Chapter 4

Four-Membered Ring Systems

Benito Alcaide
Grupo de Lactamas y Heterociclos Bioactivos, Departamento de Química Orgánica I, Unidad Asociada al CSIC, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, Spain
alcaideb@quim.ucm.es

Pedro Almendros
Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006-Madrid, Spain
Palmendros@iqog.csic.es

4.1 INTRODUCTION

The search in the field of four-membered heterocycles, where a non-carbon atom is part of the ring, has been actively pursued in 2009 within Organic Chemistry, Inorganic Chemistry, Medicinal Chemistry, and Material Science. In particular, the synthesis and chemistry of oxygen- and nitrogen-containing heterocycles dominate the field in terms of the number of publications. It should be clearly stated that a comprehensive description of all the aspects of the vast research area of four-membered heterocyclic chemistry can not be fully covered in this book chapter. Instead, the present overview presents a personal selection of the topics which we believe are the more relevant.

4.2 AZETIDINES, AZETINES, AND RELATED SYSTEMS

The synthesis and reactivity of 3-haloazetidines, 3-sulfonyloxyazetidines, and 2-methylenezetidines have been reviewed in several contributions. A review on azetidines as new tools for the synthesis of higher nitrogen heterocycles has been published. A novel series of azetidinyl ketolides for the treatment of susceptible and multidrug resistant community-acquired respiratory tract infections has been discovered. Theoretical and experimental results have provided evidence that the 2-alkyl-2-carboxyazetidine scaffold is able to efficiently induce γ-turns when incorporated into short peptides, irrespective of their localization in the peptide chain. Chiral azetidino amino alcohol ligands bearing an additional stereogenic center were readily prepared and used as catalysts for the asymmetric addition of alkynylzinc to aromatic aldehydes. The phosphine-free Sonogashira coupling reaction of aryl halides catalysed by palladium(II) complexes of azetidine-derived polyamines under mild conditions has been accomplished. The enantioselective epoxidation of chalcone has been catalyzed by an azetidin-2-ylmethanol derivative. Preparation by mixing 3,3-dinitroazetidine (DNAZ) and 3-nitro-1,2,4-triazol-5-one (NTO) in ethanol solution, non-isothermal decomposition kinetics, heat capacity and adiabatic time-to-explosion of NTO center dot DNAZ have been described.
determinations on Cu(II) and Zn(II) complexes of tridentate and quadridentate azetidine derivatives show the ligands to be facultative for square-pyramidal and trigonal bipyramidal coordination geometries <09MI65>. DFT calculations have been performed in order to simulate the ring enlargement of azetidine into the corresponding 3-chloro pyrrolidine <09MI26>. The chemistry and pharmacology of nicotinic ligands based on 6-[5-(azetidin-2-ylmethoxy)pyridin-3-yl]hex-5-yn-1-ol for possible use in depression have been reported <09MI1279>.

The development of two synthetic routes to the azetidine-based drug CE-178,253-26, a CB1 antagonist for the treatment of obesity, has been documented <09T3292>. Base-induced cyclization of enantiopure (2-aminoalkyl)oxiranes allowed the stereospecific formation of 2-(hydroxymethyl)azetidines <09JOC7859>. Simple azetidines have been synthesized in good yields via cyclization of 3-(ammonio)propyl sulfates in water under the influence of microwave-assisted heating <09TL6590>. A new route to two 2-azetidinylglycine derivatives has been developed from Garner’s aldehyde <09TA1213>. A convenient and rapid synthesis of L-azetidine-2-carboxylic acid <09EJO2729> has been described starting from commercially available L-aspartic acid after double activation with the SES group with conservation of the chiral center <09AG(E)4381>. The first synthesis of 3-fluoroazetidine-3-carboxylic acid <09JOC2250>, a cyclic fluorinated β-amino acid derivative with high potential as building block in medicinal chemistry, has been disclosed. The synthesis of 3-aryl-3-azetidinyl acetic acid esters, including a novel spiroazetidine ring system, by rhodium(I)-catalysed conjugate addition of organoboron reagents has been reported <09TL3909>. Treatment of N-tosylaldimines with acetophenone at room temperature in the presence of BF₃·OEt₂ as a catalyst furnished N-tosyl β-amino ketones, which after subsequent reduction and cyclization afforded 2,4-disubstituted N-tosylazetidines <09JOC9505>. It has been reported that enantiomerically pure N-allyl azetidinium ions undergo a stereoselective [2,3]-sigmatropic shift to give azetidines with an α-quaternary center <09SL767>. Two pairs of cis and trans 1-benzyl- and 1-allyl-2-cyano-3-phenylazetidines have been synthesized and subjected to flash vacuum thermolysis <09T9322>. Highly efficient and enantioselective biotransformations of racemic azetidine-2-carbonitriles and their synthetic applications have been carried out <09JOC6077>. It has been
described that indoles undergo smooth alkylation with N-tosylazetidines in the presence of indium(III) bromide to produce the corresponding C3 substituted indole derivatives <09SL727>.

Beginning with a 1,3-dibromopropane derivative, readily available from inexpensive epibromohydrin, a scaleable synthesis of the novel 6-oxo-2-azaspiro[3.3]heptane ring system exemplified by compound 9 has been described <09OL3523>. The transformation of anti-Mannich adducts into azetidin-2-amides has been described <09AG(E)3353>. Azetidin-2-imines have been isolated as minor components of the copper-catalyzed multicomponent reaction of sulfonyl azides, terminal alkynes and α,β-unsaturated imines <09ASC1768>. A bicyclic azetidine bearing a CF3 substituent has been formed as major component during the iodocyclization reaction of a chiral allylmorpholinone <09OL209>. The synthesis of tricyclic 3-aminopyridines, including fused azetidine 10, through intramolecular Co(I)-catalyzed [2+2+2] cycloaddition between ynamides, nitriles, and alkynes has been accomplished <09CEJ2129>. The first synthesis of 2,6-diazabicyclo[3.2.0]heptanes 11, a fused azetidine with high potential to be used as a building block in medicinal chemistry, has been developed from trans-3-hydroxy-L-proline <09TL7280>. A polyhydroxylated 1-azabicyclo[5.2.0]nonane, a fused azetidine isomeric of the indolizidine castanospermine, has been obtained as minor component on route to the former alkaloid <09JOC8886>.

A strategy for copper-mediated S<sub>N</sub>2 type nucleophilic ring-opening followed by [4+2] cycloaddition reactions of 2-aryl-N-tosylazetidines 12 with nitriles to afford substituted tetrahydropyrimidines 13 has been reported <09TL1105>. It has been reported that the [6+2] cycloaddition reaction of 2-vinylazetidines with tosyl isocyanate proceeded smoothly in the absence of catalyst to yield 1,3-diazocinones 14 <09OL5438>. The ring expansion of enantiomerically pure 2-alkenyl azetidines has provided 1,2,3,6-azocines upon reaction with activated alkynes <09SL3182>. Simple N-substituted azetidines were heated with diazocarbonyl compounds in the presence of catalytic Cu(acac)<sub>2</sub> to furnish substituted pyrrolidines via [1,2]-shift <09JOC2832>. A synthesis of substituted nonracemic homomorpholines via an S<sub>N</sub>2-type ring opening of activated azetidines by suitable

Key: i) (a) NBS, Et<sub>3</sub>N·3HF; (b) NaCNBH<sub>3</sub>. ii) (a) H<sub>2</sub>, Pd/C, Boc<sub>2</sub>O; (b) CAN, MeCN–H<sub>2</sub>O, −10 °C. iii) 5 mol% RuCl<sub>3</sub>, NaIO<sub>4</sub>, MeCN–H<sub>2</sub>O. iv) (a) NaBH<sub>4</sub>, MeOH; (b) TsCl, KOH, THF.

Beginning with a 1,3-dibromopropane derivative, readily available from inexpensive epibromohydrin, a scaleable synthesis of the novel 6-oxo-2-azaspiro[3.3]heptane ring system exemplified by compound 9 has been described <09OL3523>. The transformation of anti-Mannich adducts into azetidin-2-amides has been described <09AG(E)3353>. Azetidin-2-imines have been isolated as minor components of the copper-catalyzed multicomponent reaction of sulfonyl azides, terminal alkynes and α,β-unsaturated imines <09ASC1768>. A bicyclic azetidine bearing a CF3 substituent has been formed as major component during the iodocyclization reaction of a chiral allylmorpholinone <09OL209>. The synthesis of tricyclic 3-aminopyridines, including fused azetidine 10, through intramolecular Co(I)-catalyzed [2+2+2] cycloaddition between ynamides, nitriles, and alkynes has been accomplished <09CEJ2129>. The first synthesis of 2,6-diazabicyclo[3.2.0]heptanes 11, a fused azetidine with high potential to be used as a building block in medicinal chemistry, has been developed from trans-3-hydroxy-L-proline <09TL7280>. A polyhydroxylated 1-azabicyclo[5.2.0]nonane, a fused azetidine isomeric of the indolizidine castanospermine, has been obtained as minor component on route to the former alkaloid <09JOC8886>.

A strategy for copper-mediated S<sub>N</sub>2 type nucleophilic ring-opening followed by [4+2] cycloaddition reactions of 2-aryl-N-tosylazetidines 12 with nitriles to afford substituted tetrahydropyrimidines 13 has been reported <09TL1105>. It has been reported that the [6+2] cycloaddition reaction of 2-vinylazetidines with tosyl isocyanate proceeded smoothly in the absence of catalyst to yield 1,3-diazocinones 14 <09OL5438>. The ring expansion of enantiomerically pure 2-alkenyl azetidines has provided 1,2,3,6-azocines upon reaction with activated alkynes <09SL3182>. Simple N-substituted azetidines were heated with diazocarbonyl compounds in the presence of catalytic Cu(acac)<sub>2</sub> to furnish substituted pyrrolidines via [1,2]-shift <09JOC2832>. A synthesis of substituted nonracemic homomorpholines via an S<sub>N</sub>2-type ring opening of activated azetidines by suitable
halogenated alcohols in the presence of Lewis acid followed by base-mediated intramolecular ring closure of the resulting haloalkoxy amine has been described <09JOC7013>. An approach for the preparation of oxazocines through a Ag(i)-catalyzed cascade reaction of azetidines with propargyl alcohols has been presented <09JOC8813>. Azetines have been proposed as intermediates of the gold-catalyzed reaction between 1,3-dienes and aldmines yielding ciclopent-2-enimines <09OL13>. N-Heterocyclic carbenes have been found to be efficient catalysts for the formal [2+2] cycloaddition of aryl(alkyl)ketenes and diazene di-carboxylates to give the correspondingaza-β-lactams 15 in good yields with up to 91% ee <09JOC7585>. It has been documented the catalytic asymmetric cycloaddition of ketenes with nitroso compounds leading to the synthesis of 1,2-oxazetidin-3-ones 16, which in addition to serving as potentially bioactive target molecules, can be transformed into other important classes of compounds such as α-hydroxycarboxylic acid derivatives <09AG(E)2391>. The rearrangement of β-chloro N-oxides to hydroxylamines has been described to be stereospecific in accord with the presence of a cyclic oxazetidinium intermediate, which is opened by nucleophiles <09JOC2254>.

\[
\begin{align*}
\text{Ar} & \quad \overset{i}{\text{RCN, Cu(OTf)2, 80 °C.}} \\
\text{N} & \quad \text{Ts} \\
\text{12} & \quad \text{13 (55–72%)} \\
\text{Bn} & \quad \text{O} \\
\text{N} & \quad \text{Ts} \\
\text{14 (52–89%)} \\
\text{Ar} & \quad \text{R} \\
\text{N} & \quad \text{CO2R1} \\
\text{15} \\
\text{Ar}^1 & \quad \text{R} \\
\text{N} & \quad \text{CO2R1} \\
\text{16}
\end{align*}
\]

Key: i) RCN, Cu(OTf)₂, 80 °C.

### 4.3 MONOCYCLIC 2-AZETIDINONES (β-LACTAMS)

A compendium on the generation of the β-lactam ring covering different methods has been reported <09CSY325>. The stereoselectivity in the synthesis of 2-azetidinones from ketenes and imines via the Staudinger reaction has been reviewed <09ARK21>. The preparation of β-lactams by catalytic asymmetric reactions of ketenes and ketene enolates has been reviewed <09T6771>. An overview presenting recent progresses on the metal-catalyzed one-step synthesis of heterocycles, including the β-lactam nucleus, has been published <09CEJ302>. A statin therapy in combination with ezetimibe 17 in patients with a high risk of atherosclerotic disease has been successfully used <09MI2180; 09MI798>. The effects of ezetimibe add-on therapy for high-risk patients with dyslipidemia have been documented <09MI41>. The new biocatalyst burkholderia cenocepacia has been proven efficient for the bioreduction of ezetimibe <09MI1369>. A simple high-performance liquid chromatography method has been developed and validated for the simultaneous determination of ezetimibe and simvastatin from their combination drug products <09MI527>. In vitro inhibition assays against human histone deacetylase (HDAC) isoforms have shown an interesting isoselectivity of β-lactams towards HDAC6 and HDAC8 <09MI1991>. 3-Substituted-3-hydroxy-β-lactams 18, with two new adjacent stereogenic centers, have been prepared in a single step by a rhodium-catalyzed, three-component reaction between azetidine-2,3-diones, ethyl diazoacetate and alcohols <09JOC8421>. Pd(0)/InI-mediated allylic addition to 4-acetoxy-2-azetidinone has provided derivatized cyclopentenes 19 in high regio- and diastereoselectivity <09OL1293; 09JOC5730>. A series of chiral trans-β-lactams has been obtained via Staudinger cycloaddition with low diastereoselectivity (up to 54% de) induced by a chiral amine component of the imine <09T10339>. A stereoselective synthesis of novel
3-methylthio-β-lactams and their Lewis acid mediated functionalization has been described <09T10060>. The cycloaddition reactions of 1,3-diazabuta-1,3-dienes with conjugated alkylnyl ketenes have provided interesting azetidinones bearing an alkylnyl moiety <09T4664>. The halodecarboxylation reaction of 4-alkylidene-β-lactams has been described <09EJO4541>.

Key: i) Rh\(_2\)(OAc)\(_4\), R\(^3\)OH, CH\(_2\)Cl\(_2\), ∆.

A convenient method for the synthesis of azetidin-2-ones 20 using electrochemical oxidation has been exploited <09T9742>. The one-pot synthesis of N-tert-butyl-trans-α-ethoxycarbonyl-β-phenyl-β-lactam by the octacarbonyldicobalt-catalyzed carbonylation of ethyl diazoacetate in the presence of N-tert-butylbenzaldehyde has been described <09EJO1994>. Mannich adducts have been transformed into trans-azetidin-2-ones and α-fluoro-β-lactams <09AG(E)1838; 09AG(E)7604>. The copper-catalyzed synthesis of β-lactams by intramolecular C–H insertion of diazocompounds has been achieved <09OBC4777>. Asymmetric imidazolium-dithiocarboxylates have been found to be highly selective catalysts for the Satudinger reaction <09CC1040>. 3,4-Diaryl β-lactams 21 have been prepared with high stereoselectivity by a palladium-catalyzed [2+2] carbonative cycloaddition of benzyl halides with heteroarylidene amines <09TA368>. It has been reported that α-oxoamides are stable axially chiral atropisomers, undergoing enantiospecific photochemical γ-hydrogen abstraction to yield β-lactams <09JA11314>. A β-lactam derivative has been synthesized as application of the catalytic asymmetric alkylation of α-cyanocarboxylates and acetoacetates with an alkyl halide under phase-transfer conditions <09TA2530>. α-Alkylidene-β-lactams 22 have been prepared in good yields by olefin cross metathesis of electron poor α-methylene-β-lactams with 1,1-disubstituted alkenes <09TL1020>. The [2+2]-cycloaddition reaction of glycosidic enol ethers has provided glycosylated β-lactams with only trans-stereoselectivity <09TA1646>. Ultrafast time-resolved infrared spectroscopy study of the photochemistry of N,N-diethyldiazoacetamide has shown that in chloroform, β-lactam is formed immediately after the laser pulse <09JA9646>.

Key: i) −2e, 4F/mol, NaI (0.5 equiv), MeCN. ii) CO (400 psi), Pd(OAc)\(_2\), Et\(_3\)N, PPh\(_3\), THF.

The copper-catalyzed skeletal rearrangement of O-propargyl arylaldoximes has produced 4-arylidene-2-azetidinones 23 in good to excellent yields <09JA2804>. Access to poly-β-peptides with functionalized side chains and end groups via controlled ring-opening polymerization of β-lactams has been described <09JA1589>. A series of mono- and bimetallic Pd and Pt macrocyclic β-lactam molecules has been synthesized <09CEJ6940>. A study using a combination of experiments and DFT calculations has been conducted to understand the torquoselectivity and the electronic effects of the Staudinger reaction <09JA1542>. A stereoselective synthesis of (1′S,3R,4R)-4-acetoxy-3-((2′-fluoro-1′-)
trimethylsilyloxyethyl)-2-azetidinone as a new fluorine-containing intermediate towards β-lactams, has been described <09TL2676>. A number of 2-azetidiones have been synthesized in good yields by a novel reaction between Schiff bases, substituted acetic acids and alkoxyethylene-\(N,N\)-dimethyliminium salts <09TL1568>. The diastereo- and enantioselective synthesis of functionalized β-lactams from oxiranecarboxaldehydes and lithium ester enolates has been carried out <09EJO565>. The stereodivergent synthesis of both cis- and trans-β-lactams using thermal rearrangement of aminocyclobutenones has been documented <09OL3266>. The enantioselective Kinugasa reaction of nitrones with terminal alkynes in the presence of 20 mol % of IndaBox–Cu(OTf)\(_2\) and di-sec-butylamine (1.5 equiv) produced β-lactams with high level of enantiomeric excess <09TL4969>. Micelle-promoted, copper-catalyzed multicomponent Kinugasa reactions have been studied in aqueous media <09TL1893>. The preparation of β-lactams by Mannich-type addition of ethyl(trimethylsilyl)acetate to \(N\)-(2-hydroxyphenyl)aldimine sodium salts has been achieved <09SL2437>. It has been shown that sequence-random nylon-3 copolymers containing β-lactam nucleus can mimic favorable properties of host-defense peptides <09JA16779>, and it has also been documented structure–activity relationships in this polymer family <09JA9735>.

\[
\begin{align*}
&\text{Ar}^1\text{C} &\text{O} &\text{N} &\text{Ar}^2 \\
&\text{Ar}^1\text{C} &\text{O} &\text{N} &\text{Ar}^2
\end{align*}
\]

Key: i) 10 mol % CuBr, toluene, 100 °C. ii) \(R^3\text{CH}_2\text{COOH}, \text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2\).

The diastereoselective synthesis of trans-β-lactams using a phosphonium fluoride multifunctional catalyst has been achieved <09SL1651>. Cyclization of diazoacetamides catalyzed by \(N\)-heterocyclic carbene dirhodium(II) complexes has yielded β- and γ-lactams <09S3519>. It has been demonstrated that antiaromaticity is playing the prime role in suppressing the β-stabilizing effect of silicon in 3-silylated monocyclic β-lactams <09OL5722>. Staudinger ketene-imine cycloaddition reaction has been applied to bis-o-allyloxyarylidenamines affording the corresponding bisallyloxyazetidinones as the cis-cis diastereomers, exclusively obtained as a mixture of cis-syn-cis and cis-anti-cis <09JOC4305>. Mechanistic details of the Mg\(^{2+}\) ion-activated enantioselective reduction of methyl benzoyleformate have been investigated at a B3LYP/6-31G* theory level, using peptide NADH models rigidified with a β-lactam ring <09JOC6691>. The diastereoselective synthesis of bicyclic γ-lactams by ring expansion of monocyclic chloro-β-lactams via \(N\)-acyliminium intermediates has been accomplished <09JOC1644>. Aminophosphonic acids, potential inhibitors of penicillin-binding proteins, has been obtained starting from 4-acetoxyazetidinone <09EJO85>. An enantioselective formal synthesis of (S)-dapoxetine, a selective serotonin re-uptake inhibitor type of drug against depression and a potential cure of premature ejaculation in men, has been achieved from a substituted 3-hydroxy β-lactam in 17% overall yield <09T2605>. The synthesis of (E)-arylimino-acetonitriles has been described via thermal fragmentation of 1-aryl-4-cyano-β-lactams <09T10581>. The mechanism of the \(N\)-heterocyclic carbene-catalyzed ring-expansion of 4-formyl-β-lactams to succinimides has been studied using DFT methods at the B3LYP/6-31G** level <09T3432>. A highly enantioselective synthesis of oseltamivir has been achieved starting from \(L\)-methionine, in which Staudinger reaction to build a β-lactam ring is utilized for the alignment of three contiguous chiral centers of oseltamivir <09SL787>. The enantioselective total
synthesis of \((-\)\)-himandrine has been benefited from the hydrolysis of a \(N\)-vinyl \(\beta\)-lactam \(<09JA9648\>). A first generation process for the synthesis of sitagliptin, a dipeptidyl peptidase inhibitor for the treatment of type 2 diabetes mellitus, has been documented \(<09JA8798\>). \(\beta\)-Lactam-based preparation of novel 2-alkoxy-3-amino-3-arylpropan-1-ols and 5-alkoxy-4-aryl-1,3-oxazinanes with antimalarial activity has been published \(<09JMC4058\>). The preparation of fucose\(\rightarrow\)saccharosamine disaccharide glycals using \(\beta\)-lactam chemistry has been developed \(<09OL4850\>). Isoxazoline-fused cispentacins have been prepared by the 1,3-dipolar cycloaddition of nitrile oxides to \(\beta\)-amino esters derived from \(\beta\)-lactams \(<09TL2605\>). An enantioselective synthesis of (2\(S\),3\(R\),4\(R\))-D-xylo-phytosphingosine has been achieved from \(\beta\)-lactam derived from D-mannitol triacetonide \(<09TL3296\>). The efficient synthesis of 3,4- and 4,5-dihydroxy-2-amino-cyclohexanecarboxylic acid enantiomers has been reported \(<09TA2220\>). Fused \([4.2.0]\)aminocyclobutane-containing \(\delta\)-lactams have been accessed from \(N\)-vinyl-\(\beta\)-lactams \(<09OL1281\>). The enzymatic synthesis of carnosine derivatives from a \(\beta\)-lactam and a protected \(\alpha\)-amino acid has been performed \(<09TA1641\>.

\[
\begin{align*}
\text{RO} & \xrightarrow{\text{i}) AgBF}_4, \text{pyridine, toluene.} \text{Cl} \\
\text{RO} & \xrightarrow{\text{H}} \text{XH} \\
\text{N} & \text{O} \\
\text{25 (38–57\%)} \\
\end{align*}
\]

Key: i) AgBF\(_4\), pyridine, toluene.

### 4.4 FUSED AND SPIROCYCLIC \(\beta\)-LACTAMS

The principal characteristics of carbapenems and their clinical implications have been reviewed \(<09CME564\>). A review article on recent advances in the chemistry and biology of naturally occurring antibiotics has appeared \(<09AG(E)660\>). A fully automated method for the detection of \(\beta\)-lactam antibiotics, including six penicillins (amoxicillin, ampicillin, cloxacillin, dicloxacillin, oxacillin, and penicillin G) and four cephalosporins (cefaclor, cefotaxime, cefoperazone, and cefalexin) in bovine milk samples based on online solid-phase extraction-liquid chromatography/electrospray tandem mass spectrometry has been developed \(<09ANC4285\>). It has been discovered that 30 \(\beta\)-lactams derived from (3\(R\),4\(R\))-3\(-[\text{[(R)}-1\'(\text{t}-\text{butyldimethylsilyloxy})-ethyl\]-4-acetoxy-2-azetidinone are selective inhibitors of human fatty acid amidase hydroxylase versus human monoacylglycerol lipase \(<09JMC7054\>). The reactions between the only \(\beta\)-lactamase inhibitors in clinical use, tazobactam, sulbactam, and clavulanic acid, with a class A \(\beta\)-lactamase have been examined in single crystals using a Raman microscope \(<09JA2338\>). The structural basis of the inhibition of class A \(\beta\)-lactamases and penicillin-binding proteins by 6-\(\beta\)-iodopenicillanate have been published \(<09JA15262\>). Structures and labelling mechanisms of the fluorescent probes on \(\beta\)-lactam cleavage by class A \(\beta\)-lactamases have been described \(<09JA5016\>). The structural characterization of a true dizinc metallo-\(\beta\)-lactamase has been performed \(<09JA11642\>). 6-Aminopenicillanic acid \(28\) and two of its derivatives have been evaluated as catalysts for use in direct cross-aldol reactions for the first time \(<09EJO3155\>). The synthesis of 2-azetidinones incorporating carbenechromium(0) moieties and their use in the preparation of penicillin- and cephalosporin-containing peptides has been achieved \(<09EJO2998\). An efficient biocatalyst for the esterification of 7-aminocephalosphoranic acid has been designed \(<09EJO1384\>. The synthesis of regio- and stereoselectively deuterium-labelled derivatives of \(L\)-glutamate semialdehyde for studies on carbapenem biosynthesis has been accomplished \(<09OBC2770\). An enantiocontrolled entry to the spiro-\(\beta\)-lactam core of chartellines has
been developed by oxidative nitrogen atom transfer methodology based on chiral Rh-nitrenoid species \(<09CC6265>\). The synthesis of spirocyclic \(\beta\)-lactams 29 by palladium-catalyzed domino cycloisomerization/cross-coupling of \(\alpha\)-allenols and Baylis–Hillman acetates has been performed \(<09CEJ3344>\). Spirocyclic \(\beta\)-lactams have been synthesized under mild conditions by using (chloromethylene)dimethylammonium chloride as a versatile acid activator reagent for the direct \([2+2]\) ketene–imine cycloaddition \(<09T2927>\).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{CO}_2\text{H} \\
\text{CO}_2\text{PMB} & \quad \text{CO}_2\text{Me} \\
\text{PhCH}_2\text{CONH} & \quad \text{NHAc} \\
\text{H}_3\text{C}_7 & \quad \text{PhCH}_2\text{CONH} \\
\text{Ar} & \quad \text{Ar} \\
\text{S} & \quad \text{S} \\
\text{SAr} & \quad \text{SAr}
\end{align*}
\]

Key: i) 5 mol % Pd(OAc)_2, K_2CO_3, TDMPP, DMSO, RT.

A novel Pd(II)-catalyzed C–H lactamization reaction, including the formation of spiro-\(\beta\)-lactams has been achieved \(<08JA14058>\). New oxidative dearomatization procedures leading to spiro \(\beta\)-lactams have been developed \(<09OL2820>\). Regiospecific synthesis of 6α-(1R-hydroxyoctyl)penicillanic acid 30 and 6β-(1R-hydroxyoctyl)penicillanic acid as mechanistic probes of class D \(\beta\)-lactamases have been achieved \(<09OL2515>\). Efficient synthesis of epithienamycin A in its readily deprotected form 31 has been reported where three contiguous stereocenters are established in a single catalytic asymmetric azetidinone-forming reaction \(<09OL3606>\). An entry to 6-ruthenocenyl-substituted penicillins has been accomplished \(<09CEJ593>\). The electrolysis of 3-arylthiomethyl-\(\Delta^3\)-cephems 32 possessing various substituents on the arylthio moiety undergoing chemoselective and product-selective electrooxidation to give several different products has been carried out \(<09S3449>\). By using a ring-closing metathesis strategy, non-traditional bicyclic \(\beta\)-lactams featuring high conformational adaptability have been prepared with the aim of developing novel inhibitors of penicillin-binding proteins \(<09EJO1757>\). A non traditional approach for designing reactive \(\beta\)-lactams and possibly new anti-bacterial agents has been explored, based on large, flexible 1,3-bridged 2-azetidinones featuring a “planar amide” instead of the traditional “twisted amide” found in the penicillin family \(<09EJM2071>\).

A systematic investigation of the metal (Au, Ag, Pt, Pd, and La)-catalyzed heterocyclization reaction of 2-azetidinone-tethered \(\gamma\)-allenols establishing a regiocontrolled versatile route to a variety of enantiopure fused tetrahydrofuran-, dihydropyran-, and tetrahydroxepine-\(\beta\)-lactams 33–36 has been reported \(<09CEJ1901>\). Besides, the mechanisms of these metal-catalyzed cycloetherification reactions have been theoretically investigated \(<09CEJ1909>\). It has been described the stereoselective insertion of allyl-seleno moieties at the C4 position of azetidinones and further ring-closing metathesis to afford novel selenium-containing bicyclic \(\beta\)-lactams 37 \(<09OBC2591>\). A short, enantioselective Lewis acid catalyzed synthesis of 3,4-benzo-5-oxacephams has been reported \(<09EJO338>\). The asymmetric Kinugasa reaction of cyclic nitrones and nonracemic acetylenes has been
performed to build the carbapenam skeleton <09JOC3094>. A cinchona alkaloid has catalyzed the enantioselective synthesis of 4-aryloxyazetidinones and 3,4-benzo-5-oxacephams <09JOC5687>. An entry to 4-aryl-azetidinones via alkylation of nucleophilic arenes using four-membered acyliminium cations has been accomplished <09T4440>. N-heterocyclic carbene-catalyzed reactions of α,β-unsaturated aldehydes and a variety of electrophiles allow the facile preparation of a diverse array of annulation products including bicyclic β-lactams <09JA8714>. Chiral induction during the photoelectrocyclization of pyridones included within an achiral hydrophobic capsule to yield bicyclic β-lactams has been established <09T7277>. Enantiopure 1,3-dioxolanyl-substituted bicyclic β-lactams has been established <09CEJ11632>. The diastereocontrolled Lewis acid-catalyzed preparation of enantiopure carbacephem derivatives has been developed starting from 2-azetidinone-tethered enals <09CAJ1604>. Chemo- and regioselectivity control in the palladium-catalyzed O–C cyclization of γ,δ-allendiols providing access to bicyclic β-lactams has been achieved <09CEJ2496>. An efficient Cu-promoted preparation of bis(β-lactam) fused cyclobutenes in a totally controlled fashion using alkyne homocoupling as well as double [2+2] cyclization in a cascade sequence has been accomplished <09CEJ9987>.

4.5 OXETANES, DIOXETANES, DIOXETANONES AND 2-OXETANONES (β-LACTONES)

A review aiming to provide an overview of the synthesis and reactivity of small strained spiroheterocycles, including spirooxetanes, and to illustrate their applications in synthetic endeavors has appeared <09T5879>. Hydrolytic kinetic resolution as an emerging tool in the synthesis of bioactive molecules such as tetrahydrolipstatin has been reviewed <09SL1367>. A review on total syntheses of sesquiterpenes from *Illicium* species, including the highly oxygenated cage architecture of anisatin which contains a spiro β-lactone has been published <09T6271>. The reactivity of oxazolones and their application in the synthesis of natural products, including β-lactones, have been reviewed <09S2825>. An overview on future perspectives in the total synthesis of natural products such as paclitaxel has appeared <09JOC951>. It has been reported that an N-aryltransferase has broad aroyl CoA specificity *in vitro* with analogues of N-dearoylpaclitaxel <09JA5994>. The synthesis of 4-deacetyl-1-dimethylyl-7-triethylsilylbaccatin III has been carried out <09JOC2186>. A simple route to the paclitaxel side chain and its analogues based on the (R)-proline-catalyzed addition of aldehydes to N-(phenylmethylene)benzamides, followed by oxidation of the resulting protected α-hydroxy-β-benzoylaminodehydes has been presented <09CEJ4044>. A water-soluble derivative of the chemotherapeutic agent taxol has been synthesized with

![Chemical structures](image)
bioconjugation functionality and attached to capsids of the bacteriophage <09AG(E)9493>. An overview on the basic concepts of rotational-echo double nuclear magnetic resonance and its application to the structural study of natural products such as taxol in biological matrices has been reported <09CC5664>. The biomimetic transannular oxa-conjugate addition approach to the 2,6-disubstituted dihydropyran of laulimalide has yielded an unprecedented transannular oxetane 39 <09JOC1454>. 3-(Silyloxy)oxetanes and 3-aminooxetanes have been obtained through the Paternò-Büchi reactions of aldehydes with silyl enol ethers and enamides <09S4268>. \(\beta\)-Naphthoquinone methides have been generated by photolysis of 3-ethoxymethyl- and 1-(ethoxymethyl)-2-naphthols, being 2H-naphthoxetes 40 and 41 their precursors <09JA11892>.

![Chemical structures](image)

Using quantum-chemical calculations it was found that the main DNA lesions induced by solar UV radiation, in addition to be repaired via a mechanism involving an oxetane intermediate, a non-oxetane pathway is also probable <09JA17793>. Introduction of oxetan-3-yl groups into heteroaromatic systems that have found important uses in the drug discovery industry, such as the preparation of heteroaryloxetanes 42 derived from the marketed inhibitor gefitinib, has been achieved by using a radical addition method (Minisci reaction) <09JOC6354>. Enantioenriched tetrahydrofurans have been accessed by enantioselective intramolecular openings of oxetanes 43 catalyzed by (salen)Co(III) complexes <09JA2786>. 2,2-Disubstituted oxetanes have been synthesized by using a one-pot double methylene transfer catalyzed by a chiral heterobimetallic La/Li complex <09AG(E)1677>. A fused oxetane has been proposed as intermediate for the rearrangement of a propargyl aziridine into a pyrrole <09OL4002>. Polycyclic aldehydes have been prepared by protolytic oxametathesis of fused strained oxetane systems <09OL3886>. The wavelength-dependent diastereodifferentiating Paternò–Büchi reaction of chiral cyanobenzoates with diphenylethene has provided chiral oxetanes <09JA17076>. A library of 1,4-disubstituted 1,2,3-triazoles including oxetan-3-yl substituents has been synthesized using a copper flow reactor <09ASC849>. A solvent-controlled oxidative cyclization for the divergent synthesis of highly functionalized oxetanes has been published <09OL3156>. The strong substituent effect of alkynyl groups on the highly stereoselective olefination of alkynyl ketones with ynolates through oxetene intermediates has been described <09JA2092>. The effects of C–S and C–Se bonds on torquoselectivity for the stereoselective olefination of \(\alpha\)-thio- and \(\alpha\)-selenoketones with ynolates through oxetene intermediates have been reported <09T8832>. Decomposition pathways for the thermolysis of 1,2-dioxetanediene 44 have been postulated <09JA2770>. The unimolecular chemiluminescent decomposition of unsubstituted dioxetanone 45 has been studied at the complete active space self-consistent field level of theory combined with the multistate second-order multiconfigurational perturbation theory energy correction <09JA6181>. The proposed mechanism for the gold-catalyzed oxidative cleavage of aryl-substituted alkynyl ethers using molecular oxygen has involved a dioxetane intermediate <09CC4046>. The chemiluminescence of bicyclic
dioxetanes bearing a hydroxyaryl group has enhanced when these dioxetanes were decomposed with alkaline metal ions <09TL2340>.

Enantiomerically pure cyclopropylboronic esters have been utilized in the synthesis of a cyclopropylamine, a key building block for the total synthesis of the proteasome inhibitor belactosin A 46 <09EJO5998>. A three-dimensional structure-activity relationship study of belactosin A and its stereo- and regioisomers has been documented <09OBC1868>. The first asymmetric total synthesis of the β-lactone-containing natural product vittatalactone has featured the divergent synthesis of two diastereomers to assign the absolute configuration of the natural product <09OL4767>. The utility of the asymmetric synthesis of anti-aldol segments via a nonaldol route has been demonstrated by the synthesis of the lipase inhibitor (−)-tetrahydrolipstatin 47 <09JOC4508>. An asymmetric synthesis of (−)-tetrahydrolipstatin from a β-hydroxy-δ-oxo sulfoxide has been described <09SL1285>. A palladium catalyzed Wacker-type reaction to convert an alkene to a ketone, highly diastereoselective reduction of a β-hydroxy ketone, selective oxidation of a diol, and modular synthesis have been the key features of the successful approach toward the asymmetric synthesis of (−)-tetrahydrolipstatin <09T10083>. The formal synthesis of salinosporamide A 48, a potent 20S proteasome inhibitor and anti-cancer therapeutic, has been achieved via N-heterocyclic carbene catalyzed intramolecular lactonization from enals <09T4957>. A new series of coenzyme A-tethered polyketide synthase extender units have been discovered in relation to the biosynthesis of the anticancer agents of the salinosporamide A family from the marine bacterium Salinispora tropica <09JA10376>. The synthesis of a propellane derivative of salinosporamide A having increased stability under physiological-like conditions, by taking advantage of a substrate-controlled stereoselective Ugi 4-center 3-component reaction to construct the required syn-bicyclic pyrrolotactic acid framework, has been reported <09T5899>. A formal synthesis of salinosporamide A starting from D-glucose has been accomplished <09S2983>.

The highly diastereo- and enantioselective synthesis of β-trifluoromethyl-β-lactones 50 bearing two contiguous stereocenters has been realized by chiral N-heterocyclic carbene-catalyzed formal cycloaddition reaction of alkyl(aryl)ketenes and trifluoromethyl ketones <09OL4029>. A general method for the organocatalytic dimerization of ketoketenes by tri-n-butylphosphine to yield ketoketene dimmers 51 has been described <09JOC1777>. KHMDS
and KOtBu have been applied as highly active Lewis base catalysts for the formal [2+2] cycloaddition of ketenes with aldehydes to afford β-lactones <09OBC4009>. A tethered Lewis acid-Lewis base bifunctional catalyst has promoted the asymmetric [2+2] cycloaddition reaction between ketene and aldehydes rapidly <09SL1675>. Chiral triazolium-derived N-heterocyclic carbene catalysts have promoted the direct annulation of α,β-unsaturated aldehydes and achiral α-hydroxy enones to afford cyclopentane-fused β-lactones with high enantioselectivity <09OL677>. The asymmetric synthesis, structure, and reactivity of unexpectedly stable spiroepoxy-β-lactones including facile conversion to tetrionic acids have been reported <09JOc4772>. The desymmetrization of 1,3-diketones using N-heterocyclic carbenes has resulted in the formation of enantioenriched cyclopentenes through the expulsion of carbon dioxide in a bicyclic β-lactone intermediate <09S687>. The one-pot synthesis of 2,3-dihydro-1,5-benzodiazepin-2-ones 52 bearing a phosphono-succinate substituent has been described from diketene <09T2684>. α-Stabilized phosphorus ylides have been obtained from the reaction between primary amines, diketene, and dialkyl acetylenedicarboxylate in the presence of triphenylphosphine <09S464>. The solid-phase generation of acetylketene through sequential treatment of ketene dimer with hydrogen chloride and sodium carbonate has been reported <09TL1295>. The ring-opening polymerization of a mixture of enantiomerically pure but different β-lactone monomers using an yttrium complex as initiator has proceeded readily at room temperature to give the corresponding highly alternating polyester <09JA16042>. The enantioselective syntheses of the glucosidase inhibitors schulzeines B and C have been achieved by employing a Pictet–Spengler reaction of a β-lactone-derived, masked bishomoserine aldehyde <09OL1143>. Aromatic aldehydes and ketones have reacted with ketene under Lewis acid catalysis to produce β-lactones, which in situ react with another molecule of ketene to produce 3-arylglutaric anhydrides <09TL2334>. The opening of a β-lactone has been used during the stereocontrolled synthesis of iriomoteolide, a smaller but equally cytotoxic congener of amphidinolides <09AG(E)8780>. The synthesis of highly substituted pyrazolo[3,4-b]pyridine-5-carboxamide and 1,4-dihydro-1,8-naphthyridine-3-carboxamide derivatives starting from diketene has been developed via two different one-pot four-component reactions <09TL2911; 09TL6355>. The reaction of ketoketene dimer β-lactones with organolithium reagents has afforded 1,3-diketones <09TL6919>.

![Chemical Structures](image)

Key: i) 12 mol% NHC derived from L-pyroglutamic acid, 10 mol% Cs2CO3, toluene, –40 °C. ii) CH2Cl2, RT.

4.6 THIETANES, β-SULTAMS, AND RELATED SYSTEMS

The intramolecular S-vinylation of thiols with bromides has been implemented without the help of an additional ligand for the preparation of thietaenes 53 <09JOC459>. The synthesis of the highly constrained adenosine derivative 54 featuring at spirothietane at C-4′, which may be considered as a rigid analogue of methylthioadenosine, has been described <09TL463>. A full account of the intramolecular vinlylic substitution reaction of bromoalkenes having an acetylthio moiety, which give 2-alkyldenethietane derivatives 55
has been presented <09T6888>. A synthetic route to functionalized thietanes has been developed by employing diastereoselective three-component coupling reaction of O,O-diethyl hydrogen phosphorodithioate, aromatic aldehydes, and activated olefins <09SL1055>. A computational study at the MP2(Full)/6-311++G(d,p)//MP2(Full)/6-31+G(d) level of the ammonolysis of halogen substituted thietanes has been performed in the gas phase and in acetonitrile <09OBC4496>.

$$\begin{align*}
\text{R}^2\text{S} &\quad \text{R}^1 \quad \text{SH} &\quad \text{(85–99\%)} \\
\text{Br} &\quad \text{R}^1 \quad \text{S} &\quad \text{O} \\
\text{i} &\quad 10 \text{ mol\% CuI, K}_3\text{PO}_4\cdot3\text{H}_2\text{O, dioxane, 90 °C.} &\quad \text{ii) K}_2\text{CO}_3, \text{MeOH, N,N-dimethylimidazolidinone, 120 °C.}
\end{align*}$$

Key: i) 10 mol\% CuI, K$_3$PO$_4$·3H$_2$O, dioxane, 90 °C. ii) K$_2$CO$_3$, MeOH, N,N-dimethylimidazolidinone, 120 °C.

β-Thiolactones 56 monosubstituted in the 3-position by alkyl and carbamoyl groups have undergone nucleophilic ring opening by arenethiolates through a process involving an S$_\text{n}$2-type attack at the 4-position leading to 3-arylthiopropionates substituted in the 2-position <09JOC3389>. 1-Thietane 1,1-dioxides 57 have been prepared by oxidation of 2-alkylidenethietanes 55 with m-chloroperbenzoic acid <09T6888>, β-Sultams 58, biologically interesting sulfonyl analogues of β-lactams, have been prepared by an organocatalytic asymmetric formal [2+2]-cycloaddition approach of non-nucleophilic imines with alkyl sulfonyl chlorides <09CEJ8204>. 1,3-Disubstituted thioureas have reacted with bis(trichloromethyl) carbonate in the presence of a base such as NaHCO$_3$ to form 4-(arylmino)-1,3-thiazetidin-2-ones 59 almost quantitatively <09SL607>.

**4.7 SILICON AND PHOSPHORUS HETEROCYCLES. MISCELLANEOUS**

The development, mechanistic investigations, and applications in natural product total synthesis of palladium-catalyzed cross-coupling reactions of silicon derivatives, including siletanes have been discussed <09JOC2915>. The synthesis, reactivity, and indirect oxidative cleavage of para-siletanylbenzyl ethers 60 have been reported <09JOC1876>. The synthesis, structure, photoluminescence and photoreactivity of 2,3-diphenyl-4-neopentyl-1-silacyclobut-2-enes have been studied <09CEJ8625>. A remarkable base-stabilized bis(silylene) 61 with a silicon(I)-silicon(I) bond has been prepared by the reduction of amidinatotrichlorosilane with potassium graphite <09AG(E)8536>. A bridging square-planar cyclo-P$_4$ unit has been formed by reduction of a zirconium diamidodiphosphine macrocycle in the presence of white phosphorus <09AG(E)115>. Triphosphacyclobutadiene intermediates have been engaged in [2+4]-cycloaddition reactions with an organic diene and a phosphaalkyne to yield
tetraphosphabenzences <09AG(E)934>. A new catalytic system for the C–N bond formation between aryl bromides/chlorides with amines, using Pd$_2$dba$_3$ and an inexpensive cyclodiphosphazane ligand 62 has been presented <09TL6004>. Chlorination of 1,2,3,4-tetracyclohexyl-cyclo-tetraphosphine by PhICl$_2$ or PCl$_3$ in the presence of Me$_2$SiOTf or GaCl$_3$ has provided a stepwise approach to salts of the first cyclo-phosphino-chlorophosphonium cations [Cy$_4$P$_4$Cl]$^+$ 63 and [Cy$_4$P$_4$Cl$_2$]$^{2+}$ 64 <09JA17943>.

An efficient two-step method for the preparation of a series of novel 2,5-disubstituted 1,3,4-selenadiazoles by selenating with 2,4-bis(phenyl)-1,3-diselenadiphosphetane-2,4-diselenide (Woollins' reagent) 65 has been reported <09EJO1612>. Woollins' reagent 65 has reacted with cyanamides in refluxing toluene to afford a series of novel selenazadiphospholaminediselenides <09T6074>. 2-Imidazolines and imidazoles have been accessed by an aza-Wittig sequence involving the azaoxaphosphetane intermediate 66 <09CC1900>. The organocatalytic α-fluorination of aldehydes and trapping of the intermediate providing optically active propargylic fluorides has proceeded via an oxaphosphatane intermediate <09JA7153>. It has been reported that diselenadisiletane 67, formed from direct reaction of a racemic silylene with elemental selenium, gives the first bis(silaselenone) with two donor-stabilized Si=Se bonds upon hydrolysis with water <09AG(E)4069>. A one-step protocol for the conversion of carboxylic acids to thioesters, using Lawesson’s reagent 68, has been developed <09TL6684>. A mild one-pot protocol for the synthesis of 1,3,4-oxadiazoles from carboxylic acids and acylhydrazides using Burgess reagent has been developed <09TL6435>. The convenient oxidative synthesis of a 16-electron organophosphorus iron sandwich complex analogue of bis(1111-cyclobutadiene)iron(0) has been accomplished <09AG(E)3104>. Unusual structural rearrangements that involve reversible Si–C(sp$^3$) and Si–C(sp$^2$) bond activation in four-membered nickel and palladium silyl pincer complexes have been reported <09AG(E)8568>. It has been documented that the rhodium-catalyzed [2+2+2] cycloaddition between terminal alkyl alkenes and alkenyl isocyanates proceeds through a CO migration pathway involving a rhodazetine intermediate <09AG(E)2379>. The reaction of diazo compounds with alkenes has afforded metathesis or cyclopropanation products depending on the steric and electronic properties of the substituents in the ruthenacyclobutane intermediate <09CEJ1516>. A ruthenacyclobutane has been involved on the proposed mechanism of the triple-cascade catalysis to generate the stereocentres of aromadendranediol <09AG(E)4349>. The synthesis of a four-membered thorium tuck-in complex has been developed <09CEJ12204>. A ruthenium amido pincer complex has catalyzed the dehydrocoupling of dimethylamineborane to its four-membered cyclic dimer (Me$_2$NBH$_2$)$_2$ <09CEJ10339>. Typical zeolite prenucleating solutions containing Ga and Ge have been studied by mass spectroscopy, pointing to a Ga and Ge incorporation into the oligomers in different ways, such as the heterocatom of a four-membered ring <09CEJ5920>. The proposed mechanism for the conversion of aryl azides into amines by using Al(OTf)$_3$/NaI based on a mass spectroscopy analysis has involved an aluminatriazete <09CEJ7215>. The formation of a 2-platinumoxetane from an oxo complex and norbornene has been mediated by a hydroxo complex, which itself may react with norbornene to give a protonated 2-platinumoxetane <09JA8736>. Dumbbell-like Au-Fe$_3$O$_4$ nanoparticles have been made and coupled with Herceptin and a platinadioxetane complex
N-(1'-Alkoxy)cyclopropyl-2-haloanilines have been transformed to 3,4-dihydro-2(1H)-quinolinones via palladium-catalyzed cyclopropane ring expansion involving a four-membered azapalladacycle intermediate. Conjugated dienes have been produced with complete regio- and stereoselectivity by the titanocene(II)-promoted alkylation of propargyl carbonates via the formation of 2,3,4-trisubstituted titanacyclobutenes. It has been prepared a double cubane structure in organoplatinum(IV) chemistry. Treatment of vinylidene ruthenium complexes with methyl propiolate in the presence of a catalytic amount of HBF₄ has resulted in the corresponding cycloaddition products, an unusual ruthenacyclobutene species. The synthesis and characterization of a novel four-membered germanium bismethanediide complex has been accomplished.

4.8 REFERENCES

09AG(E)7604 X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, Angew. Chem. Int. Ed. 2009, 48, 7604.

**Autores:** Alcaide, B.; Almendros, P.

**Título:** Four-Membered Ring Systems, chp. 4, pp 85-107