b and 40c were prepared by microwave-induced cycloaddition using N-methylmorpholine (NMM) as the base in CH$_2$Cl$_2$ [56].

The 4-(thiethyl)pyrazolyl- and 4-pyrazolo[5,1-b]thiazolyl-3-acetoxy-2-azetidinone hybrids 40d and 40e were synthesized by reacting a suitable aromatic imine with acetoxy-acetyl chloride and triethylamine in toluene at reflux temperature [55,57]. Under these conditions, trans-adducts were formed with complete selectivity. A similar reaction in CH$_2$Cl$_2$ at 0 °C afforded the cis-40d (Ar = 4-MeOC$_6$H$_4$) isomer in 25% yield.

Racemic 3-acetoxy-β-lactams 40f and 40g were synthesized via the Staudinger synthesis and converted into optically active 3-hydroxy-β-lactams (78–94% ee). In particular, 40f...
and 40g were sequentially hydrolyzed to 3-hydroxy-β-lactams, oxidized to azetidine-2,3-diones, and enantioselectively reduced to optically active 3-hydroxy-β-lactams by dynamic kinetic resolution (DKR) using Ni-catalyzed asymmetric hydrogenation (Schemes 28 and 29) [58].

\[
\begin{align*}
\text{AcO} & \quad \text{N}\quad \text{O} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{40f/40g} & \quad \text{i) NaHCO}_3, \text{Na}_2\text{CO}_3, \text{MeOH}, \text{rt, overnight} \\
\text{O} & \quad \text{N}\quad \text{R}^1 \\
\text{R}^2 & \quad \text{ii) P}_2\text{O}_5, \text{DMSO}, 0 \degree \text{C, rt, overnight} \\
\text{O} & \quad \text{N}\quad \text{R}^1 \\
\text{R}^2 & \quad \text{Ni(OAC)}_2 (5 \text{ mol%)} \\
\text{Phosphoric acid (1 equiv)} & \quad \text{(S)-Binapene (5.5 mol%)} \\
\text{toluene, H}_2 (60 \text{ bar}), 80 \degree \text{C, 36 h} \\
\text{dr} & \quad 20:1; 45-94% \\
\text{78-94% ee} & \quad \text{Scheme 29. Synthesis of optically active 3-hydroxy-2-azetidinones.}
\end{align*}
\]

Condensation of piperidinone 41 with p-anisidine afforded the unstable imine 42. This was directly reacted with 2-acetoxyacetyl chloride in the presence of triethylamine at −78 °C to give the spiro-fused β-lactam 43 in 55% yield over the two steps (Scheme 30) [59].

\[
\begin{align*}
\text{Boc-N} & \quad \text{O} \\
\text{41} & \quad \text{toluene} \\
\text{p-anisidine} & \quad \text{reflux} \quad 20 \text{ h} \\
\text{Boc-N} & \quad \text{O} \\
\text{42} & \quad \text{PMP} \\
\text{AcO} & \quad \text{COCl} \\
\text{Et}_3\text{N, CH}_2\text{Cl}_2 & \quad -78 \degree \text{C to rt} \quad 16 \text{ h} \\
\text{Boc} & \quad \text{55% over two steps} \\
\text{Scheme 30. Synthesis of 4-spiro-fused-3-acetoxy-2-azetidinone 43.}
\end{align*}
\]

2.2.5. Ketene Generated In Situ from 2-Phenylthioacetyl Chloride

Phenylthioacetyl chloride was used to prepare 3-phenylthio-2-azetidinones via Staudinger [2+2] cycloaddition (Scheme 31) [60,61]. Trans-β-lactams 44 were obtained with complete diastereoselectivity by microwave-induced reaction of diarylimines with phenylthioacetyl chloride in the presence of N-methylmorfoline (NMM). Under similar conditions, imines derived from the condensation of diethyl-2-oxomalonate with aromatic amines afforded β-lactams 45. Decarboxylation of 45 under Krapcho’s reaction conditions (LiCl, DMSO, 120–130 °C, mw) provided an equimolar mixture of cis- and trans-3-phenylthio-4-carboxethoxy-2-azetidinones.

\[
\begin{align*}
\text{PhS} & \quad \text{O} \\
\text{EtO}_2\text{C} & \quad \text{N} \\
\text{C} & \quad \text{Cl} \\
\text{45} & \quad \text{O} \\
\text{N-methylmorfoline} & \quad \text{Ar} \quad \text{mw} \quad 300 \text{W} \quad 5-10 \text{ min} \\
\text{PhS} & \quad \text{O} \\
\text{EtO}_2\text{C} & \quad \text{N} \\
\text{C} & \quad \text{Cl} \\
\text{44} & \quad \text{O} \\
\text{N-methylmorfoline} & \quad \text{Ar}^1 \quad \text{mw} \quad 300 \text{W} \quad 10-30 \text{ min} \\
\text{Ar} & \quad \text{= Ph (70%), 4-MeC}_6\text{H}_4 (75%), 4-\text{MeOC}_6\text{H}_4 (80%), 4-\text{F}_2\text{C}_6\text{H}_4 (65%), 4-\text{ClC}_6\text{H}_4 (60%).} \\
\text{Ar}^1 & \quad \text{= Ph, Ph (75%); 4-\text{MeOC}_6\text{H}_4, Ph (80%); Ph, 4-\text{MeOC}_6\text{H}_4 (70%); Ph, 4-\text{F}_2\text{C}_6\text{H}_4 (65%); 4-\text{MeOC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4 (60%).}
\end{align*}
\]


2.2.6. Ketene Generated In Situ from 2-Chloroacetyl Chloride

Many differently decorated 3-chloro-azetidinones have been synthesized using commercially available and inexpensive chloroacetyl chloride with an imine in the presence of a base. In this section, the structures of the 3-chloro-β-lactams are grouped according to the type of N-substituent (alkyl, aryl, heteroaryl, heteroarylamino, carboxamido, ureido, and tosyl groups) (Schemes 32–42). The bioactivity assays described in the cited articles are listed together with the corresponding β-lactam structures.
PhCHO + i-PrNH2

\[ \text{PhCHO + i-PrNH2} \rightarrow \text{Ph-N} = \text{N} \]

\[ \text{ClICH₂COCl} \rightarrow \text{toluene, reflux, 2 h then 80 °C, 12 h 68% (two-step yield)} \]

Scheme 32. Synthesis of 3-chloro-1-isopropylalkylazetidin-2-one 46.

\[ \text{Cl₅C} \rightarrow \text{Ar} \rightarrow \text{Mg-Al hydroxide (MAH)} \rightarrow \text{DMF mw (300 W) 2 min} \]

Scheme 33. Synthesis of N-acetate- and N-hexanoate-3-chloro-azetidin-2-ones 47.

<table>
<thead>
<tr>
<th>Ar¹</th>
<th>Ar²</th>
<th>cis-48</th>
<th>trans-48</th>
<th>49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>40%</td>
<td>52%</td>
<td>n.d.</td>
</tr>
<tr>
<td>Ph</td>
<td>4-MeOC₆H₄</td>
<td>36%</td>
<td>53%</td>
<td>10%</td>
</tr>
<tr>
<td>Ph</td>
<td>4-O₂NC₆H₄</td>
<td>47%</td>
<td>38%</td>
<td>n.d.</td>
</tr>
<tr>
<td>Ph</td>
<td>4-FC₆H₄</td>
<td>39%</td>
<td>54%</td>
<td>n.d.</td>
</tr>
<tr>
<td>4-O₂NC₆H₄</td>
<td>Ph</td>
<td>29%</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>4-BrC₆H₄</td>
<td>Ph</td>
<td>25%</td>
<td>33%</td>
<td>34%</td>
</tr>
<tr>
<td>4-CIC₆H₄</td>
<td>3-CIC₆H₄</td>
<td>55%</td>
<td>32%</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ar¹</th>
<th>Ar²</th>
<th>cis-48</th>
<th>trans-48</th>
<th>49</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-ClC₆H₄</td>
<td>2-thienyl</td>
<td>22%</td>
<td>22%</td>
<td>39%</td>
</tr>
<tr>
<td>4-ClC₆H₄</td>
<td>2-furyl</td>
<td>0%</td>
<td>0%</td>
<td>40%</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>4-O₂NC₆H₄</td>
<td>55%</td>
<td>40%</td>
<td>n.d.</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>4-MeOC₆H₄</td>
<td>46%</td>
<td>31%</td>
<td>12%</td>
</tr>
<tr>
<td>4-ClC₆H₄</td>
<td>4-ClC₆H₄</td>
<td>48%</td>
<td>40%</td>
<td>n.d.</td>
</tr>
<tr>
<td>4-ClC₆H₄</td>
<td>2,4-Cl₂C₆H₃</td>
<td>42%</td>
<td>43%</td>
<td>n.d.</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>PhCH=CH</td>
<td>26%</td>
<td>32%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Scheme 34. Synthesis of N-aryl-3-chloro-azetidin-2-ones 48.

In the search for molecules with enhanced bioactivity, hybrid compounds with more than one bioactive moiety have often been synthesized. Considering that many heterocyclic derivatives are among the most biologically active compounds and possess important pharmacological properties, the design of 3-chloro-azetidinones variously linked to different heterocyclic nuclei is not surprising. Indeed, there are many examples of such compounds in this section. Although these molecules are racemic, promising bioactivity has been observed in some cases.

Benzaldehyde and isopropylamine were condensed in the presence of MgSO₄ to give the corresponding imine, which was filtered on Celite® and then reacted directly with chloroacetyl chloride using 2,6-lutidine as the base (Scheme 32). Trans-azetidinone 46 was obtained in 68% yield after recrystallization. The 3-chloro-β-lactam 46 was found to be inferior to 3-bromo analogues 59d (see Scheme 44 below) as a substrate in cobalt-catalyzed α-arylation with aryl Grignard reagents [62].

Solid MAH was used as a heterogeneous catalyst in the Staudinger synthesis of azetidinones under microwave irradiation (Scheme 33, see also 40a, Scheme 28; 48, Scheme 34; 58a, Scheme 43; and 59b, Scheme 44). The reaction was fast and afforded 47 in good yields with complete trans-selectivity [54].
Scheme 35. Synthesis of 1,4-diaryl-3-chloro-2-azetidinones 50. (Tested activities are in italics).

Under the same conditions, N-aryl azetidinones 48 were formed as a mixture of cis- and trans-isomers (Scheme 34). The MAH catalyst could be recovered and reused up to six times without any significant loss of catalytic activity. In some cases, MAH induced partial or complete cleavage of the N-C4 bond of adducts 48 with formation of enones 49. The structure of the isomeric β-lactams cis-48 and trans-48 (Ar1 = 4-MeOC6H4, Ar2 = 4-O2NC6H4) as well as of the enone 49 (Ar1 = Ph, Ar2 = 4-MeOC6H4) was confirmed by X-ray analysis [54].
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conditions: Et$_3$N, 1,4-dioxane, 0–5 °C, then rt, 5–6 h
then rt, 5–6 h
R = H (80%), 4-Cl (68%), 4-Br (63%), 4-HO (65%), 4-MeO (62%), 4-Cl (71%), 2.3-HO (67%), 3-Me (67%).

Scheme 36. Synthesis of 1-aryl-3-chloro-4-heteroaryl-2-azetidinones 51. (Tested activities are in italics).

1,4-Diaryl-3-chloro-2-azetidinones 50 were prepared by reaction of chloroacetyl chloride and aromatic imines using Et$_3$N as a base in different solvents (Scheme 35) [31,43,63–66].

The 4-propargyloxyphenyl-substituted β-lactam 50a was formed as a cis/trans-mixture in CH$_2$Cl$_2$ at room temperature. The reaction of 50a with NaN$_3$ and KI in DMF at 150 °C afforded a β-lactam-fused benzotriazolo-oxazocane derivative via conversion of 50a into the corresponding 3-azido-2-azetidinone followed by a spontaneous intramolecular azide–alkyne click reaction (83%) [43].

3-Chloro-azetidinones 50b–50g were designed and synthesized to test their potential bioactivity. In most cases, the Staudinger synthesis was carried out at room temperature or in refluxing CH$_2$Cl$_2$. As shown in Scheme 35, the yields range from very low to very good (3–92%), but it must be said that in some cases the yields were not optimized, as the main aim of the research was the biological tests. Compound 50b was synthesized from the syringic imine of 4-aminophenol with chloroacetyl chloride [63]. 1,4-Diaryl-2-azetidinones 50c–50e were isolated exclusively as the trans-isomer. The only exception was 50e (Ar = 4-MeO-3FC$_6$H$_4$) which was formed as a cis/trans-mixture (ratio 1:1.9). The stereochemistry of these two diastereomers as well as of the two trans-azetidinones 50e (Ar = 4-MeO-3FC$_6$H$_4$ and Ar = 4-MeO-3ClC$_6$H$_3$) was confirmed by X-ray analysis [31,64].
Scheme 37. Synthesis of 3-chloro-1-heteroaryl-2-azetidinones. (Tested activities are in italics).

Scheme 37. Synthesis of 3-chloro-1-heteroaryl-2-azetidinones. (Tested activities are in italics).
Hybrid adducts 50f featuring a pyrazine, a 1,3,4-oxadiazole, and an azetidinone moiety showed interesting antimicrobial activity. In particular, a high antitubercular activity of the two derivatives 50f (R = 4-Cl and R = 4-MeO) was reported (MIC 3.12 μg/mL against Mycobacterium tuberculosis) [65]. β-Lactams 50g presenting a thiazolyl nucleus were synthesized with complete trans-selectivity and evaluated as antimicrobial agents [66].

Heterocyclic hybrids of β-lactams 51a–51e were prepared via the Staudinger synthesis by reaction of chloroacetyl chloride with heterocyclic imines in the presence of Et3N as a base (Scheme 36) [55,67–69]. Azetidinones with coumarin [67,69], indole [68], thiazole [69], and (thiényl)pyrazole moieties [55] were formed in good yields. Several conditions were tested for the synthesis of β-lactams 51e. No product formation was observed in CH2Cl2 at 0 °C. In refluxing CHCl3, THF, 1,4-dioxane, and toluene the reaction was completely selective in favor of trans-β-lactams. The structure of 51e (R = 4-MeC6H4) was confirmed by X-ray analysis [55].

The structures of hybrid compounds with heterocyclic moieties directly linked to the nitrogen atom of the 3-chloro-β-lactam ring are shown in Scheme 37 [32,63,70–79]. Triethylamine was used as the base in all the syntheses, except for the pyridine derivative 52i. Indeed, 2-((3-nitrobenzylidene)amino)-4,6-diarylnicotinonitrile was reacted with chloroacetyl chloride at a high temperature (DMF, reflux) without any base. In this case, the use of microwave heating reduced the reaction time (0.5 min versus 10 h) and increased the yield (84% versus 57%) [77].

Scheme 38. Synthesis of 3-chloro-1-heteroarylaminoo-2-azetidinones. (Tested activities are in italics.)
by mw irradiation were faster (A: 16–24 h; B: 30–45 min) and afforded the products with higher yields (A: 50–60% vs B: 81–96%) [85]. The acetamido linker was used to attach various cyclic moieties to the azetidinone, including thymol (54b, [86]), 2-aminothiazole (54c, [87]), 2-(thien-2-yl)-2,3-dihydro-1H-benzo[d]imidazole (54d, [88]), and 1,4-benzoxazin-3-one (54e, [89]). Symmetrical bis-azetidinones 54f with a central pyromellitic diimide tricyclic system were also prepared by the same approach [90].

Scheme 39. Synthesis of 1-acetamido-3-chloro-2-azetidinones. (Tested activities are in italics).

Adducts 52a and 52b were prepared from 4-amino-antipyrine [63,70]. The triazole derivative 52c was obtained in low yield by reaction in refluxing CH2Cl2 [70]. Azetidinones 52d with a 1H-1,2,4-triazole-5(4H)-thione as a heterocyclic linker for attachment of morpholine (or thiomorpholine) and thiadiazol-2-amine moieties were obtained in good yields (70–84%) [71]. The Staudinger approach was also applied to the synthesis of oxadiazole [32], thiadiazole [69–71], benzothiazole [75,76], pyrimidine [78], and naphthyridine [79] derivatives 52f,g,h,j,k.
Scheme 40. Synthesis of 1-benzamido- and 1-(heteroarenecarboxamido)-3-chloro-2-azetidinones. (Tested activities are in italics).

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Scheme 41. Synthesis of 3-chloro-1-ureido-2-azetidinones. (Tested activities are in italics).

Scheme 42. Synthesis of 4-aryl-3-chloro-1-tosyl-2-azetidin-ones. (Tested activities are in italics).
2.2.7. Ketene Generated In Situ from 2,2-Dichloroacetyl Chloride

2,2-Dichloroacetyl chloride was reacted with imines in the presence of a base to give 3,3-dichloro-2-azetidinones (Scheme 43) [31,54,64,94]. 1,4-Diaryl derivatives 58a were obtained in high yields using solid MAH as heterogeneous base in DMF under microwave irradiation (see also 40a, Scheme 28; 47, Scheme 33; 48, Scheme 34; and 59b, Scheme 44). In contrast to the monochloro derivatives (Scheme 34), no formation of open products was observed [54].

Scheme 43. Synthesis of 1-aryl- and 1-amido-3,3-dichloro-2-azetidinones. (Tested activities are in italics).

Aryl/heteroaryl hydrazones prepared from aryl/heteroaryl aldehydes and heteroaryl hydrazines were reacted with chloroacetyl chloride to give 3-chloro-N-heteroarylamino-2-azetidinones (Scheme 38) [80–84]. The synthesis of imidazole derivatives 53a was carried out under ultrasoundation at a frequency of 35 kHz [80]. Both conventional and microwave (mw) heating were used for the preparation of azetidinones 53b (conditions A and B). The comparison showed that mw irradiation was a superior method. It afforded the products with higher yield and purity in a shorter reaction time [81]. Hybrid compound 53c, which contains three other potential pharmacophores besides the β-lactam, i.e., a thiazole, a 1,2,4-triazole, and a pyrazole moiety, showed significant cytotoxic activity against the HeLa (human cervical cancer) tumor cell line (IC₅₀ = 4.12 µg/mL) [82]. Pyrimidine and quinazoline derivatives 53d [83] and 53e [84] were obtained in moderate to good yields by Staudinger synthesis without the use of any base.

1-Acetamido-3-chloro-2-azetidinones 54 were prepared by Staudinger synthesis between chloroacetyl chloride and N'-arylidene acetohydrazide derivatives in the presence of Et₃N (Scheme 39) [85–90]. The syntheses of β-lactams 54a were carried out under conventional and microwave (mw) heating (conditions A and B). The reactions promoted by mw irradiation were faster (A: 16–24 h; B: 30–45 min) and afforded the products with
higher yields (A: 50–60% vs. B: 81–96%) [85]. The acetamido linker was used to attach various cyclic moieties to the azetidinone, including thymol (54b, [86]), 2-aminothiazole (54c, [87]), 2-(thien-2-yl)-2,3-dihydro-1H-benzo[d]imidazole (54d, [88]), and 1,4-benzoxazin-3-one (54e, [89]). Symmetrical bis-azetidinones 54f with a central pyromellitic diimide tricyclic system were also prepared by the same approach [90].

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1,4-Diaryl-3,3-dichloro-2-azetidinones 58c–58f were prepared by the Staudinger synthesis of chloroacetyl chloride and arylaldehyde and isopropylamine were condensed in the presence of MgSO$_4$ [90] to give chloro derivatives due to the halogen exchange with the chlorinated solvent. All adducts of bromoacetyl chloride or bromide with arylimines were obtained in lower yields, mainly as trans-isomers. The X-ray crystal structure of 59a was determined [64], and density functional theory (DFT) calculations [97] were performed.

Similar to 3-chloro-1-ureido-2-azetidinones 55a–55c prepared in good yields by Staudinger synthesis of chloroacetyl chloride and N'-arylidene benzohydrazide derivatives in the presence of Et$_3$N afforded 1-benzamido-3-chloro-2-azetidinones 55d–55e containing a 2-(pyridin-4-yl)quinazolin-4(3H)-one and a thieno[3,2-d]pyrimidin-4-amine group, respectively, attached to the benzamido moiety. Hybrid β-lactams 55f [93] and 55g [94] were prepared analogously using substituted pyrazole-3-carboxyhydrazides and thieno[3,2-b]pyrrole-5-carboxyhydrazide, respectively (Scheme 40).

Variously decorated 3-chloro-1-ureido-2-azetidinones 56 (Scheme 41) [95] and 3-chloro-1-tosyl-2-azetidinones 57 (Scheme 42) [96] were also obtained in good yields by Staudinger [2+2] cycloaddition.

2.2.7. Ketene Generated In Situ from 2,2-Dichloroacetyl Chloride

2,2-Dichloroacetyl chloride was reacted with imines in the presence of a base to give 3,3-dichloro-2-azetidinones (Scheme 43) [31,54,64,94]. 1,4-Diaryl derivatives 58a were obtained in high yields using solid MAH as heterogeneous base in DMF under microwave irradiation (see also 40a, Scheme 28; 47, Scheme 33; 48, Scheme 34; and 59b, Scheme 44). In contrast to the monochloro derivatives (Scheme 44), no formation of open by-products was observed [54].

The reaction of dichloroacetyl chloride with the condensation products of 4-benzylthieno[3,2-b]pyrrole-5-carboxyhydrazide with acetaldehyde and furfural in the presence of DIPEA gave β-lactams 58b in higher yields than the analogous 3-chloro derivative 55e (see Scheme 40). In contrast, the reaction with the corresponding isobutyaldehyde hydrazone
did not give the [2+2] adduct and afforded the open isomer 4-benzyl-N'-(dichloroacetyl)-N'-2-methylpropyl)-4H-thieno[3,2-b]pyrrole-5-carboxyhydrazide in 52% yield [94].

1,4-Diaryl-3,3-dichloro-2-azetidinones 58c–58f were prepared by the Staudinger synthesis in yields ranging from 7 to 63% [31,64]. Silyl derivative 58e (Ar = 4-MeO-3-TBDMSO-C6H5) was not isolated but directly treated with TBAB to give the phenolic product 58e (Ar = 4-MeO-3-HOC6H5). The structure of 58e (Ar = 4-MeO-3-MeC6H3) was confirmed by X-ray analysis [64].

Instead of the expected 3,3-dichloro-β-lactams, the reaction of 2,2-dichloroacetyl chloride with 2,2-dimethyl-1,3-dioxolan-4-yl)methanamines yielded 2,2-dichloro-N-(chloromethyl)acetamides. This peculiar reactivity has been studied experimentally and by density functional theory (DFT) calculations [97].

2.2.8. Ketene Generated In Situ from 2-Bromoacetyl Chloride/Bromide

Some 3-bromo-azetidin-2-ones have recently been synthesized by reaction of 2-bromoacetyl chloride or bromide with arylimines (Scheme 44) [54,62,64,98].

When the reaction was carried out in dichloromethane, the 3-bromo-β-lactams 59a were obtained as a mixture with the corresponding 3-chloro-β-lactams in a ratio of 1:2, due to the halogen exchange with the chlorinated solvent. All adducts of 59a were isolated as trans-isomers. The X-ray crystal structure of 59a (Ar = 4-MeO-3-CIC6H5) was reported. In general, the 3-bromoazetidiones were less active than the corresponding 3-chloro derivatives [64].

Similar to 3-acetoxy-, 3-chloro-, and 3,3-dichloro-2-azetidinones (see: 40a, Scheme 28; 47, Scheme 33; 48, Scheme 34; 58a, Scheme 43), 3-bromo-β-lactams 59b were prepared by the use of solid MAH as a heterogeneous base in DMF under microwave heating. These derivatives were obtained in lower yields, mainly as cis-adducts [54].

Arylaldehyde and isopropylamine were condensed in the presence of MgSO4 to give the corresponding imine, which was filtered on Celite® and directly reacted with bromoacetyl bromide using 2,6-lutidin as the base (Scheme 44). The reaction afforded trans-azetidinones 59c as the sole adducts, except in the case of 59c (Ar = 2-MeOC6H4) and 59c (Ar = 2-FC6H4), which were obtained as a mixture of cis/trans-isomers. Following the same protocol, trans-1-allyl- and trans-1-benzyl-3-bromo-β-lactams 59d were also synthesized. 3-Bromo-2-azetidinones 59c and 59d were used to prepare trans-3,4-diaryl- and trans-3-allyl-4-aryl-β-lactams via a cobalt-catalyzed cross-coupling reaction with aryl Grignard and diallylzinc reagents [62,98].

2.3. Ketene Generated In Situ from Carboxylic Acids

In general acyl chlorides are characterized by low stability and high toxicity, so in many synthetic approaches ketenes are generated in situ from carboxylic acids under different reaction conditions. Commonly, the process requires an acid activator (AX), such as p-TsCl, POCl3, SOCl2, acyl chlorides, Mukaiyama reagent, etc., and a base (B) (Scheme 45).

![Diagram](image)

**Scheme 45.** General protocol to access ketenes from carboxylic acids.

2.3.1. Ketene Generated In Situ from Carboxylic Acids and p-TsCl/Base

Jarrahpour and coworkers achieved the [2+2] imine–ketene cycloaddition (Staudinger synthesis) in a one-pot sequential multicomponent fashion exploiting the efficient in situ generation of imines by thermal melting of equimolar amounts of aryl/heteroaryl aldehydes and primary amines. The freshly generated imines were then dissolved in dry CH2Cl2 and treated with arylxyacetic acids and p-toluensulfonyl chloride, as acid activator, in the
presence of triethylamine for ketene generation, at room temperature. Substituted β-lactams 60 were synthesized in 70–93% yields, with exclusive cis-stereoselection (Scheme 46) [99].

\[
\text{R-NH}_2 + \text{Ar}^1\overset{\text{trans}}{\rightarrow} \text{O} \quad \text{solvent-free thermal melt} \quad \text{Ar}^2\overset{\text{cis}}{\rightarrow} \text{COOH} \quad \text{TsCl, Et}_3\text{N, dry CH}_2\text{Cl}_2, \text{rt} \quad \text{N} \quad \text{Ar}^2\overset{\text{cis}}{\rightarrow} \text{O} \quad \text{R} \quad 60 \quad 70-93\%
\]

R = 4-ClC\(_6\)H\(_4\), 4-EtOC\(_6\)H\(_4\), 4-BrC\(_6\)H\(_4\), c-Hex, CHMePh

Ar\(^1\) = 2-chloroquinol-3-yl, 2-chloro-6-methylquinol-3-yl, 2-furyl, 4-O\(_2\)NC\(_6\)H\(_4\), 3-O\(_2\)NC\(_6\)H\(_4\), 4-ClC\(_6\)H\(_4\), 4-Ph\(_2\)NC\(_6\)H\(_4\)

Ar\(^2\) = Ph, 4-ClC\(_6\)H\(_4\), 2-naphthyl

Scheme 46. One-pot sequential multicomponent synthesis of β-lactams 60.

The same protocol was applied to previously prepared and purified imines. The use of C-aryl-N-aryl-substituted Schiff bases and 2-(4-formylphenoxy)acetic acid gave rise to cis-β-lactams 61, containing a benzaldehyde moiety, in 70–88% yields. The further synthetic elaboration of the formyl group allowed access to chromeno β-lactam hybrids of type 62 (Scheme 47). All the azetidinone derivatives were screened for anti-inflammatory and anticancer activities, evidencing good antitumour activity against the SW1116 (colon cancer) cell lines, without notable cytotoxicity towards the HepG2 control cell line. Compound 61 (Ar\(^1\) = 4-ClC\(_6\)H\(_4\), Ar\(^2\) = 4-MeC\(_6\)H\(_4\)) was more active than the well-known dexamethasone corticosteroid used for the treatment of rheumatism and skin inflammation [100].

\[
\text{R-N=Ar} \quad \text{OHC} \quad \text{COOH} \quad \text{HOC} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{R} \quad 61 \quad 80-95\%
\]

R = 4-ClC\(_6\)H\(_4\), 4-MeC\(_6\)H\(_4\), Cl, OMe, OEt, OEt, NMe, OMe, anthracen-9-yl

Scheme 47. Synthesis of 1,4-diaryl-3-aryloxy-2-azetidinones 61.

In a similar way, operating with DMF as solvent, cis-1-aryl-4-(4-methylsulfonylphenyl)azetidine-2-ones 63 were synthesized (Scheme 48) and their biological activity as selective cyclooxygenase-2 (COX-2) inhibitors was evaluated. All compounds were selective inhibitors of the COX-2 isozyme and the 1-(3,4,5-trimethoxyphenyl) derivative showed the highest COX-2 inhibitory selectivity and potency. The analgesic activity was also investigated [101].
The [2+2] cycloaddition of heteroaryl-substituted imines, such as 64, and different aryloxyacetic acids allowed the synthesis in 75–90% yields of cis-β-lactam hybrids 65 containing 2-mercaptopbenzothiazole and benzoquinoline systems (Scheme 49). Biological studies showed a good antibacterial activity against either the Gram-negative \textit{E. coli} and \textit{P. aeruginosa} or the Gram-positive \textit{S. aureus} mainly when \textit{Ar} = Ph and low cytotoxicity effects on eukaryotic cells [102].

Applying this procedure to suitably substituted acetic acid derivatives and Schiff bases, structurally complex β-lactams bearing different heterocyclic systems were efficiently prepared (Figure 1).

On the basis of the mechanistic hypothesis outlined in Scheme 2 for the Staudinger [2+2] cycloaddition, it is difficult to predict the stereochemical outcome of the β-lactam adducts due to the influence of several factors, in particular when large polycyclic aryl substituents are present in the imine or ketene partners. These groups are responsible for larger or smaller steric interactions depending on spatial arrangements as well as π-π interactions that can be either attractive (π-stacking) or electronically repulsive in their nature. For instance, naphthalimido hybrids of type 66 were obtained from aryloxyacetic acids exclusively as cis-stereoisomers (1H NMR analysis; single crystal X-ray analysis on β-lactam with \textit{R} = OMe and \textit{Ar} = 4-ClC₆H₄). On the contrary, a bulky bis-arylimidoacetic acid derivative reacted with anthracenyl-substituted imines leading to trans-bis-β-lactams 67 and the same stereochemical outcome was observed with aryl and fluorenyl imines (Figure 1). Antioxidant and anticancer activities were evaluated as well as DNA interaction. In particular, bis-adducts 67 showed excellent antioxidant activity and in vitro anticancer activity against the \textit{MCF-7} and \textit{TC-1} cancer cell lines, without noticeable cytotoxicity towards healthy cells, as well as the ability to bind to calf-thymus DNA (CT-DNA) [103].

The synthesis of tripodal β-lactams 68 with a 1,3,5-triazine core was performed using \textit{s}-triazine-based tris-imines (Figure 1). NMR analysis evidenced the all-cis-relative stereochemistry of the three β-lactam rings (even if the presence of different “all-cis-diastereomers” was not definitively established). The tris-β-lactams displayed good inhibitory behavior against the K562 human leukemia cell line and antioxidant properties as radical scavengers while moderate antibacterial activity against Gram-positive bacteria \textit{S. aureus} was observed for phenoxy derivatives with \textit{X} = \textit{Y} = H and \textit{Z} = \textit{Me} or OEt [104].
Figure 1. Cont.
Figure 1. Structurally complex β-lactams 66–73 bearing different heterocyclic substituents. The blue part of the structure comes from the acetic acid derivative. For compounds 67 and 68 only one possible diastereomer is reported.

Completely stereoselective processes were also observed with different morpholino-1,3,5-triazine imines affording triazine-containing cis-β-lactam hybrids 69, 70, and 71 (Figure 1). Some derivatives of type 69 and 70 showed excellent growth inhibitory activity (in vitro IC$_{50}$ < 5 µM) against SW1116 cells, comparable to that of the clinically used anticancer agent doxorubicin (IC$_{50}$ = 6.9 µM). Strong interactions with CT-DNA were also observed for 69 [105].

Moreover, monocyclic 1H-phenanthro[9,10-d]imidazole β-lactam conjugates 72 were synthesized exclusively as cis-stereoisomers in 70–95% yields from 1H-phenanthro[9,10-d]imidazole imines and aryloxyacetic acids (Figure 1). They exhibited significant cytotoxicity towards various mammalian cancer cell lines [106].

Cis-β-lactam rings 73 with a piperazine moiety in the appended side chain were also prepared in 28–68% yields from piperazinyl-substituted imines and 2-PhO/MeO-acetic acids (Figure 1). A high inhibitory activity on inducible nitric oxide synthase (iNOS) as well as anti-inflammatory activity were observed mainly when a naphthyl moiety was present at the C-4 position (Ar = 2-naphthyl). Good antibacterial activity against *S. aureus* and *E. coli* was also evidenced [107].

Applying the well-established protocol to morpholino-substituted imines 74, the use of 2-ArO/MeO-acetic acids afforded N-morpholino-β-lactams 75 in 23–79% yields whose cis-stereochemistry was confirmed by $^1$H NMR analysis. When 9H-xanthene-9-carboxylic acid was applied as ketene precursor, spiro derivatives 76 were obtained in 41–71% yields (Scheme 50). Compounds 75 showed high anti-inflammatory activity toward human inducible nitric oxide synthase (iNOS) and cytotoxic evaluation toward HepG2 cell lines evidenced their nontoxicity and biocompatibility [108].

Scheme 50. Synthesis of cis-β-lactams 75 and spirocyclic derivatives 76.
β-Lactam-isatin conjugates 77 were synthesized from different C-styryl-N-aryl imines and 2-(2,3-dioxoindolin-1-yl) acetic acid by treatment with TsCl/Et3N in dry CH2Cl2 at 0 °C (Scheme 51). The diastereoselectivity of the reaction is strongly dependent on the electronic nature of the substituents in the N-phenyl imine moiety. Strong electron-donating groups at the para-position promoted cis-selectivity likely due to the increased electron density on the imine nitrogen favoring the direct ring closure of the 2-azabutadiene intermediate. Strong electron-withdrawing groups at the same position reversed the diastereoselectivity presumably by facilitating the isomerization of the intermediate. Variable results were observed for substituents at the meta-positions, probably depending on both electronic and steric factors. DFT calculations supported the experimental outcome [109].

Analogously, mono-spiro and bis-spiro isatin-tethered 2-azetidinones 78, 79, and 80 were prepared from isatin-based imines and bis-imines (Figure 2). For derivatives 78 the antimalarial activity was successfully evaluated against the P. falciparum K1 strain, while compounds 79 and 80 showed moderate to excellent anti-cell-proliferation behavior against two cancer cell lines (MCF-7 and HeLa). β-Lactams 79 were also able to interact with protein BSA and CF-DNA [110,111].

A one-pot procedure led to 1,3-bis-aryl spiroxindolo-β-lactams 81 by treatment of substituted phenylacetic acids with TsCl and disopropylethylamine (DIPEA) in dry o-xylene at 100 °C, for ketene generation, followed by isatin Schiff base addition at room temperature. The reactions showed high diastereoselectivity in favor of the cis-isomers (except for 4-MeO-phenylacetic acid). An increase in trans-isomers was observed by raising the temperature and solvent polarity. Using N-aryl-2-oxo-pyrrolidine-3-carboxylic acids as the ketene source and isatinimines, totally diastereoselective processes afforded trans-dispiroxindolo-β-lactams 82, evaluated for cytotoxic and antibacterial activities (Figure 2) [112,113].
2.3.2. Ketene Generated In Situ from Carboxylic Acids and POCl₃/Base

Monocyclic β-lactams are generally more stable in hydrolysis by β-lactamases in comparison to other β-lactams. Thus, in the light of the search for new agents to fight the serious problem of antimicrobial resistance, monobactams are an attractive platform for studying the effects of synthetic modifications. In this context, 3-(p-substituted-phenylthio)-azetidin-2-ones 83 were prepared via [2+2] Staudinger cycloaddition and applied in Lewis-acid-catalyzed nucleophilic substitutions. 2-Arylthioacetic acids were reacted with C-aryl-N-aryl Schiff bases in the presence of triethylamine and phosphorous oxychloride in refluxing toluene to give trans-3-arylthio-β-lactams 83 as the major products (minor amounts of the cis-stereoisomers were also formed from 1,2-diphenylmethanimine) (Scheme 52) [114]. Compounds 83 were subjected to chlorination with sulfuryl chloride leading to cis-3-chloro-3-arylthio-β-lactams 84 whose stereochemistry was confirmed by correlation of spectral data with those of compounds analyzed via X-ray crystallography. The following Lewis-acid-catalyzed C-3 functionalization allowed the preparation of different derivatives such as cis-3-allyl-β-lactams 85 with allyltrimethylsilane. Oxidation with Selectfluor led to (S)-cis-3-allyl-3-arylsulfanyl-β-lactams 86 as single stereoisomers in excellent yields [115].

Schiff bases prepared from amino-benzenesulfonamides and vanillin or salicylaldehyde were treated with thioglycolic or 2-seleno-glycolic acid in the presence of Et₃N and POCl₃ in dry dichloromethane from 0 °C up to room temperature to afford 3-mercapto or 3-hydroseleno azetidine-2-ones 87 bearing benzenesulfonamido substituents at position 1 (Figure 3). The antibacterial activity was tested in vitro against Staphylococcus aureus, Bacillus, Escherichia coli, and Pseudomonas aeruginosa, as well as the antioxidant and anticancer efficiency [116].

The same protocol was applied to 2-hydroxynaphthyl-substituted imines and chloroacetic acid to give 3-chloro-azetidin-2-ones 88 (Figure 3) whose antibacterial activity was evaluated against different Gram-negative and Gram-positive bacteria. In compounds 87 and 88 the presence of hydroxy groups seems very important in enhancing the antioxidant, anticancer, and antibacterial activities. Unfortunately, the relative stereochemistry was not determined for compounds 87 and 88 [117].
Compounds 83 were subjected to chlorination with sulfuryl chloride leading to lactams and their synthetic elaboration.

The treatment of Schiff bases bearing heterocyclic substituents and variously functionalized acetic acid derivatives (or acetyl chlorides) with POCl₃/Et₃N (or simply Et₃N in the case of acetyl chlorides) in refluxing toluene allowed access to different β-lactam/heterocycle hybrids 89–92 (Figure 4) via almost exclusively trans-diastereoselective processes. The observed stereochemistry, determined on the basis of ¹H NMR analysis and definitively confirmed via single-crystal X-ray crystallography in representative cases, can be rationalized on the basis of both steric hindrance (bulky group at C-4 and N-1) and the zwitterionic intermediate isomerization/electrocyclization pathway (see, Scheme 51), favoring the thermodynamically more stable product [55,57,118,119].

Figure 4. β-Lactam/heterocycle hybrids 89–92. The blue part of the structure comes from the acetic acid derivative.
2.3.3. Ketene Generated In Situ from Carboxylic Acids and SOCl₂/Base

Azetidin-2-ones 93 and 94 bearing an oxazolidinone moiety were synthesized from (oxazolidin-3-yl)acetic acid derivatives and imines by treatment with SOCl₂ and Et₃N in MeOH at 40 °C (Figure 5). These compounds showed significant antibacterial activities against Gram-positive and Gram-negative bacteria like B. subtilis and E. coli. Moreover, fluorescence studies revealed excellent sensing capabilities for divalent metal cations [120,121].

\[
\text{R} = \text{R} = \text{n-Pr}, \text{Ph}
\]

Figure 5. β-Lactam/oxazolidinone hybrids 93 and 94. The blue part of the structure comes from the acetic acid derivative.

2.3.4. Ketene Generated In Situ from Carboxylic Acids and Acyl Chlorides/Base or Trifosgene/Base

Ketenes were also generated from carboxylic acids via activation with acyl chlorides to generate mixed anhydrides as reactive precursors. For instance, spiroazetidine-2-ones of type 81 (see Figure 2), even substituted on the indoline moiety, were prepared in 27–84% yields by a one-pot procedure involving addition of oxalyl chloride in dry THF to a solution of isatin imine, arylacetic acid, and DIPEA in the same solvent at room temperature (Scheme 53). Even in these conditions, compounds 81 were synthesized exclusively or mainly as cis-stereoisomers, as confirmed by X-ray diffraction analysis on specific products. The greatest diastereoselectivity was observed when electron-donating substituents were present in the N-aryl moiety of the imine (R¹ = EDG). The same authors studied the above reaction using preformed aryl acetyl chloride (prepared from the acid by addition of oxalyl chloride in DMF/THF under reflux, purified by column chromatography and recrystallization) in the presence of Et₃N in refluxing DMF. An opposite stereochemical outcome was observed leading to the trans-stereoisomers as the major products (44–64% yields) (see 5g, Scheme 7). The modified experimental conditions (likely the higher temperature) are responsible for the different stereoselectivity as well as lower yields. Preliminary in vitro cytotoxicity tests showed for cis-diastereomers a higher activity as inhibitors of the p53-MDM2 protein–protein interaction with respect to trans ones, according to molecular docking data [33].

\[
\begin{align*}
\text{Ar} = & 2,4-\text{Cl}_2\text{C}_6\text{H}_3, 3,4-\text{Cl}_2\text{C}_6\text{H}_3 \\
\text{R} = & \text{Ph}, 2,4-\text{Cl}_2\text{C}_6\text{H}_3, 3,4-\text{Cl}_2\text{C}_6\text{H}_3, 3,4-\{\text{MeO}\}_2\text{C}_6\text{H}_3
\end{align*}
\]

Scheme 53. Synthesis of cis-spiroazetidine-2-ones 81 using oxalyl chloride as acid activator.

The asymmetric synthesis of spirooxindole β-lactams 95, analogous of 81, was efficiently performed using pivaloyl chloride (PivCl) as acid activator, Et₃N as the base, and the enantipure isothiourea organocatalyst homobenzotetramisole (HBTM) in dichloromethane at low temperature. Compounds 95 were prepared in 40–98% yields as cis/trans-mixtures...
where the cis-stereoisomer was the major product (dr cis/trans from 66:34 to 93:7) with ee ≥99% (Scheme 54) [122].

![Scheme 54. Synthesis of cis-spirooxindole β-lactams 95 using pivaloyl chloride as acid activator.](image)

An analogous method was applied to synthesize diprotected 3-amino-4-substituted monocyclic β-lactams 96. Ketenes were generated from t-butyllcarbamate- or benzylcarbamate-protected glycine by treatment with ethyl chloroformate and Et₃N in dry THF at low temperature (from −60 to −40 °C) to form the mixed anhydride, then added to a solution of an aromatic imine. Compounds 96 were obtained mainly as cis-stereoisomers in 11–33% yields (Figure 6). This methodology was compared with those involving ketene generation from acyl chlorides (see 10d and 10e, Scheme 10). Deprotection methods were also investigated [39].

![Figure 6. Monocyclic β-lactams 96 and 97. The blue part of the structure comes from the acetic acid derivative.](image)

Even methyl 4,5-dichloro-6-oxopyridazine-1(6H)-carboxylate was applied as an activator of carboxylic acid for ketene generation. The reaction with phenoxyacetic acid in refluxing toluene gave rise to a mixed anhydride with elimination of 4,5-dichloropyridazine-3(2H)-one that can be recovered and recycled. The following reaction with suitable Schi bases and Et₃N in dry dichloromethane at room temperature gave monocyclic β-lactams 97 exclusively as cis-diastereomers, whose stereochemistry was definitively confirmed via X-ray crystallographic analysis (Figure 6). The potential optical and nonlinear optical properties of these products were explored as well as their antimicrobial activities against some bacteria and fungi [123].

The system triphosgene (Cl₃C-O-COO-CCl₃)/Et₃N was also applied to activate carboxylic acids towards ketene generation, likely via formation of anhydride intermediates [124]. Operating with chloroacetic acid and the suitable imine in dry dichloromethane under reflux, this approach allowed the synthesis in 34% yield of trans-3-chloro-4-(3-hydroxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)azetidin-2-one (98), that is structurally related to the tubulin polymerization inhibitor and vascular targeting agent combretastatin A-4 (CA-4) (Figure 7). This compound, as well as other 3-chloro/bromo- and 3,3-dichloro-azetidinones mainly synthesized from chloro/bromo-acetyl chloride and dichloroacetyl chloride (see 50e, Scheme 35, 58c-e, Scheme 43, and 59a, Scheme 44), was evaluated as tubulin-targeting agent and showed significant antiproliferative activity at nanomolar concentrations in a range of human cancer cell lines [64].
Figure 7. 3-Chloro-4-(3-hydroxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)azetidin-2-one (98), structurally related to combretastatin A-4 (CA-4). The blue part of the structure comes from the acetic acid derivative.

2.3.5. Ketene Generated In Situ from Carboxylic Acids and Vilsmeier Reagent/Base

(Chloromethylene)dimethyliminium chloride (Vilsmeier reagent) was used in the presence of a base as a carboxylic acid activator to generate ketenes under mild reaction conditions. Aromatic Schiff bases and substituted acetic acids were treated with triethylamine and Vilsmeier reagent in dry dichloromethane at room temperature to afford monocyclic β-lactams 99, exclusively as cis-stereoisomers (1H NMR analyses). This protocol allowed the synthesis of different nitroaryl-substituted 2-azetidinones in high yields, and the selective reduction of nitro to amino groups was efficiently performed with Fe3O4 nanoparticles in refluxing EtOH to give amino β-lactams, such as 100 (Scheme 55) [125].

![Scheme 55](image)

Scheme 55. Synthesis of cis-monocyclic β-lactams 99, using Vilsmeier reagent as carboxylic acid activator.

This protocol was applied to the synthesis of N-anthraquinon-2-yl-β-lactams 101 using imine derived from 2-aminoanthraquinone. Compounds 101 are in general synthesized as cis-diastereomers (1H NMR data) but in some cases, probably due to electronic and steric effects of the substituents, trans-derivatives were obtained (Figure 8). These compounds were evaluated for antibacterial, antifungal, and anticancer activities [126,127].

![Figure 8](image)

Figure 8. N-anthraquinon-2-yl-β-lactams 101. The blue part of the structure comes from the acetic acid derivative.

2.3.6. Ketene Generated In Situ from Carboxylic Acids and Mukaiyama Reagent/Base

The in situ generation of ketenes from carboxylic acids was also achieved using 2-chloro-N-methylpyridinium iodide (Mukaiyama reagent) as the acid activator and triethylamine. The treatment of 2-(6-methoxy-2-naphthyl) propanoic acid (naprossen) with Mukaiyama reagent and Et3N in dry CH2Cl2 under reflux was studied and was more efficient with respect to other systems for ketene generation. The presence of ketene intermedi-
ate was confirmed by its trapping with the stable free radical 2,2,6,6-tetramethylpiperidinyloxy (TEMPO). Subsequent addition of a C-aryl-N-aryl imine at the same temperature afforded 3-(6-methoxy-2-naphthyl)-3-methyl-1,4-diaryl-2-azetidinones 102 as diastereomeric mixtures containing mainly the trans-isomer (Scheme 56). Applying the same protocol to indomethacin as ketene precursor, β-lactams 103 were synthesized exclusively as trans-isomers. The steric hindrance aryl/naphthyl or aryl/indomethacinyl is probably responsible for the stereochemical outcomes. Derivatives 102 were tested for anticonvulsant activity [128,129].

Similarly, 3-amino-1,4-diaryl-2-azetidinones 104, analogues of combretastatin A-4 (CA-4), were prepared from (1,3-dioxo-1,3-dihydro-2H-isindol-2-yl)acetic acid (N-phthaloylglycine) using Mukaiyama reagent, exclusively as trans-stereoisomers (Figure 9). Analogous derivatives with different substituents at position 3 were prepared starting from acyl chlorides (see 5e, Scheme 7; 36d, Scheme 25; 37, Scheme 26; 50e, Scheme 35; 58f, Scheme 43) or ethyl bromoacetate in the presence of Zn (see Figure 11 below). They were evaluated in vitro for antiproliferative activity, antiapoptotic activity, and inhibition of tubulin polymerization [31].

![Scheme 56. Synthesis of β-lactams 102 and 103, using Mukaiyama reagent as carboxylic acid activator.](image)

**Figure 9.** 3-Amino-1,4-diaryl-2-azetidinones 104, analogues of combretastatin A-4 (CA-4). The blue part of the structure comes from the acetic acid derivative.

### 2.4. Ketene Generated In Situ from Diazo Compounds

Diazo compounds are versatile substrates that readily undergo Wolff rearrangement to ketenes, which then undergo various transformations, including cycloaddition with imines to 2-azetidinones. These transformations are usually carried out under metal catalysis, although more recently both photoinduced and thermal decompositions have been used. The mechanistic pathway of the Wolff rearrangement can be described as either concerted or stepwise (Scheme 57).
A series of papers by Kravasin et al. describe the thermally promoted preparation of substituted 2-azetidinones, combining the Wolff rearrangement and the Staudinger ketene-imine cycloaddition. Compared to previous methods, this approach does not require metal catalysts.

In a first paper, Kravasin et al. investigated the thermally assisted reaction of imines with α-acyl-α-diazoacetates 105, which had previously been reported mainly in the presence of transition metal catalysts. The reaction leads to the formation of densely substituted 2-alkoxycarbonyl-β-lactams 106 in moderate to good yields with excellent diastereoselectivities (single diastereomer except for $R^2 = 2$-FC$_2$H$_4$ and 4-F$_2$CC$_6$H$_4$ with $R^3 = R^4 = $ Me and $R^1 = $ Bn). The reaction was carried out with imines prepared either in situ or in a separate step in refluxing toluene. Notably, mechanistic analysis of energetically feasible reaction pathways using DFT calculations evidenced 1,3-oxazin-4-one species as intriguing intermediates. This finding is novel as these intermediates have not previously been implicated in the Staudinger synthesis of β-lactams. Unfortunately, initial attempts to confirm this hypothesis with experimental data were unsuccessful (Scheme 58) [130].

![Scheme 57. Wolff rearrangement–Staudinger cycloaddition.](image)

**Scheme 57.** Wolff rearrangement–Staudinger cycloaddition.

Selected examples:

- $R^2 = $ PMP (86%), p-tolyl (86%), 2,6-(MeO)$_2$C$_6$H$_3$ (0%), 4-FC$_2$H$_4$ (71%), 2-FC$_2$H$_4$ (57% contains traces of the other diastereomer), 4-F$_2$CC$_6$H$_4$ (57%, dr 8:2:1.0)
- $R^2 = $ PMP (86%), p-tolyl (86%), 2,6-(MeO)$_2$C$_6$H$_3$ (0%), 4-FC$_2$H$_4$ (71%), 2-FC$_2$H$_4$ (57% contains traces of the other diastereomer), 4-F$_2$CC$_6$H$_4$ (57%, dr 8:2:1.0)
- $R^1 = $ Et (70%), Ph (81%), c-Hex (60%), l-Bu (0%), PMP (61%, structure confirmed by X-ray), 4-F$_2$CC$_6$H$_4$ (0%)

**Scheme 58.** 2-Alkoxycarbonyl-2-azetidinones by tandem Wolff rearrangement-Staudinger ketene-imine cycloaddition.
Later the reaction was extended to other types of diazo compounds such as dialkyl diazomalonates and α-diazo-β-ketosulfones as ketene precursors. The use of dialkyl diazomalonates gave 3-alkoxy-3-alkoxycarbonyl-2-azetidinones 107 with remarkable diastereoselectivity. The reaction failed with bulky amines such as t-butylamine (Scheme 59) [131].

![Scheme 59. 3-Alkoxy-3-alkoxycarbonyl-2-azetidinones by tandem Wolff rearrangement–Staudinger synthesis.](image)

A broad range of α-diazo-β-ketosulfones 108 have been utilized in thermally promoted tandem Wolff rearrangement–Staudinger cycloaddition to afford polysubstituted β-lactam sulfones 109. There was no significant effect of the type of migrant group (R²) on the outcome of the response. Electron-withdrawing groups in the aldehyde portion (R³) of the imine led to a poorer yield. The diastereoselectivity of the reaction seems to be mainly influenced by the nature of the amine substituent (R⁴). There was a preference for the cis-diastereomer and diastereomerically pure cis-diastereomers were obtained in good yields after repeated chromatographies. The relative stereochemistry was confirmed by single-crystal X-ray crystallography (Scheme 60) [132].

A thermally promoted tandem Wolff rearrangement–Staudinger cycloaddition has also been used to prepare 3-cyano-β-lactams 111 in good to excellent yields. The particularity of the process is the use for the first time of α-cyano-α-diazo ketones 110 for the generation of the corresponding ketenes. The process works well regardless of the substitution pattern in both reaction partners, and even imines with bulky tertiary alkyl substituents can lead to high product yields (Scheme 61) [133].

In a similar thermal process, the imine was generated from the corresponding azide. Treatment of the azide 112 with triphenylphosphine leads to the formation of an iminophosphorane intermediate (Staudinger reaction), which subsequently reacts with the aldehyde (Aza wittig reaction) to give the imine. At the same time, ketene is generated from the diazo compound 113 (keto ester, keto nitrile, diketone, malonate) (Wolff rearrangement). A series of 24 novel structurally diverse β-lactams was prepared.
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Scheme 62. Diastereoselective three-component one-pot β-lactam synthesis from azides.

The N-benzyl β-lactams shown in Figure 10 were synthesized from Cbz-protected 1-amino-3-diazopropan-2-one and an imine in moderate yields. The reaction was carried out in 1,2-dimethoxyethane under microwave irradiation [39].

Figure 10. Preparation of Cbz protected 3-aminomethyl β-lactams.

Another multicomponent Staudinger synthesis has been reported by Basso et al. The process involves mixing an aldehyde, an amine, and a diazoketone in the dark and then switching on the light after the imine has formed. All of the β-lactams 114 were obtained exclusively as the trans-isomer and in moderate to good yields. The isolated yields of the three-component reaction products (red yields) are slightly lower than those of the preformed imine reaction products (blue yields). Aliphatic aldehydes gave no product (Scheme 63) [135].

Scheme 63. Photoinduced Staudinger synthesis of β-lactams.
In a report published by Munaretto and colleagues a two-step reaction was proposed in which aryl diazoacetates 115 were reacted with azides in the presence of blue light, resulting in the formation of imines 116. The imines were then reacted with aryl diazoketones, even in the presence of blue light, yielding alkyl 4-carboxylate-β-lactams 117. When two aryl substituents are present in the aryldiazoketone 118, poor diastereoselectivities were observed (117b) while when a methyl and a phenyl group are present only one diastereomer of the β-lactam 117c was observed (Scheme 64) [136]. A one-pot preparation of some β-lactams was also attempted, starting from the corresponding aryl diazoacetates and azides. The diazoketone partner was then added sequentially, but in a few cases competitive yields were obtained.

Scheme 64. Blue-light-mediated preparation of 4-alkoxycarbonyl-β-lactams 117.

A three-component reaction of N-hydroxyanilines (stable and readily available), enynones, and diazo compounds has been developed under rhodium catalysis, providing highly functionalized β-lactams 119 containing two quaternary carbon centers in good yields and with excellent diastereoselectivities (Scheme 65). This protocol involves a sequential reaction of Rh(II)-catalyzed imine formation, Wolff rearrangement, and benzoylquinine 120-catalyzed Staudinger cycloaddition [137].

A similar rhodium(II)-catalyzed three-component reaction was explored for the synthesis of β-lactams 123 using N-hydroxyanilines and diazo compounds 121 and 122, (Scheme 66) [138].

A new method for the synthesis of functionalized β-lactams has been developed based on a Rh2(esp)2-catalyzed redox/cycloaddition cascade reaction. The reaction was performed under very mild conditions, using only 0.5 mol% of the catalyst, and employing stable and readily available N-methyl nitrones as the precursors of N-methyl imines. The process is initiated by the reduction of the N-methylnitrene to the corresponding N-methylimine in the presence of a first molecule of the diazoacetacetate enone which was plausibly oxidized to the corresponding tricarbonyl compound. A second molecule of the diazoacetacetate enone then undergoes a Wolff rearrangement to form a vinyl ketene. This vinyl ketene then reacts with the in-situ-generated N-methyl imine to selectively produce a β-lactam with two contiguous stereogenic centers (Scheme 67) [139]. Complete diastereoselectivity was observed in all the transformations. The rhodium catalyst, through
the formation of the initial carbene 124, has two fundamental roles: (i) to promote the formation of the imine from the nitrone and (ii) to promote the rearrangement of the diazoacetoacetate enone to the vinyl ketene.

Scheme 64. Blue-light-mediated preparation of 4-alkoxycarbonyl-β-lactams....

Selected examples:

\[
\begin{align*}
X = H \,(X-ray, \, 85\%, \, dr > 20:1), \, OMe \,(88\%, \, dr > 20 : 1), \\
Cl \,(78\%, \, dr > 20 : 1), \, CO_2Et \,(78\%, \, dr > 20 : 1), \\
CN \,(74\%, \, dr > 20 : 1), \, Me \,(78\%, \, dr > 20 : 1)
\end{align*}
\]

\[
\begin{align*}
R^2 = XC_6H_4; \, X = 4-\text{MeO} \,(90\%), \\
CF_3 \,(71\%, \, dr > 20 : 1); \, CN \,(88\%, \, dr > 20 : 1)
\end{align*}
\]

Scheme 65. Three-component reaction of N-hydroxyanilines, enynones, and diazo compounds.

Scheme 66. Rhodium-catalyzed three-component reaction to 2-azetidinones.

Rivasankar et al. have proposed a convenient method to synthesize β-lactams. This method involves the carbonylation of diazo compounds using [Co2(CO)8] as a solid carbonyl source to produce corresponding ketenes, which are then subjected to cycloaddition with imines. This newly developed method proved successful in producing β-lactams from electronically and structurally diverse substrates under mild reaction conditions. FT-IR spectroscopy confirmed the ketene formation and the transformation of ketene into β-lactam (Scheme 68) [140].
Sivasankar et al. have proposed a convenient method to synthesize \( \beta \)-lactams. This method involves the carbonylation of diazo compounds using \([\text{Co}_2(\text{CO})_8]\) as a solid carbonyl source to produce corresponding ketenes, which are then subjected to cycloaddition with imines. This newly developed method proved successful in producing \( \beta \)-lactams from electronically and structurally diverse substrates under mild reaction conditions. FT-IR spectroscopy confirmed the ketene formation and the transformation of ketene into \( \beta \)-lactam (Scheme 68) \cite{140}.

Spirocyclic N-vinyl \( \beta \)-lactams 129 have been prepared by a two-step Rh(II)-catalyzed domino synthesis from 5-alkoxyisoxazoles 127 and acyclic \( \alpha \)-diazomalonates. The process proceeds by the formation of 2-azabuta-1,3-dienes 128 in dichloroethane (DCE) followed by a domino reaction to produce the spirocyclic \( \beta \)-lactams.
Diazo transfer reactions are well-known to involve the use of sulfonyl azides, which are potentially explosive. Interestingly, a sulfonyl-azide-free protocol for diazo transfer in aqueous medium was applied to the preparation of diazoketone 125 from in-situ-generated m-carboxybenzenesulfonyl azide. Diazoketone 125 was then used as a substrate for a Staudinger synthesis to give β-lactam 126, the structure of which was confirmed by X-ray analysis (Scheme 69) [141].

Scheme 69. Synthesis of β-lactam 126.

Spirocyclic N-vinyl β-lactams 129 have been prepared by a two-step Rh(II)-catalyzed domino synthesis from 5-alkoxyisoxazoles 127 and acyclic α-diazomalonates. The process proceeds by the formation of 2-azabuta-1,3-dienes 128 in dichloroethane (DCE) followed by the addition of diazo-Meldrum’s acid as ketene precursors for the subsequent Staudinger ketene–imine cycloaddition in trifluorotoluene (TFT) (Scheme 70). The reaction was also developed using azirines instead of isoxazoles combined with diazoketoesters [142].

Scheme 70. Synthesis N-vinyl β-lactams from 5-alkoxyisoxazoles.

2.5. Ketene Generated In Situ from α-Haloesters (Reformatsky-Type Reaction)

The reaction between imines and Reformatsky reagents, obtained from α-haloesters and Zn, can be described as a variant of the ketene–imine Staudinger cycloaddition, where the fragmentation of the Reformatsky reagent allowed ketene generation (path a). Alternatively, a two-step process involving addition of the Reformatsky reagent to the imine and cyclization of the intermediate β-amiido ester can be proposed (path b) (Scheme 71). Several studies supporting these different hypotheses have been reported [143].

Scheme 71. Mechanistic hypotheses for the Reformatsky-type β-lactam synthesis.
1,4-Diaryl-3-unsubstituted β-lactams 130a (Figure 11), analogous to CA-4 (see Figure 9), were synthesized via the microwave-assisted Reformatsky reaction in 22–37% yields, using C-aryl-N-aryl imines, ethyl bromoacetate, Zn dust, and trimethylchlorosilane in benzene at 100 °C [31].

![Chemical Structure](image)

**Figure 11.** 1,4-Diaryl-2-azetidinones 130a-c, analogues of combretastatin A-4 (CA-4). The blue part of the structure comes from the acetic acid derivative.

Applying the same protocol to ethyl bromofluoroacetate or ethyl bromodifluoroacetate, 3-fluoro- and 3,3-difluoro-azetidine-2-ones 130b and 130c (Figure 11) were synthesized in 6–65% yields with exclusive trans-stereochemistry for the monofluoro derivatives, based on spectral and X-ray crystal analyses. The fluorinated compounds, as well as the 3-unsubstituted derivatives, were evaluated for in vitro antiproliferative activity in MCF-7 human breast cancer cells [144].

A Reformatsky-type reaction, involving the treatment of N-(4-methoxybenzyl)arylamines and ethyl dibromofluoroacetate with Et₂Zn in diethyl ether at −10 °C, allowed the synthesis of 3-bromo-3-fluoro β-lactams 131 in 41–87% yields (Scheme 72). The cis-relative configuration (related to the position of fluorine and hydrogen atoms) was proposed on the basis of the 3J_H,F coupling constant (≈10.3 Hz) and confirmed via X-ray diffraction analysis on a selected derivative (R = 3,4,5-trifluorophenyl). The same authors reported the synthesis of trans-4-aryl-3-bromo-1-isopropyl β-lactams 59c (see Scheme 44) from α-bromo acetyl bromide and aryl imines. These 3-bromo derivatives were subjected to cobalt-catalyzed cross-coupling reactions with diarylzinc or diallylzinc reagents to perform the C-3 functionalization of β-lactams [98].

![Chemical Reaction](image)

**Scheme 72.** Synthesis of 3-bromo-3-fluoro β-lactams 131.

The application of the imino-difluoro-Reformatsky reaction, involving α-halo-α,α-difluoro esters, imines, and Zn, or Et₂Zn, to the asymmetric synthesis of α,α-difluoro-β-lactams has been reviewed [145].

Imines prepared from p-dimethylaminozinamaldehyde and variously substituted anilines were reacted with ethyl bromoacetates or chloroacetates in the presence of Zn dust in dry benzene under reflux to give 3-unsubstituted and 3-methyl substituted azetidin-2-ones 132 (Scheme 73). The use of different Lewis acids was studied, but Zn catalysts...
gave the best results in terms of reaction rate and yields. These compounds were tested for antibacterial activity in vitro against different pathogenic bacteria and fungi [146].

![Reactions 2024, 5](https://example.com/reactions.png)

**Scheme 73.** Synthesis of of 4-styryl-β-lactams 132.

The applicability of imines as nonclassical Reformatsky electrophiles was also briefly explored under ball-milling conditions that require no solvent, no inert gas, and no pre-activation of the zinc source. A mechanochemical Reformatsky reaction was performed with N-benzylidene aniline and ethyl bromoacetate in the presence of Zn flake. The unoptimized reaction afforded 1,4-diphenylazetidin-2-one but in only 7% yields, along with the acyclic β-amino ester (48%) [147].

The Reformatsky reagents, prepared from methyl 1-bromocycloalkane carboxylates and Zn, were reacted with N,N'-bis(arylmethylidene)benzidines in dry toluene with 10% HMPA and catalytic amounts of HgCl₂ under reflux. Bis(spiroazetidinones) 134 were then prepared in 54–84% yields, likely via nucleophilic addition to the imine C=N double bond and spontaneous cyclization of intermediates 133 with elimination of MeOZnBr (Scheme 74). The authors based this mechanistic hypothesis on previous results concerning the isolation of amino esters formed by hydrolysis of intermediates of type 133. The spectral analyses (¹H NMR) evidenced the presence of only one diastereomer in solution [148].

![Synthesis of β-lactams 134–136, using the Reformatsky reagent](https://example.com/synthesis.png)

**Scheme 74.** Synthesis of of β-lactams 134–136, using the Reformatsky reagent.

Analogously, the Reformatsky reagent prepared from methyl 1-bromocyclohexanecarboxylate reacted with N,N″-(1,4-phenylene)bis(1-arylmethanimines) to produce bis(spiro)β-lactams 136 in 58–82% yields (Scheme 74). The use of equimolar amounts of the Schiff base and Reformatsky reagent was also applied to isolate some mono(spiroazetidinones) 135 (Ar = 4-fluorophenyl 52% and 2,4-dichlorophenil 63%) [149].
2.6. Ketene Generated In Situ from Ester (or Amido) Enolates

A minireview by Sato and coworkers deals with the Rh-catalyzed reductive Mannich reaction, in which metal enolates obtained by 1,4-reduction of α,β-unsaturated esters reacted with imines to give β-lactams 137, along with minor amounts of β-amino esters. Operating with methyl acrylate and Et₂Zn and RhCl(PPh₃)₃ as catalyst in THF at 0 °C a total cis-diastereoselectivity was observed (Scheme 75). However, steric factors associated with the use of different α,β-unsaturated esters can determine the formation of trans-β-lactams. For instance, the process was applied to the synthesis of (+)-ezetimibe, a cholesterol absorption inhibitor [150].

The reaction of (E)-methyl 4-nitro-3-phenylbut-2-enolate with optically pure (E,E)-cinnamaldehyde tert-butanesulfinyl imine, in the presence of lithium hexamethyldisilyl amide (LiHMDS) in methyl tert-butyl ether (MTBE) as solvent, gave rise to the mixture of enantiopure cis-β-lactams 138 likely by cyclization of the intermediate Mannich adduct (Scheme 76). The presence of the strong electron-withdrawing nitro group can suppress the amino-Cope pathway favoring β-lactam formation. Nevertheless, a ketene intermediate cannot be ruled out [151].

$\text{CO}_2\text{Me} + \text{R}^1 \text{N}^- \xrightarrow{\text{Et}_2\text{Zn}, \text{THF or DMF, 0 °C}} \text{RhCl(PPh}_3\text{)_3}} \xrightarrow{137 \ 48-93\% \ \text{dr up to 100:0}} \text{cis-β-lactam}$

Scheme 75. Synthesis of β-lactams 137.

$\text{N}^+\text{S}^\text{Bu}^-\text{Ph} \xrightarrow{\text{LiHMDS, MTBE, -78 °C}} \text{NO}_2 \text{OMe}$

Scheme 76. Synthesis of enantiopure cis-β-lactams 138.

$\text{N-aryl-4-alkynylazetidin-2-ones 139}$ were prepared upon addition of alkynylimines to a lithium enolate solution derived from ethyl isobutyrate. Subsequent reduction afforded the corresponding azetidines, which were subjected to gold-catalyzed rearrangement to regioisomeric pyrrolo[1,2-α]indoles (Scheme 77) [152].

The synthesis of β-lactams was performed from arylacetic esters, by treatment with isothiourea catalysts in basic medium, likely via C(1)-ammonium enolates as key intermediates. The reaction of pentafluorophenyl (Pfp) arylacetic acid esters with alkynylimines, in the presence of benzotetramisole (BTM) as chiral isothiourea organocatalyst, allowed access to optically pure 4-alkynylazetidine-2-ones 140 in high yields and high enantiomeric excesses (Scheme 78). The absolute configuration of some derivatives was determined by single-crystal X-ray diffraction analysis [153].
From a mechanistic point of view, this reaction can be described as a formal [2+2] cycloadDITION of the alkene intermediate to a lithium enolate solution derived from ethyl isobutyrate. Subsequently, the resulting ketene were achieved in the presence of disilyl amide (LiHMDS) in methyl tert-butyl ether (TBE).

The reaction of pentafluorophenyl (Pfp) arylacetic acid esters with alkenes, particularly those with electron-rich properties, is a robust and relatively mild approach for the synthesis of chilled amides. The presence of the strong electron withdrawing group (Schiff base) has been used as useful synthon for the stereoselective transannulation to β-lactam. Thermal ring opening and subsequent capture of the resulting ketene were achieved in the presence of N-(4-methoxyphenyl)-1-phenylmethanamine (Scheme 79) [154].

2,3-Disubstituted-cyclobut-2-en-1-one 141 has been used as useful synthon for the stereoselective transannulation to β-lactam 142. Thermal ring opening and subsequent capture of the resulting ketene were achieved in the presence of N-(4-methoxyphenyl)-1-phenylmethanamine (Scheme 79) [154].

The reaction between electron-deficient isocyanates, such as chlorosulfonyl isocyanate, and alkenes, particularly those with electron-rich properties, is a robust and relatively mild approach for the synthesis of β-lactams.

From a mechanistic point of view, this reaction can be described as a formal [2+2] cycloaddition allowed under thermal conditions with a supra-antara approach, analogous to the ketene–imine (Staudinger) cycloaddition. However, due to the sterically demanding factors involved in this process, unconcerted or pseudoconcerted mechanisms have also been proposed and some theoretical studies have even supported concerted suprafacial approaches [155]. Overall, the mechanism of this reaction (as well as the Staudinger cycloaddition) is still under investigation and discussion.
A one-pot, two-step reaction of styrene with chlorosulfonyl isocyanate at room temperature yielded the β-lactam intermediate 143 which was directly hydrolyzed by dilution with methanol to the β-amino acid 144. The latter contains a sulfamate group, which is the closest congener and bioisostere to the primary sulfonamide group (Scheme 80). Other examples involving endocyclic alkenes have been reported [156].

Scheme 80. Use of a β-lactam intermediate for the preparation of a sulfamate β-amino acid.

Chlorosulfonyl isocyanate has been used for β-lactam annulations onto natural compounds bearing exocyclic double bonds. The reaction of aromadendrene, a sesquiterpene possessing a fused dimethylcyclopropane ring on a hydroazulene skeleton, with chlorosulfonyl isocyanate resulted in the formation of spiro-β-lactam 145 in 25% yield with high diastereoselectivity. This cycloaddition proceeds with high selectivity likely controlled by the allylic stereocenter and overall topology of the tricyclic natural product, including a fused gem-dimethyl cyclopropane (Scheme 81). Similarly, the reaction of chlorosulfonyl isocyanate with caryophyllene oxide produced the spiro-β-lactam 146 by [2+2] cycloaddition on the exocyclic double bond. Notably, besides this reaction, O-acylation occurs, which leads to the opening of the epoxide ring, followed by its expansion to a cyclic carbonate, and hydrolysis (Scheme 81) [157].

Scheme 81. Annulation of a spiro-β-lactam onto large methylene cycloalkanes.

The racemic cis-β-lactam 148 was prepared from the alkene 147 by cycloaddition with chlorosulfonyl isocyanate followed by hydrolysis of the phthalimido protecting group and amine protection as carbamate (Scheme 82). The cycloaddition is stereospecific and the reaction with the corresponding E alkene gives rise to the trans-β-lactam isomer. Lactam 148 and its trans-isomer have been used to prepare amphiphilic nylon-3 isomers. The interest in these polymers is related to their reported ability to mimic the biological activities
of natural antimicrobial peptides, with strong activity against bacteria and low toxicity to eukaryotic cells [158].

![Scheme 82. Synthesis of the β-lactam 148 subunit in nylon-3 polymers.](image)

[1.1.1]Propellane, a highly strained small molecule, has been involved in processes for the preparation of spiro-β-lactams due to the exceptional reactivity of the central bond between the two bridgehead carbons. Indeed, this property has allowed the preparation of interesting methylenecyclobutane derivatives that reacted effectively with chlorosulfonyl isocyanate.

The synthesis of imidized methylenecyclobutane 149 was carried out in aqueous acetonitrile via a strain-release-driven addition reaction of [1.1.1]propellane with benzoic acid (Scheme 83). Subsequently, the reactivity of methylenecyclobutane 149 has been investigated by cycloaddition with chlorosulfonyl isocyanate to afford β-lactam 150 in a 31% yield [159].

![Scheme 83. Preparation of spiro-β-lactam 150.](image)

A [2+2] cycloaddition with chlorosulfonyl isocyanate of methylenespiro [2.3]hexane 151 gave spiro-β-lactam 152 in a modest yield. Alkene 151 was prepared via a nickel-catalyzed cyclopropanation of 4-vinylbiphenyl with [1.1.1]propellane. The latter process involves cationic addition, which cleaves the cage system leading to an exomethylenecyclobutane (Scheme 84) [160].

![Scheme 84. Preparation of a spirocyclobutane β-lactam.](image)

The kinetic of the reaction of tosyl isocyanate with ethyl vinyl ether and trimethyl-(2-methyl-propenyl)-silane was studied by $^1$H NMR spectroscopy. Azetidinones 153 with the donor substituent in the 4-position were formed in good yields in CH$_2$Cl$_2$. However, the kinetic data showed that the reactions proceeded five times faster in CD$_3$CN than in CD$_2$Cl$_2$. 
These results indicated a moderate increase in polarity from the reactants to the transition state, likely supporting the formation of zwitterionic intermediates (Scheme 85) [161].

Reactions of $p$-toluenesulfonyl isocyanate (less reactive than chlorosulfonyl isocyanate) with electron-rich alkenes were investigated to prepare various β-lactams including interesting monofluoro-tosyl-β-lactams 154 ($R^2 = F$). The process was conducted under mild neat conditions which prevent the opening of the tosyl-β-lactam products 154 (Scheme 86) [162].

Formation of β-lactams by cycloadditions of oxymethane isocyanates (O-isocyanates) 156 with allylsilanes and enol ethers has been the subject of both experimental and density functional theory (DFT) investigations. The results of these studies provide valuable insights into the mechanism involved in this transformation. Specifically, O-isocyanate 156 was generated from O-phenyl carbamate, by thermal loss of phenol, and involved in a [3+2] cycloaddition with alkenes and subsequent formation of the ylides 157. The latter, through a ring-opening–ring-closure sequence, gives the β-lactams 155 (Scheme 87) [163]. The factors that determine the substrate reactivity (regio- and stereoselectivity) of electron-rich alkenes (glycals) in isocyanate cycloaddition have been deeply investigated [164].

Azetidinones 160, as well as dihydropyrimidinedione and oxazinone derivatives, were obtained from the reaction of isopropyl isocyanate with heterocumulene ylides 158 (Scheme 88). The reaction proceeded via the formation of a dipolar intermediate 159, which in the case of (N-phenyliminovinylidene)triphenylphosphorane (158, $X = NPh$) cyclizes to 160 or adds another molecule of isopropyl isocyanate to give dihydropyrimidinedione 161 and oxazinone 162.

For (triphenylphosphoranylidene)ketene (158, $X = O$), Bestmann’s ylide [165]), cyclization was faster than addition and only β-lactam 160 was observed. The reaction was then extended to phenyl isothiocyanate which reacted with 2-oxovinylidene)triphenylphosphorane (158, $X = O$) to give the corresponding thioxoazetidinone 163 in an 85% yield [166].
R2 = H, X = O (75%), F (10%), NPh (15%), OCOCH3 (3%), OCOCH2CH3 (15%)


Scheme 88. Preparation of β-lactams from heterocumulene ylides.

4. Azetidin-2-Ones from Nitrones
4.1. Nitrones and Alkynes (Kinugasa Reaction)

In 1972 Kinugasa and Hashimoto discovered that the reaction of copper acetylide with a nitrone affords β-lactams. Basically, the reaction is a cascade process that involves a 1,3-dipolar cycloaddition of a copper acetylide onto the nitrone, followed by a rearrangement step (Scheme 89) [167].

Since then, the “acetylide reaction” (Kinugasa reaction) is used as a highly effective method for the synthesis of β-lactams. This is due to its high atom efficiency, use of easily accessible starting materials, and convergent approach. Additionally, the Kinugasa reaction has increased in utility through the implementation of asymmetric synthesis of β-lactams [168].
The mechanism of the Kinugasa reaction has been re-evaluated using density functional theory (DFT) calculations and recent experimental results. According to the calculations, an isoaxazoline intermediate is formed after a two-step cycloaddition initiated by two copper ions. This intermediate can undergo a rapid and irreversible cycloreversion to give an imine and a copper ketenyl intermediate. The reaction can then proceed by cyclization through an intramolecular nucleophilic attack of a copper amide on the ketene carbonyl. This is in contrast to the previous proposal of a [2+2] Staudinger synthesis (in blue in Scheme 90). Importantly, the new mechanism is linked to the Staudinger pathway by a protonation event, which means that the relative energies of the two pathways depend on the strength of the base used in the experiments (or more precisely, on the strength of its conjugate acid) (Scheme 90) [169].

Various sulfur-containing chiral \( \beta \)-lactams 164 and 165 with two consecutive stereogenic centers have been synthesized by an asymmetric three-component interrupted Kinugasa reaction. In this process, PhSO\(_2\)SR or TsSSi-Bu were used as a source of electrophilic sulfur, which competes with the proton for the copper(I) intermediate formed during the Kinugasa reaction. By using the box ligand 166 the chiral \( \beta \)-lactams 164 and 165 were prepared with a wide substrate scope in modest to good yields and with excellent diastereo- and enantioselectivity (Scheme 91) [170].

![Scheme 90. Mechanism of the final stages of the Kinugasa reaction.](image)

![Scheme 91. Preparation of chiral 3-alkythio- and 3-\( \text{tert} \)-butyldisulfanyl-2-azetidinones 164 and 165.](image)
A similar process has been reported in which an interrupted Kinugasa reaction leads to the formation of a new C-C bond on the C-3 carbon of the 2-azetidinone. This reaction involves a synergistic system in which copper catalyzes the Kinugasa reaction while palladium catalyzes the allylic alkylation reaction in the presence of phosphine 168 (Scheme 92). As a result, 3,3′-disubstituted chiral β-lactams 167 have been prepared in high yields and with stereoselectivity. This method allows the synthesis of 2-azetidinones not available by other synthetic approaches [171].

Selected examples:

\[
\begin{array}{ccc}
R^1 & R^2 & R^3 \\
\text{PMP} & \text{Ph} & (X \text{ ray, } 75\%, 96:4 \text{ er}) \\
4-\text{FC}_{6}H_{4} & (72\%, 93.5:6.5 \text{ er}) \\
4-\text{ClC}_{6}H_{4} & (60\%, 93.5:6.5 \text{ er}) \\
4-\text{MeC}_{6}H_{4} & (72\%, 93.5:6.5 \text{ er}) \\
2-\text{naphthyl} & (65\%, 93.7 \text{ er})
\end{array}
\]

\[
\begin{array}{ccc}
R^1 & R^2 & R^3 \\
\text{PMP} & \text{Ph} & 53\%, 94.5:5.5 \text{ er} \\
4-\text{FC}_{6}H_{4} & (68\%, 94.5:5.5 \text{ er}) \\
4-\text{ClC}_{6}H_{4} & (66\%, 91.9 \text{ er}) \\
4-\text{PhC}_{6}H_{4} & (80\%, 93.7 \text{ er}) \\
4-\text{MeC}_{6}H_{4} & (55\%, 92.8 \text{ er}) \\
2-\text{naphthyl} & (52\%, 92.8 \text{ er}) \\
\text{piperonyl} & (78\%, 95.5:4.5 \text{ er})
\end{array}
\]

Scheme 92. Synthesis of 3,3′-disubstituted chiral 2-azetidinones.

The scope of chiral ligands employed in the Kinugasa reaction is limited and the highly enantioselective catalytic Kinugasa reaction is still a challenge. Recently, a novel class of chiral ligands such as 170 derived from TsDPEN [N-(p-tosyl)-1,2-diphenylethylene-1,2-diamine] has been developed and applied to the copper-catalyzed asymmetric Kinugasa reaction (Scheme 93). This method provides an efficient way to synthesize β-lactams 169 in good to excellent yields (up to 93%) and with good to excellent diastereo- and enantioselectivities (dr up to 17.5:1, ee up to 91%). This Kinugasa reaction protocol is ineffective for aliphatic alkynes and phenylacetylenes with a strong electron-donating group. A proposed Cu complex working model, optimized by DFT calculations, has been suggested to explain the observed stereoselectivities. The model involves the [2+2] cycloaddition between ketene and imine as the stereocontrolling step [172].

Application of magnetic copper ferrite (CuFe₂O₄) nanoparticles as a magnetically separable and recyclable heterogeneous catalyst in the Kinugasa reaction has been reported. Under mild conditions at room temperature, the reaction was efficient, affording cis-2-azetidinones 171 with a wide range of functional groups in good to excellent yields after crystallization (Scheme 94) [173].
Application of magnetic copper ferrite (CuFe$_2$O$_4$) nanoparticles as a magnetically

tuned catalyst in the intramolecular and intermolecular double deprotonation of ketenes

Propargyl nitrones were generated using tartaric acid derivatives as substrates for

intramolecular Kinugasa reactions. The dibenzyl ether of diethyl tartrate was easily

converted to the corresponding propargyl aldehyde through a standard reaction sequence. The

intramolecular Kinugasa reaction, via in situ formation of the nitrone group, produced the

bicyclic product 172 with the $\beta$-lactam fragment fused to the seven-membered ring in a

54% yield. Finally, hydrogenative debenzylation was followed by the oxidative opening of

the diol with lead tetraacetate, which afforded cis-$\beta$-lactam 173 as the only stereoisomer

(Scheme 95) [174].

Scheme 93. Synthesis of chiral-2-azetidinones 169 with imine-containing ligands.

Scheme 94. CuFe$_2$O$_4$ nanoparticle-catalyzed synthesis of cis-2-azetidinones 171.

Scheme 95. Synthesis of monocyclic $\beta$-lactam 173 via an intramolecular Kinugasa reaction.
A series of N-substituted cis- and trans-3-aryl-4-(diethoxyphosphoryl)azetidin-2-ones 174 and 175 were synthesized by the Kinugasa reaction of N-methyl- or N-benzyl-C-(diethoxyphosphoryl)nitrone and aryl alkynes (Scheme 96). All obtained azetidin-2-ones were tested against a wide range of DNA and RNA viruses to evaluate their antiviral activity [175].

\[
\begin{align*}
\text{R, } \text{Ar} &= \text{Me, Ph (75-80%); Me, 2-FC₆H₄ (84-86%); Me, 3-FC₆H₄ (74-88%); Me, 4-FC₆H₄ (64-85%); Me, 2,4-F₂C₆H₄ (60-92%); Me, 3-Me-4-FC₆H₄ (65%); Bn, Ph (57-79%); Bn, 2-FC₆H₄ (65-78%); Bn, 3-FC₆H₄ (63-82%); Bn, 4-FC₆H₄ (54-66%); Bn, 2,4-F₂C₆H₄ (61-67%); Bn, 3-Me-4-FC₆H₄ (45-54%).}
\end{align*}
\]

Scheme 96. Synthesis of 4-diethoxyphosphoryl)-2-azetidinones 174 and 175.

N-propargylated nucleobases have been heated with N-substituted-C-(diethoxyphosphoryl)nitrone in the presence of copper iodide to afford a mixture of diastereoisomeric 3-substituted-(4-diethoxyphosphoryl)azetidin-2-ones cis-176 and trans-177, always containing the trans-isomer predominantly. The mixtures of the cis-176 and trans-177 were prepurified on a silica gel column and then separated by HPLC. In most cases at least small amounts of both diastereoisomers were isolated, which were sufficient for biological screening. Of the 84 compounds obtained, some showed moderate activity against varicella-zoster (VZV). Among these, compounds 178 and 179 were found to be the most effective in inhibiting the thymidine kinase (TK)-VZV strain, with EC₅₀ values of 13.4 and 10.5 μM, respectively (Scheme 97) [176].

\[
\begin{align*}
\text{R, Ar} &= \text{Me, Bn; } R^2 = \text{nucleobases}
\end{align*}
\]

Scheme 97. Synthesis of 4-diethoxyphosphoryl-2-azetidinones 176 and 177.

A copper(II)-catalyzed protocol has been developed for the construction of trans-β-lactams from oximes and methyl propiolate. This approach showed good substrate scope and diastereoselectivity (up to >99:1 dr). The method is based on a 1,3-dipolar cycloaddition of a copper acetylide onto the nitrone which is generated by 1,3-azaprotio transfer of oximes and methyl propiolate. For example, nitrone 181 was generated from oxime 180 to selectively give lactam 182 in good yield (Scheme 98).
The method was extended to exocyclic ketoximes, affording spirocyclic β-lactams 183–185 with various carbo and heterocyclic rings (Figure 12) [177].

A copper(I)-catalyzed Kinugasa/aryl C-C coupling cascade reaction has been employed in the asymmetric synthesis of a series of spirocyclic β-lactams 186. The reaction of N-(2-iodoaryl)propiolamides and nitrones using Cu(MeCN)₄PF₆ as the catalyst, a chiral bis-oxazoline ligand 187, and t-BuOLi as a base leads to the formation of functionalized chiral spiro[azetidine-3,3′-indoline]-2,2′-diones 186 as single diastereomers in good yields and with high enantiomeric ratios. No β-lactams were obtained in the presence of organic bases. Control experiments indicated that the diastereo- and enantio-determining step of this protocol is the Kinugasa reaction. This process uses intramolecular aryl-C coupling to capture the copper intermediate 188 formed during the Kinugasa reaction (Scheme 99) [178].

A CuI-catalyzed Kinugasa reaction of the nitrone 189 with methyl propiolate selectively afforded the trans-β-lactam rac-190, which was reduced by sodium borohydride to the corresponding racemic rac-191 which bears a hydroxymethyl group on the β-lactam nucleus. Subsequent optical resolution of racemic rac-191 by esterification with Boc-L-proline and subsequent chromatographic separation of the two diastereomers allowed isolation of the enantiopure alcohol 191 after ester hydrolysis. Treatment of the latter with diethylaminosulfur trifluoride (DAST) yielded the corresponding fluoride 192 with retention of the relative configuration. The β-lactam 192 was employed in the synthesis of a series of compounds, which were subsequently evaluated for their anticancer activity (Scheme 100) [179].

Low stereoselectivity has been observed in reactions of chiral copper acetylides and nonchiral, C-aryl acyclic nitrones. To circumvent this problem, the subsequent separation of Kinugasa adducts has been developed (Scheme 101). As a selected example, the reaction of nitrone 193 with acetylene 194 gave a mixture of four stereoisomers which after column chromatography provided the cis-adduct 195 along with an inseparable mixture of the other three adducts 196 (Scheme 101). The absolute configuration at the C-4 carbon atom of 195 was established by electronic circular dichroism (ECD) spectroscopy [180].

**Scheme 98.** Synthesis of 2-azetidinones initiated by 1,3-azaprotio transfer of oximes and methyl propiolate.

**Figure 12.** Synthesis of spirocyclic β-lactams 183–185.
The method was extended to exocyclic ketoximes, affording spirocyclic \( \beta \)-lactams 183–185 with various carbo and heterocyclic rings (Figure 12)[177].

**Figure 12.** Synthesis of spirocyclic \( \beta \)-lactams 183–185.

A copper(I)-catalyzed Kinugasa/aryl C–C coupling cascade reaction has been employed in the asymmetric synthesis of a series of spirocyclic \( \beta \)-lactams 186. The reaction of N-((2-iodoaryl)propiolamides and nitrones using Cu(MeCN)\(_4\)PF\(_6\) as the catalyst, a chiral bis-oxazoline ligand 187, and \( t \)-BuOLi as a base leads to the formation of functionalized chiral spiro[azetidine-3,3′-indoline]-2,2′-diones 186 as single diastereomers in good yields and with high enantiomeric ratios. No \( \beta \)-lactams were obtained in the presence of organic bases. Control experiments indicated that the diastereo- and enantiodetermining step of this protocol is the Kinugasa reaction. This process uses intramolecular aryl C–C coupling to capture the copper intermediate 188 formed during the Kinugasa reaction (Scheme 99)[178].

**Scheme 99.** Asymmetric Kinugasa/aryl C–C coupling cascade reaction of N-(2-iodoaryl)propiolamides with nitrones.

A CuI-catalyzed Kinugasa reaction of the nitrone 189 with methyl propiolate selectively afforded the trans-\( \beta \)-lactam rac-190, which was reduced by sodium borohydride to the corresponding racemic rac-191 which bears a hydroxymethyl group on the \( \beta \)-lactam nucleus. Subsequent optical resolution of racemic rac-191 by esterification with Boc-L-proline and subsequent chromatographic separation of the two diastereomers allowed isolation of the enantiopure alcohol 191 after ester hydrolysis. Treatment of the latter with diethylaminosulfur trifluoride (DAST) yielded the corresponding fluoride 192 with retention of the relative configuration. The \( \beta \)-lactam 192 was employed in the synthesis of a series of compounds, which were subsequently evaluated for their anticancer activity (Scheme 100)[179].

**Scheme 100.** Optical resolution of a racemic \( \beta \)-lactam rac-191.

Low stereoselectivity has been observed in reactions of chiral copper acetylides and nonchiral, C-aryl acyclic nitrones. To circumvent this problem, the subsequent separation of Kinugasa adducts has been developed (Scheme 101). As a selected example, the reaction of nitrone 193 with acetylene 194 gave a mixture of four stereoisomers which after column chromatography provided the cis-adduct 195 along with an inseparable mixture of the other three adducts 196 (Scheme 101). The absolute configuration at the C-4 carbon atom of 195 was established by electronic circular dichroism (ECD) spectroscopy[180].

**Scheme 101.** Kinugasa reaction with a chiral alkyne.

The aqueous Kinugasa reaction has been developed for bioorthogonal chemistry applications, with reaction rate acceleration made possible by the use of surfactant micelles. The reaction was optimized with acyclic nitrones using sodium lauryl sulfate.
The aqueous Kinugasa reaction has been developed for bioorthogonal chemistry applications, with reaction rate acceleration made possible by the use of surfactant micelles. The reaction was optimized with acyclic nitrones using sodium lauryl sulfate (SDS) as a surfactant and L-proline as a copper ligand (Scheme 102). The speed and efficiency of the reaction were found to be strongly influenced by the choice of alkyne. Biological lipids were found to be the most efficient surfactants. Alkynes with electron-withdrawing groups, such as propiolic esters and propiolamides, are the more reactive and give higher yields, while unactivated terminal and aryl alkynes led to lower yields of β-lactams. Membrane protein modification was possible using this process [181].

Scheme 102. Screening of alkynes in micelle-assisted Kinugasa reactions.

A chiral copper/prolinol-phosphine catalyst 198, optimized for steric and electronic properties, allowed the highly enantioselective coupling of nitrones and propargyl alcohol derivatives (Scheme 103). The resulting chiral 3-alkyldiene-β-lactams 197 were obtained in moderate to high yields and served as precursors of other β-lactams through the transformation of their α,β-unsaturated carbonyl system [182].

A new protocol for the Kinugasa reaction has been developed for the one-pot synthesis of N-aryl-β-lactams 200 using calcium carbide (CaC$_2$) as the acetylene source. CaC$_2$ was activated by tetra-N-butylammonium fluoride (TBFA) in the presence of CuCl/N-methylimidazole (NMI) (copper–fluoride catalysis). The facile synthesis and the utilization of inexpensive chemicals enable quick and efficient access to substantial quantities of β-lactams unsubstituted on the C-3 position (Scheme 104). The reaction failed to give N-alkyl β-lactams 200d [183].

The on-DNA combinatory synthesis of β-lactams through a copper-promoted Kinugasa reaction of nitrones 202 and DNA-conjugated alkynes 201 has been developed (Scheme 105). The alkynes were prepared by acylation of a double-stranded DNA oligonucleotide (DNA-NH$_2$) with alkynyl carboxylic acids or acylation of alkynyl amines with DNA-bound carboxylic acid (DNA-CO$_2$H), while nitrones are generated in situ by reaction of nitro compounds with various aldehydes using zinc powder as a reductant (Scheme 105). Aromatic nitro compounds gave the β-lactams with conversions ranging from moderate to excellent while aliphatic nitro compounds were not effective [184].
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**Scheme 102.** Screening of alkynes in micelle-assisted Kinugasa reactions. A chiral copper/prolinol-phosphine catalyst optimized for steric and electronic properties, allowed the highly enantioselective coupling of nitrones and propargyl alcohol derivatives (Scheme 103). The resulting chiral 3-alkylidene-β-lactams were obtained in moderate to high yields and served as precursors of other β-lactams through the transformation of their α,β-unsaturated carbonyl system [182].

**Scheme 103.** Synthesis of chiral 3-alkylidene-β-lactams 197.

**Scheme 104.** Kinugasa reaction from calcium carbide. A computational analysis of the Kinugasa reaction conducted with the presence of an unconventional catalyst, such as an oriented external electric field (OEEF), revealed that β-lactams can still be formed even without copper(I). However, no experimental data have been reported to support this hypothesis (Scheme 106) [185].
Fluorinated isoxazolidines 203 prepared by 1,3-DC of nitrones with hexafluoropropene (HFP) and 2H-pentafluoropropene (PFP) undergo ring contraction under reductive conditions to give 3-trifluoromethyl-β-lactams 204. The process involves cleavage of the N-O bond followed by HF elimination and intramolecular cyclization of the acyl fluoride intermediate (Scheme 107) [186].

Recently, this protocol was applied to the diastereoselective synthesis of spiro-fused β-lactams 206 starting from ketonitrone 206 and PFP (Scheme 108) [187].

A recent report describes the development of an original protocol for the preparation of β-lactams 208 that are not readily accessible by conventional methods. The approach
Involves the use of 1,3-dipolar cycloaddition of nitrones and methylenecyclopropane derivatives, followed by thermal rearrangement of the resulting 5-spirocyclopropaneisoxazolidines under acidic conditions (Scheme 109). The reaction also produces ethylene. Advantages of this strategy include the preservation of the relative and absolute configuration of the stereocenters established in the 1,3-dipolar cycloaddition and the possibility of obtaining highly strained spiro-fused β-lactams in good yields. For example, 3-spirocyclopropane-2-azetidinone 209 was synthesized via a one-pot three-component reaction from N-(4-methoxybenzyl)hydroxylamine, methyl glyoxalate, and bicyclopentylidene in a 78% overall yield. Experimental and computational studies of the mechanism for this peculiar fragmentative rearrangement are described [188].

Scheme 109. Synthesis and thermal fragmentative rearrangement of 5-spirocyclopropaneisoxazolidines.

Mo et al. synthesized spirofluorenyl-β-lactams 211 by a three-/four-step protocol involving a 1,3-DC of N-aryl fluorenone nitrones with 2-cyclopropylideneacetate, followed by reduction of the ester group, possible alkylation of the primary alcohol, and acid-catalyzed fragmentative rearrangement of the bis-spiro-fused isoxazolidines 210 (Scheme 110). Only the final products 211 were purified by chromatography. Accordingly, the yields given in Scheme 110 are calculated over three/four steps [189].

Scheme 110. Synthesis of spiro-fused 2-azetidinones 211. Yields are based on three or four steps (conditions B and C, respectively).
5. Miscellanea
5.1. Formal [1+1+2] Cycloadditions

A general strategy for the asymmetric formal [1+1+2] reaction affording chiral β-lactams 213 has been established. Azetidinones 213 were mainly synthesized as trans-isomers, with high yields and high enantio- and diastereoselectivities. In this approach, the key step is the catalytic generation of C(1)-ammonium enolates from benzyl bromides and CO, through the combination of Pd-catalyzed carbonylation (likely via acylpalladium intermediates converted by the base into ketenes) and chiral Lewis base organocatalysis using (R,S)-fused-BTM 212, an isothiourea catalyst, for the subsequent asymmetric cascade reactions with N-tosylimines (Scheme 111). The process was applied to the synthesis of the antiproliferative β-lactam 214 [190].

![Scheme 111. Synthesis of optically pure β-lactams 213.](image)

Efficient palladium-catalyzed carbonylation/cycloaddition processes of alkenes and imines in the presence of CO have been described. A wide variety of alkenes and imines have been converted into variously substituted monocyclic and spirocyclic β-lactams in high yields, with complete regioselectivities and moderate to excellent diastereoselectivities usually in favor of the cis-stereoisomer (determined by X-ray diffraction analyses on some derivatives). The success of this approach can be ascribed to the choice of a cooperative palladium/acid/base catalytic system (that depends on the type of alkene or diene employed) as well as the use of N-methyl-2-pyrrolidone (NMP) as solvent. The best results in terms of yields and stereoselectivities were observed with acrylonitrile leading to 3-cyanoazetidin-2-ones 215 in 37–95% yields (Scheme 112). From a mechanistic point of view, the reaction pathway involves acylpalladium intermediates, likely converted into ketenes by base [191].

![Scheme 112. Synthesis of 3-cyanoazetidin-2-ones 215.](image)
Polysubstituted spirocyclic β-lactams 217 have been prepared in 47–90% yields through an efficient protocol involving the Pd-catalyzed carbonylation of ortho-bromoarylimines 216. Likely, an alkylpalladium intermediate I is generated, via oxidative addition and subsequent CO and imine C=N bond insertion. Operating at 60 °C, a second CO insertion occurs leading to intermediate II, converted to the final compound by reaction with a second molecule of bromoarylimine, directly or via ketene formation (Scheme 113). The favored stereochemistry was determined on the basis of single-crystal X-ray diffraction studies on some products [192].

![Scheme 113. Synthesis of polysubstituted spirocyclic β-lactams 217.](image)

5.2. Formal [3+1] Cycloadditions

The efficient and highly diastereoselective assembly of 3,3′-spiro[β-lactam]-oxindoles 218 has been reported (Scheme 114). The process can be described as a [3+1] cycloaddition of oxindole-based azoxyallyl cations and sulfur ylides, generated from N-(benzyloxy)-3-chloro-2-oxoindoline-3-carboxamides and sulfonium salts, respectively, by treatment with cesium carbonate. The mechanistic hypothesis involves the nucleophilic attack of sulfur ylide on azoxyallyl cation affording a zwitterionic intermediate that cyclizes into the spiroazetidin-2-one with elimination of dimethyl sulfide [193]. The application of azoxyallyl cations in [3+m] cycloadditions has been reviewed by Singh et al. [194].

![Scheme 114. Synthesis of 3,3′-spiro(β-lactam)-oxindoles 218.](image)

Mono-β-lactams 219, synthesized via 3-MCR Ugi reactions from β-amino acids, were converted into bis-β-lactams 220 in moderate yields by NaH-triggered diiodomethane addition (Scheme 115). The process was also performed in one-pot conditions, starting from amino acid, aldehyde, and isocyanide, without isolation of the mono-β-lactam species. The structure of compounds 220 was confirmed by X-ray diffraction analysis on one derivative (R1 = c-Hex, R2 = 4-PhC6H4) [195].

![Scheme 115. Synthesis of bis-β-lactams 220.](image)
Scheme 115. Synthesis of bis-β-lactams 220.

3-Methylene-β-lactams 221 have shown interesting biological activities. When alkyny-lamides, obtained by aluminiation/amidation of terminal alkynes with isocyanates, were reacted with bromoacetophenone and potassium carbonate, in the presence of potassium iodide, compounds 221 were isolated in 72–81% yields (Scheme 116) [196].

Scheme 116. Synthesis of 3-methylene-β-lactams 221.

6. Conclusions

Monobactams are molecules that continue to be of great interest because of their applications as potential drugs and as versatile intermediates in organic synthesis. In the field of their synthesis via cycloaddition reactions, the Staudinger [2+2] cycloaddition is still the most widely used approach due to the easy accessibility of the reagents, its practical simplicity, the wide access to differently decorated β-lactams, and the good control of the diastereoselectivity. An emerging field of research is the use of photocatalysis in the Staudinger synthesis of 2-azetidinones from diazo compounds. The recent application of asymmetric catalysts in the Kinugasa reaction is gaining importance for the enantioselective synthesis of β-lactams.

Most of these approaches are based on stepwise mechanisms, which are still under investigation because, although experimental and theoretical research is constantly providing new data, many aspects of these intriguing reactions remain to be elucidated.

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