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An update on the synthesis and reactivity of spiro-fused β-lactams

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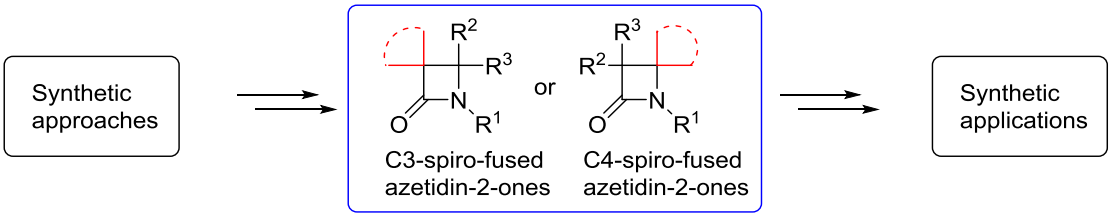
Abstract

β-Lactam ring-containing compounds play a pivotal role in drug design and synthetic chemistry. Spirocyclic β-lactams, representing an important β-lactam subclass, have recently attracted considerable interest with respect to new synthetic methodologies and pharmacological applications. The aim of this manuscript is to review the recent progress made in this field, covering publications disseminated between 2011 to 2018 concerning the synthesis and application of spirocyclic β-lactams. In the first part, new approaches to the synthesis of spirocyclic β-lactams, including Staudinger synthesis, cyclization and transformation reactions, will be presented. The reactivity and biological properties of spiro-β-lactams will be described in the second and third part, respectively.



Keywords: β-Lactams, spiroazetidin-2-ones, spiro-β-lactams, fused rings

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1. Introduction

The β-lactam (azetidin-2-one) ring is one of the most significant azaheterocycles studied from both a synthetic and medicinal chemistry point of view in the last decades. Its prominence is due to the presence of the β-lactam core in many antibiotics (*e.g.*, penicillins, carbapenems, monobactams and sulbactams) used in the fight against pathogenic bacteria. In addition to their antibacterial properties, β-lactams possess other pharmacological activities such as cholesterol absorption inhibition, anti-inflammation, anti-tubercular and anti-HIV activity.[1] Over the years, β-lactams have also emerged as versatile building blocks (β-lactam synthon method) for the synthesis of amino acids, alkaloids and taxoids with potential biological properties.[2-5] In the light of these excellent applications, much attention has been devoted to development of novel and more effective β-lactam compounds and the evaluation of their biological and synthetic potential.[1,6] On the other hand, the overuse of β-lactam antibiotics leads to an increasing number of resistant bacterial strains. These new challenges have given impetus to the search for the replacement or modification of the available β-lactam structures to meet current urgent needs.[7-9]

Spirocyclic β-lactams, which contain a (small) ring spiro-fused at the C3 or C4 position of a β-lactam core (Figure 1), have recently been found to be eligible candidates for drug discovery. They have, for example, been exploited as antibacterial agents, antiviral agents and cholesterol absorption inhibitors. In that respect, structure-activity relationship studies have identified 3-spiro-cyclohexyl-β-lactams SCH 54016 A and SCH 58053 B as two potential cholesterol absorption inhibitors.[10] In addition, spiro-β-lactams have been used as β-turn mimetics in peptidomimetic chemistry. It has been found that spiro-β-lactams also act as poliovirus and human rhinovirus 3C-proteinases inhibitors. Thus, the search for new spiro-β-lactam derivatives comprises a relevant research topic.[10] In addition, spiro-β-lactams have been used as starting materials to prepare α- and β-amino acids, alkaloids, heterocycles, taxoids[11] and other relevant compounds.[12] In that respect, several new methodologies for the synthesis of spiro-β-lactams have been developed, as is evident from the many reviews in the field.[11-13]

As an extension of the review article by De Kimpe in 2011, this review is constructed in a similar way, including synthetic approaches, reactivity, and biological activities of spiro-fused azetidin-2-ones, spanning publications from 2011 to 2018.[13]

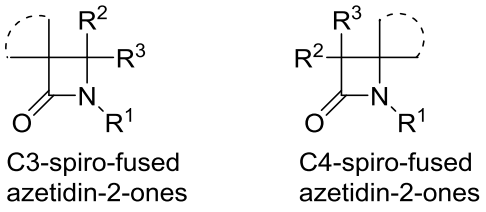


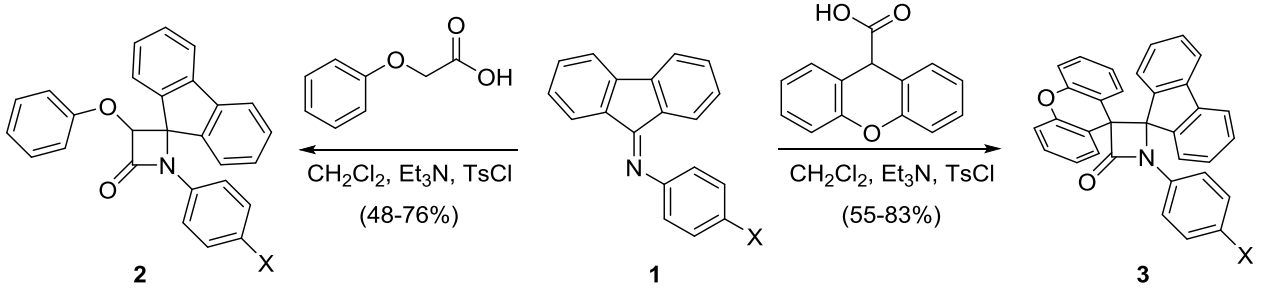
Figure 1. General representation of C3 and C4 spiro-fused azetidin-2-ones.

2. Synthesis of Spiro-fused β-lactams

2.1. Cyclocondensation reactions

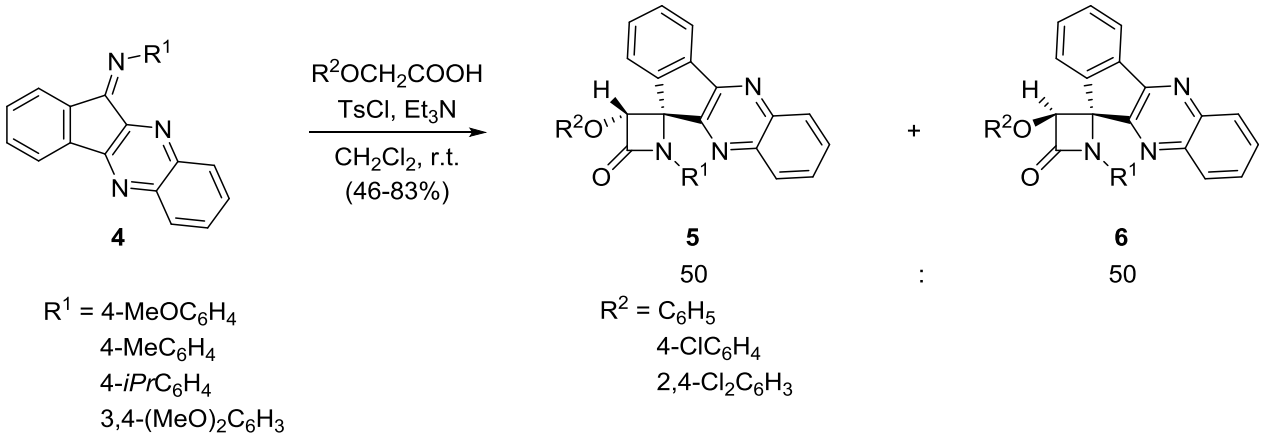
The Staudinger [2+2]-cyclocondensation of ketenes and imines is the most widely used method for the synthesis of the β-lactam ring skeleton. Although, according to IUPAC guidelines, the term 'cycloaddition' can be used for this two-step process via zwitterionic intermediates, this method is mostly referred to as a cyclocondensation reaction. Spiro-fused β-lactams can also be prepared in this way employing various types of ketenes and imines. Depending on the ketenes and imines applied, two different types of spiro-fused azetidin-2-ones can be synthesized. More specifically, the reaction of an acyclic ketene with a cyclic imine will furnish C4 spiro-fused azetidin-2-ones, whereas the reaction of a cyclic ketene with an acyclic imine will afford C3 spiro-fused azetidin-2-ones.

2.1.1. Reactions of acyclic ketenes. Jarrahpour and co-workers have explored the potential of the Staudinger synthesis to access new spiro-fused β-lactams. In particular, the [2+2]-cyclocondensation of imines **1**, which were prepared from 9*H*-fluoren-9-one and substituted anilines with a catalytic amount of acetic acid in ethanol, with either phenoxyacetic acid or 9*H*-xanthene-9-carboxylic acid in the presence of triethylamine and tosyl chloride afforded spiro-β-lactams **2** or dispiro-β-lactams **3**, respectively (Scheme 1). This strategy has also been extended to the synthesis of several bis-spiro- and bis-dispiro-β-lactams.[6,14] The spiro-β-lactams **3** could be further converted into the corresponding NH-spiro-β-lactams in excellent yields by eluting them over a column packed with 10% SiO_2-$NaSO_3$, 10% CAN-SiO_2 and little silica gel.[15]



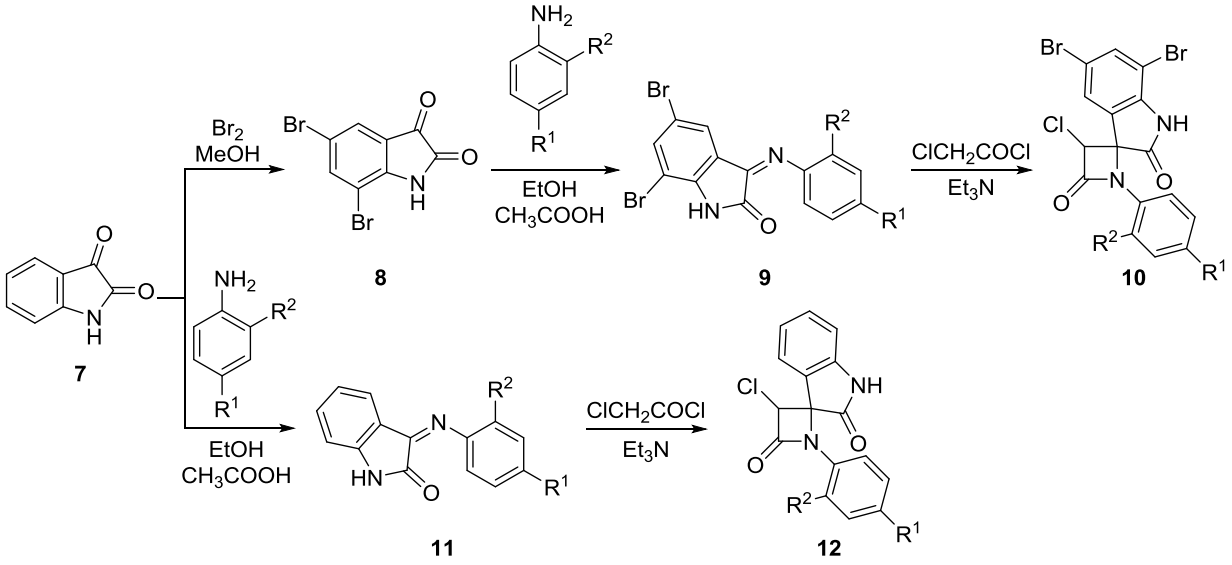
Scheme 1

The spirocyclic indeno[1,2-*b*]quinoxaline β-lactams **5** and **6** were prepared by treatment of *N*-phenyl-11*H*-indeno[1,2-*b*]quinoxalin-11-imine derivatives **4** with various phenoxyacetic acid derivatives in the presence of triethylamine and tosyl chloride in anhydrous CH_2Cl_2 at room temperature (Scheme 2). The diastereomeric ratio of **5** and **6** (50:50) was determined by the integration of the proton H-3. The structures of β-lactams **5** and **6** were further confirmed by X-ray crystallography.[16]



Scheme 2

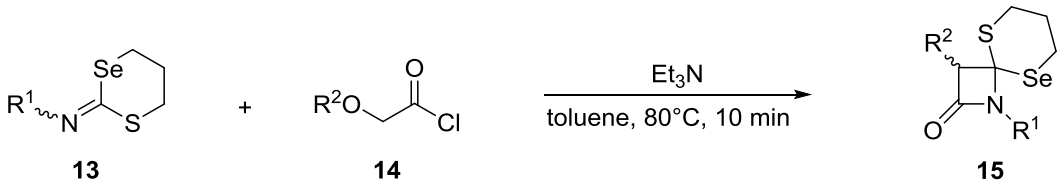
The synthesis and pharmacological evaluation of isatin-derived compounds has attracted the attention of many research groups.[13,17-20] For example, in the course of a screening study for β-lactam compounds possessing antibacterial and antifungal activities, Shah and co-workers successfully synthesized a number of novel spiro[azetidine-2,3′-indole]-2′,4(1′*H*)-diones **10** and **12** by means of the Staudinger synthesis (Scheme 3). The preparation of imines **9** and **11** was performed by reaction between either dibromoisatin **8**, which was obtained by treatment of isatin **7** with bromine in methanol, or isatin **7** with different primary aromatic amines in absolute ethanol in the presence of glacial acetic acid. Subsequently, treatment of imines **9** and **11** with chloroacetyl chloride in the presence of a tertiary base at 80 °C to reflux temperature led to the target spiro-β-lactams **10** and **12**. The antibacterial and antifungal activities of these spiro β-lactams were evaluated.[21]



Scheme 3

In addition, the cyclocondensation of isatin-3-arylimine with various diazoketo esters catalyzed by rhodium(II) also gave rise to spiro(oxindolyl)-β-lactams.[22] Recently, the Kandile group has reported the generation of bis-spiroazetidinone derivatives by the reaction of bis-Schiff bases, derived from 5-substituted isatins, with chloroacetyl chloride.[23] Concurrently, Xu and co-workers have disclosed a direct asymmetric [2+2]-annulation reaction of simple aliphatic aldehydes with isatin-derived ketimines *via N*-heterocyclic carbene (NHC) catalysis furnishing enantioenriched spiroindole β-lactams.[24]

The synthesis of spiro-fused seleno-β-lactams has been studied by using *Z*/*E* isomers of α-selenium-substituted exocyclic imines **13** with various types of acyl chlorides, such as methoxy-, chloro-, propionyl-, phenyl-, cyclohexyl-, phenoxy-, and *p*-chlorophenoxyacetyl chloride under optimized Staudinger synthesis conditions (Scheme 4). The reaction of exocyclic imines **13** with acetyl chlorides **14** gave rise to spiro-β-lactams **15** in excellent yields as mixtures of stereoisomers. The diastereomeric ratio (*d.r.*) of the resulting spiro-β-lactams **15** was calculated by ^{1}H NMR spectral analysis. It should be noted that the stereochemical outcome of β-lactam formation under Staudinger reaction conditions can be explained by the electronic effects of the substituents on the ketenes, which were generated from the corresponding acid chlorides.[25]

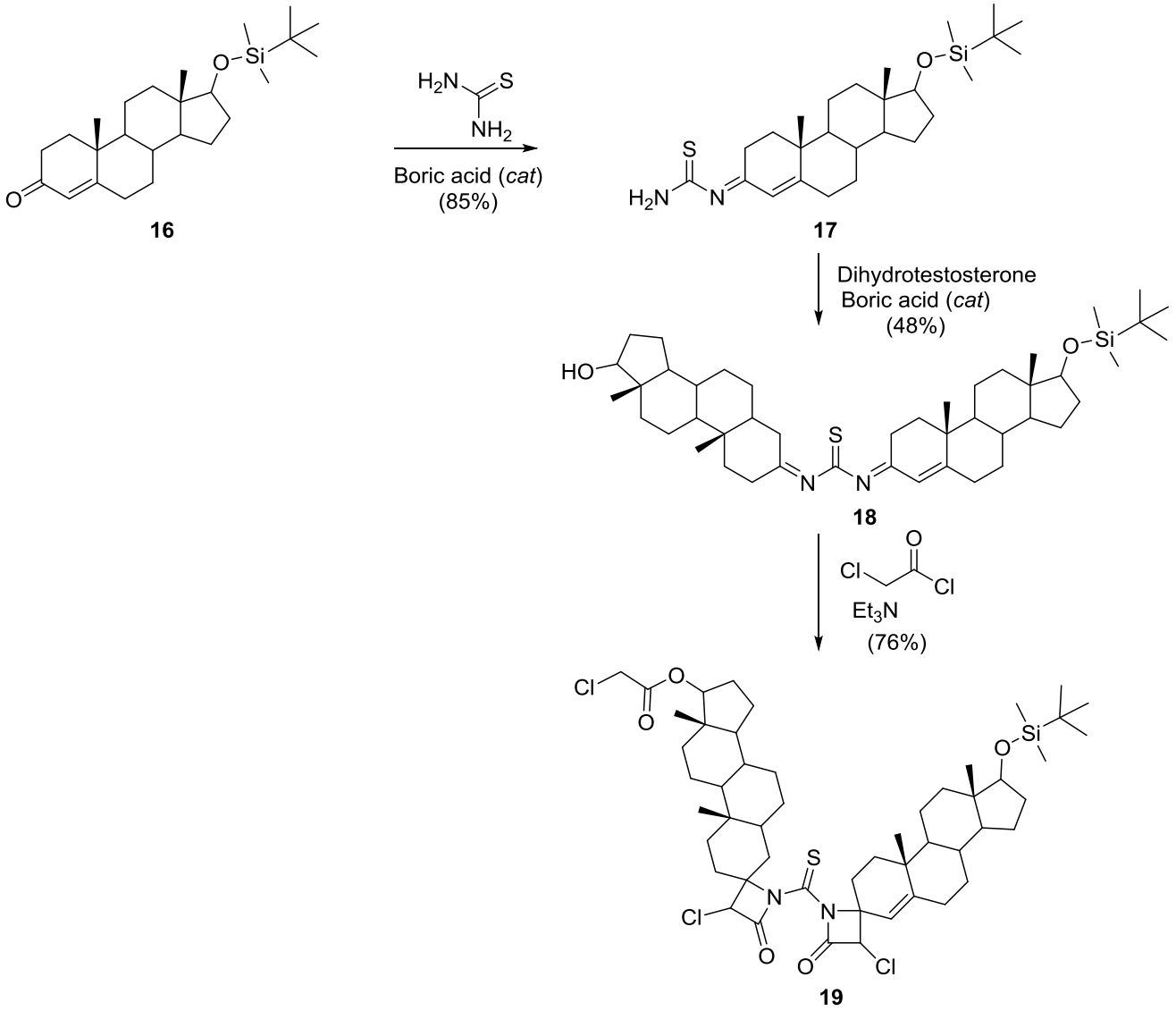


13 **14** **15**

R^1 = C_6H_5, R^2 = Me, 98%, *d.r.* = 73:27
R^1 = *p*-MeC_6H_4, R^2 = Me, 95%, *d.r.* = 71:29
R^1 = *o*-MeC_6H_4, R^2 = Me, 97%, *d.r.* = 73:27
R^1 = *p*-ClC_6H_4, R^2 = Me, 88%, *d.r.* = 73:27
R^1 = *p*-$MeOC_6H_4$, R^2 = Me, 99%, *d.r.* = 69:31
R^1 = 2-Napthyl, R^2 = Me, 93%, *d.r.* = 72:28
R^1 = $C_6H_5CH_2$, R^2 = Me, 98%, *d.r.* = 80:20
R^1 = Cyclohexyl, R^2 = Me, 98%, *d.r.* = 78:22
R^1 = C_6H_5, R^2 = *p*-ClC_6H_4, 89%, *d.r.* = 71:29

Scheme 4

The synthesis of new spiro-fused azetidinone-androgen derivative **19** began with the conversion of 17*b*-[(*tert*-butyldimethylsilyl)oxy]androst-4-en-3-one **16** to Schiff's base **17** using boric acid as a catalyst (Scheme 5). The treatment of compound **17** with dihydrotestosterone afforded thiourea **18**. The later compound **18** was further converted into the desired bis-spiro steroidal β-lactam **19** by treatment with chloroacetyl chloride in the presence of triethylamine. The Staudinger-based synthesis of androgen derivative **19** constitutes a straightforward procedure in comparison with other methodologies applied in the synthesis of steroid derivatives.[26]

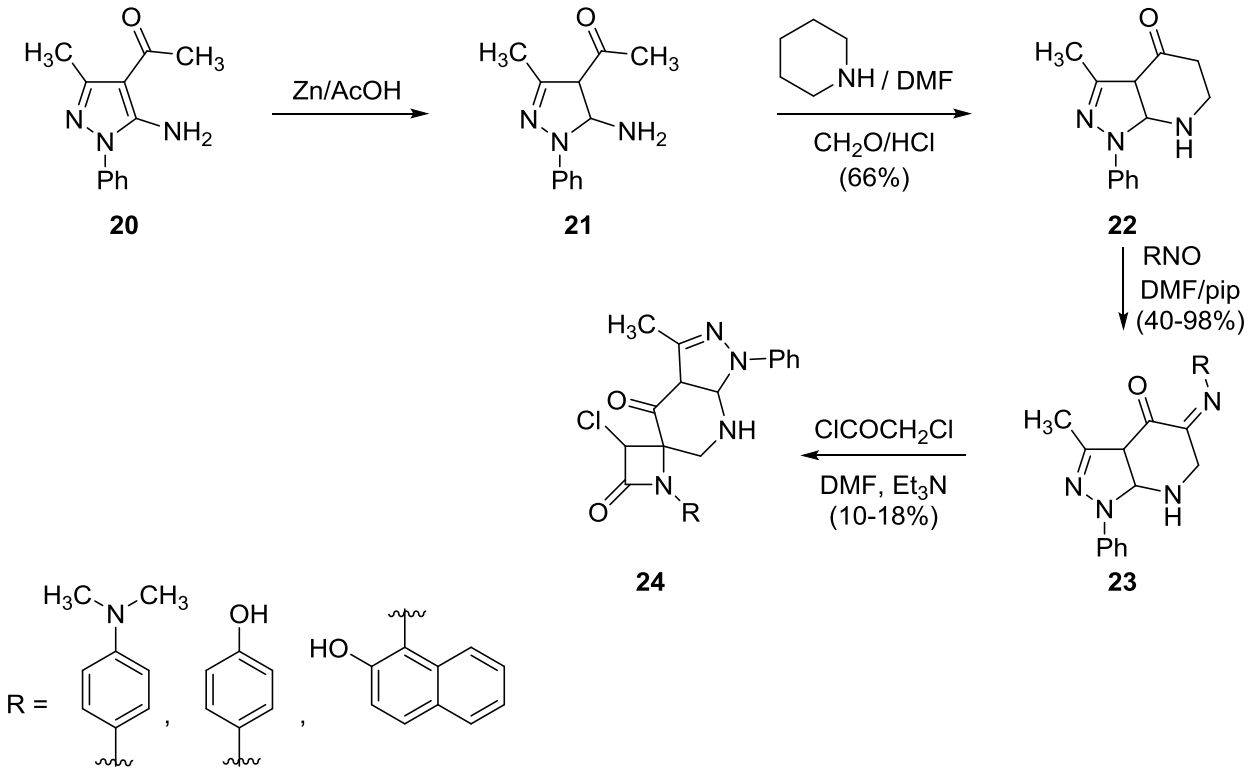


16 **17** **18** **19**

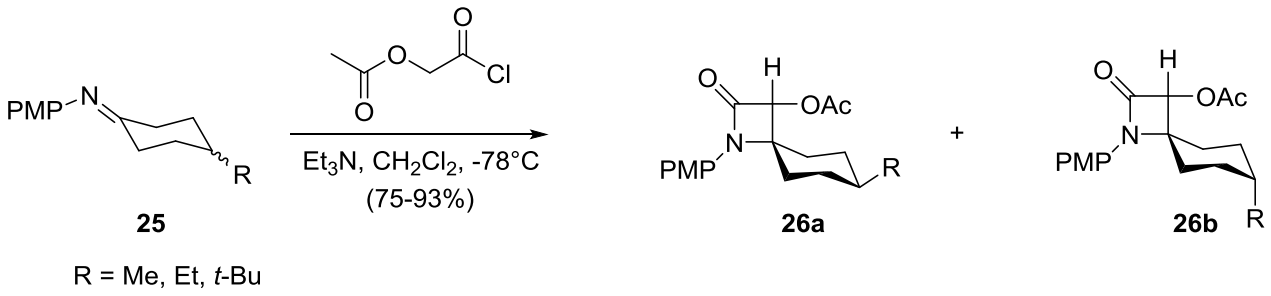
Scheme 5

The reaction of imines **23** with chloroacetyl chloride in dimethylformamide yielded the corresponding spiro-fused β-lactam derivatives **24** (Scheme 6). The required imines **23** were prepared by condensation of bicycle **22** with nitroso derivatives in dimethylformamide in the presence of piperidine as a catalyst. In turn, bicycle **22** was synthesized from 4-acetyl-5-amino-3-methyl-1-phenyl-2-pyrazoline **21** by an intramolecular Mannich reaction. Pyrazoline **21** was derived from 4-acetyl-5-imino-3-methyl-1-phenyl-2-pyrazoline **20** by a reductive reaction using Zn/AcOH.[27]

Anand and co-workers[28] have reported the facile synthesis of axial and equatorial spiro-β-lactams **26** *via* the entrapment of cyclohexanone imines **25** with acetoxyacetyl chloride in a [2+2]-cyclocondensation at -78°C (Scheme 7). The resulting conformations of 4-substituted 1-azaspiro[3.5]nonan-2-ones **26**, which could be isolated as stable, pure crystals, were confirmed by X-ray crystallography. The restricted conformers were kinetically resolved using lipases. The mechanism of spiro-β-lactam **26** formation was explored using B3LYP/6-31+G* level quantum chemical calculations.[28]



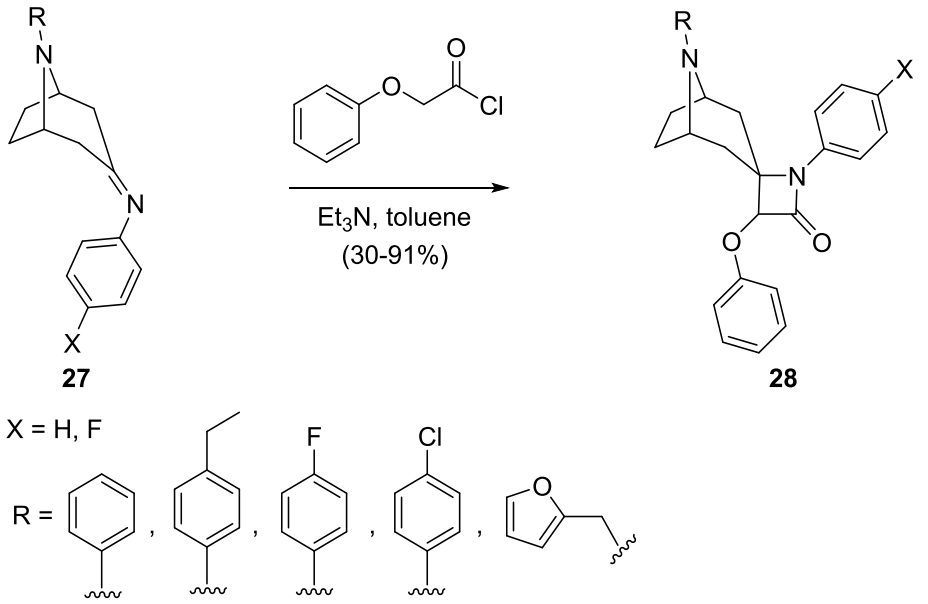
Scheme 6



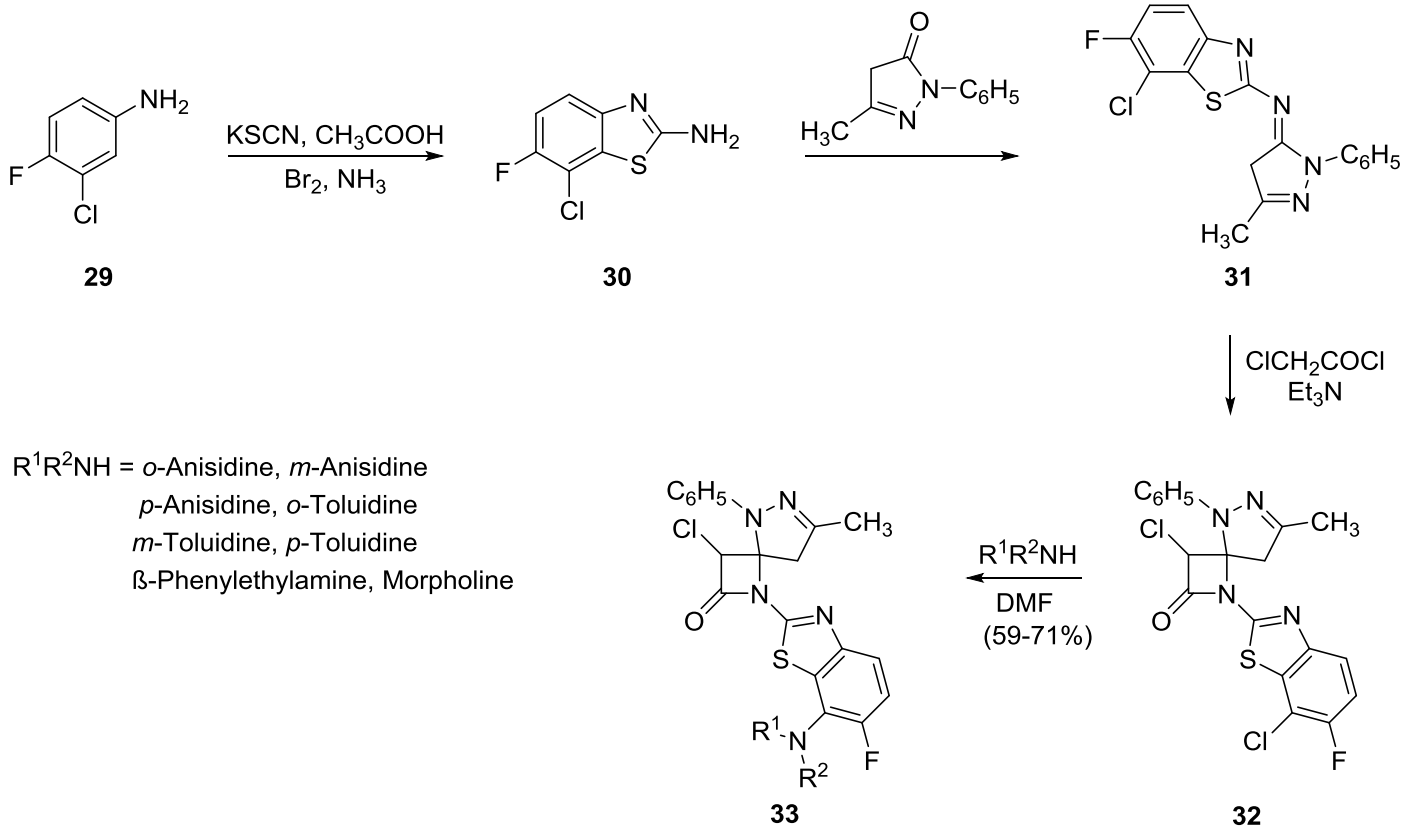
Scheme 7

Imines **27**, derived from 8-azabicyclo[3.2.1]octan-3-ones, have been shown to be interesting starting materials for the synthesis of a new class of β-lactams **28** *via* Staudinger synthesis with phenoxyacetyl chloride (Scheme 8). It is noteworthy that the stereochemical outcome of the obtained spiro-β-lactams (as single diastereoisomers) was opposite to the expected products of a [2+2]-cycloaddition reaction, which should have taken place from the *exo* face of compound **27.**[29]

The Reddy group[30] has reported on the synthesis and biological evaluation of a novel series of spiroazetidin-2-ones **33** starting from 3-chloro-4-fluoroaniline **29** (Scheme 9). Firstly, the benzothiazole **30** was synthesized from 3-chloro-4-fluoroaniline **29** and further condensed with 5-methyl-2-phenylpyrazol-3-one to yield the imine **31**, which was cyclized with chloroacetyl choride in triethylamine to obtain azetidin-2-one **32**. Finally, the resulting azetidin-2-one **32** was further condensed with different primary and secondary amines, leading to the desired spiro-fused β-lactams **33**. These β-lactams **33** exhibited moderate to significant activities in anti-inflammatory, anti-diabetic, anti-oxidant and anti-microbial tests.[30]



Scheme 8



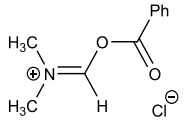
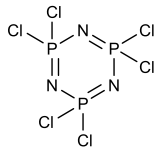
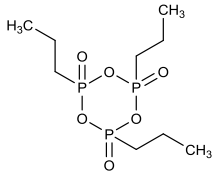
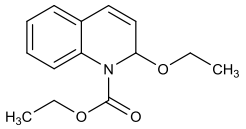
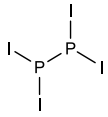
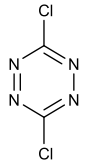
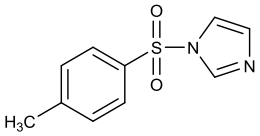
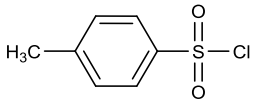
Scheme 9

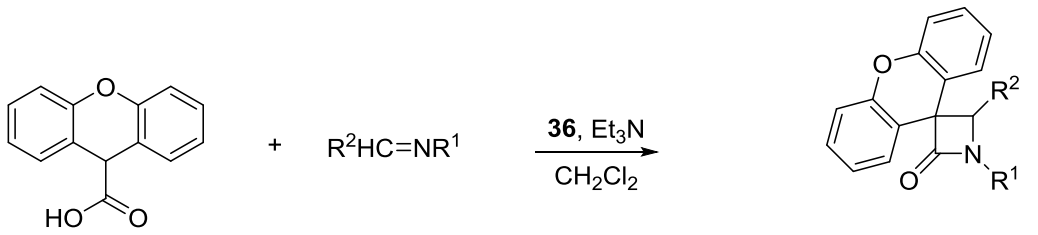
In an analogous approach, spiro-[chloroazetidinethiazolopyrimidine] derivatives were obtained by using the corresponding thiazolopyrimidine imines.[31]

2.1.2. Reactions of cyclic ketenes. The utilization of cyclic ketenes in the [2+2]-cyclocondensation with imines constitutes an alternative approach for the preparation of spiro-β-lactams.[6,32-35] The generation of ketenes by the treatment of an acyl chloride with triethylamine is one of the most common methods; however, this

approach has sometimes encountered disadvantages such as commercial unavailability, instability and difficulties related to the preparation of acid halides.[36] To deal with these difficulties, the Zarei and Sardarian groups have independently devoted efforts to the preparation of a cyclic ketene from the corresponding xanthene-9-carboxylic acid **34** using different carboxylic activators **36** to synthesize spiro-β-lactams **37** by Staudinger reaction with imines **35** (Scheme 10, Table 1).[15,36-43] The structure of 1-[3-(morpholin-4-yl)propyl]-4-(3-nitrophenyl)spiro[azetidine-3,9′-xanthen]-2-one - an analog of spiro-β-lactams **37** - was successfully determined for the first time by Akkurt *via* single-crystal X-ray analysis.[44]

Table 1. Synthesis of spiro-β-lactams **37** using different carboxylic activators **36**

Compounds 36	Compounds 37 (R^1, R^2)
	R^1 = C_6H_5, R^2 = 4-$NO_2C_6H_4$, 82% R^1 = 4-EtC_6H_4, R^2 = 4-$NO_2C_6H_4$, 87% R^1 = 4-$MeOC_6H_4$, R^2 = 4-$MeOC_6H_4$, 85%
	R^1 = Me, R^2 = 4-$MeOC_6H_4$, 82% R^1 = C_6H_5, R^2 = 4-ClC_6H_4, 87% R^1 = 4-$MeOC_6H_4$, R^2 = 4-ClC_6H_4, 85% R^1 = 4-$MeOC_6H_4$, R^2 = 4-$MeOC_6H_4$, 85%
	R^1 = 4-$EtOC_6H_4$, R^2 = 4-$NO_2C_6H_4$, 81% R^1 = 4-$MeOC_6H_4$, R^2 = 4-$MeOC_6H_4$, 87% R^1 = 4-$MeOC_6H_4$, R^2 = 4-ClC_6H_4, 83%
	R^1 = 4-$MeOC_6H_4$, R^2 = 3,4,5-$(MeO)_3C_6H_2$, 80% R^1 = 4-EtC_6H_4, R^2 = 2,4-$Cl_2C_6H_3$, 84%
	R^1 = 4-$MeOC_6H_4$, R^2 = C_6H_5, 75% R^1 = 4-ClC_6H_4, R^2 = 4-$(NMe)_2C_6H_3$, 71%
	R^1 = 4-ClC_6H_4, R^2 = 4-ClC_6H_4, 86% R^1 = 4-ClC_6H_4, R^2 = 4-$(Me_2CH)C_6H_4$, 87%
	R^1 = 4-$MeOC_6H_4$, R^2 = 2,4-$Cl_2C_6H_3$, 72% R^1 = 4-EtC_6H_4, R^2 = 3,4,5-$(MeO)_3C_6H_2$, 70%
	R^1 = 4-$MeOC_6H_4$, R^2 = 4-CH_2=$CHCOOC_6H_4$

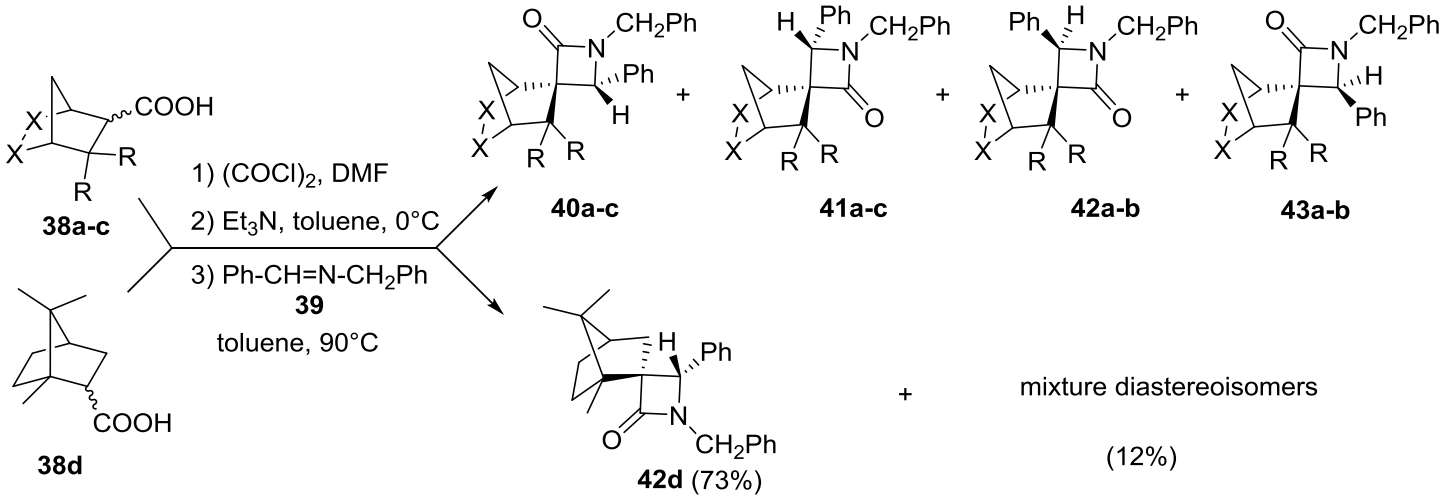


34 **35** **37**

(for R^1 and R^2, see **Table 1**)

Scheme 10

The substituted norbornane carboxylic acids **38** have been used for the formation of the corresponding bicyclic norbornane-derived ketenes by a two-step procedure. The cycloaddition of the so-formed ketenes with imine **39** led to the generation of diastereomeric norbornane C3-spiro-β-lactams **40**, **41**, **42**, **43** (Scheme 11, Table 2). It is noteworthy that the stereochemical outcome of spiro-β-lactams **40-43** is influenced by the presence of encumbering groups on the cyclic ketenes. In fact, a better selectivity was obtained when methyl groups were present near to the carbon bearing the carboxylic functional group. The ratio of diastereoisomers was determined by integration of the H-4 proton in the ^{1}H-NMR spectra of the crude reaction mixtures.[45]



38a-c **40a-c** **41a-c** **42a-b** **43a-b**

38d **42d** (73%)

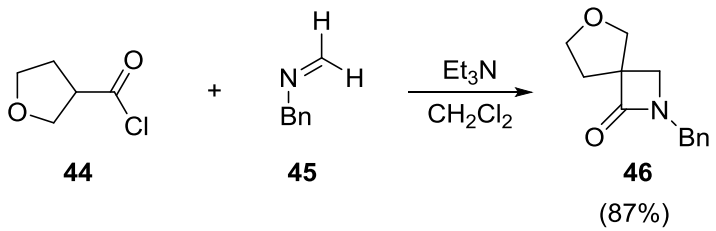
Scheme 11

Table 2. Total yields and ratios of spiro-β-lactams **40**-**43** (**a-c**)

Carboxylic acids	X-X	R	Total yield (%)	Diastereomeric ratio (%)			
				40	**41**	**42**	**43**
38a	CH=CH	H	98	46	27	20	7
38b	CH_2-CH_2	H	94	53	29	9	9
38c	CH_2-CH_2	CH_3	68	47	53	-	-

To study the synthesis of spiro-β-lactam **46** on a larger scale, the reaction of *in situ* generated ketene from compound **44** and imine **45** was conducted in both batch and flow mode (Scheme 12). The reaction outcome showed that the Staudinger synthesis in a continuous flow process was deemed a safe method for this highly

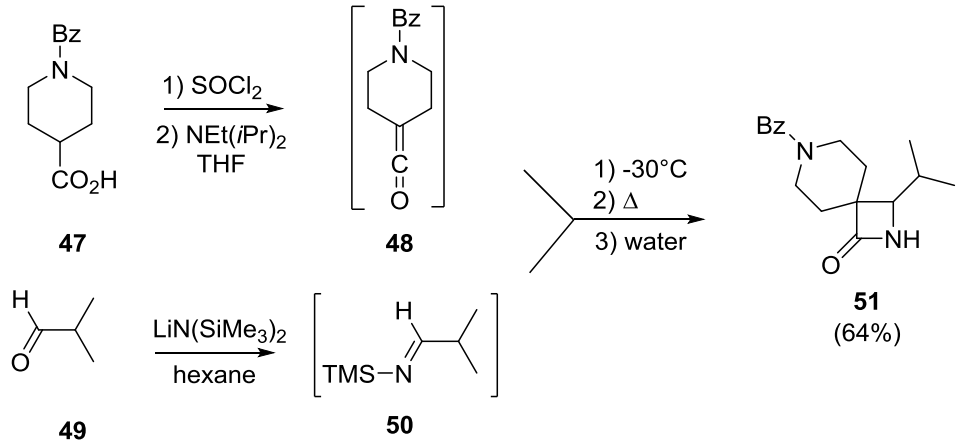
exothermic reaction. However, the precipitation of generated salts quickly blocked a glass chip and made the operation technically impossible.[46]



44 **45** **46**
(87%)

Scheme 12

Recently, the Mykhailiuk group[47,48] has reported on a new approach for the synthesis of 3-substituted piperidinyl spiro-β-lactam **51** starting from acid **47** and aldehyde **49** (Scheme 13). In this synthetic approach, acid **47** was firstly converted into the corresponding acid chloride and subsequently into ketene **48** by the sequential treatment with $SOCl_2$ and $NEt(iPr)_2$. Aldehyde **49** was converted into imine **50** upon treatment with $LiN(TMS)_2$. In analogy, a diverse number of spiro-β-lactams attached with 4-, 5-, 6-, 7-membered rings at the C-3 position were prepared in moderate to good yields. Subsequently, the reductive removal of the carbonyl group of spiro-β-lactam analogs **51** was conducted by the reducing reagent AlH_3 giving the corresponding spirocyclic azetidines, which were investigated further in drug design and as an analog of the anesthetic drug bupivacaine.[47,48]



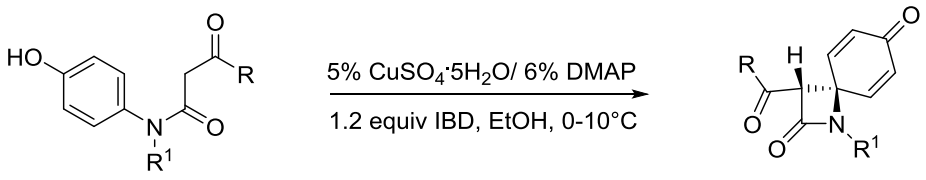
47 **48** **51**
(64%)

49 **50**

Scheme 13

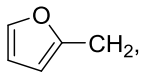
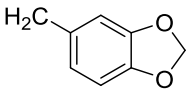
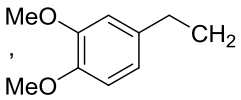
2.2. Cyclization reactions

A convenient entry toward the construction of spirocylic β-lactams comprises the cyclization of β-amino acid derivatives and β-functionalized amides.[13] In that respect, Zhang and co-workers[49] have developed novel synthetic routes to produce several spiro-4-cyclohexadienonyl-β-lactams **53** from *N*-(4-hydroxyphenyl)-3-oxopropanamides **52** through dearomatization and cyclization processes with iodobenzene diacetate (IBD) as oxidant in the presence of a stoichiometric amount of copper(II) sulfate pentahydrate and 4-dimethylamino-pyridine (DMAP).[49] Later, this method was modified by using only a catalytic amount of copper(II) sulfate pentahydrate and 4-dimethylaminopyridine (DMAP), which gave similar yields (Scheme 14).[50]



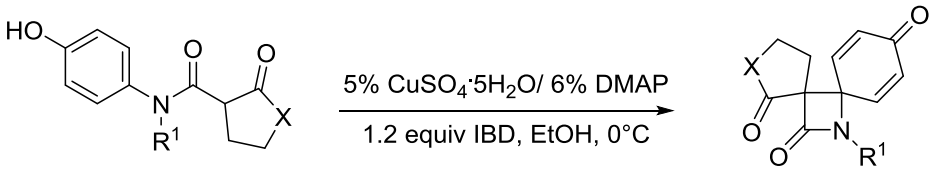
52 **53**
(45-95%)

R = CH_3, Ph, OEt, CH_3CH_2, $CH_3CH_2CH_2$, $CH_3CH_2CH_2CH_2CH_2$, $CH_3CH{=}CH_2$

R^1 = *p*-$MeOC_6H_4CH_2$, $(CH_3)_2CHCH_2$, *o*-$ClC_6H_4CH_2$, Ph, $PhCH_2$,  ,  , 

Scheme 14

In addition, this modification also allowed for the synthesis of a diverse number of spiro-4-cyclohexadienone-β-lactams **55** with cyclopentanone, γ-lactone, and γ-lactam side chains on their C3 position, starting from the corresponding amides **54** (Scheme 15).[50]



54 **55**
(80-93%)

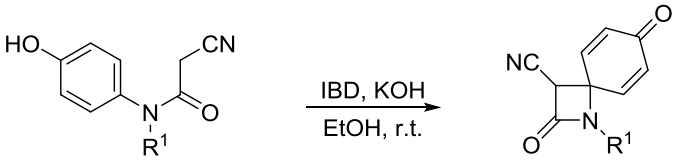
R^1 = $(CH_3)_2CHCH_2$, Bn, 4-$MeOC_6H_4$

X = CH_2, O, NBn, NBoc

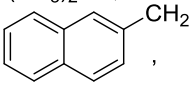
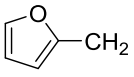
Scheme 15

Furthermore, the replacement of copper(II) sulfate pentahydrate by $[Cu_3((S)\text{-PIA})_2(1,4\text{-dioxane})(H_2O)_2]2(1,4\text{-dioxane})H_2O$ (L-1) has been shown to be equally effective in the preparation of spiro-4-cyclohexadienonyl-β-lactam analogs.[51]

In independent research, Xu has described the synthesis of 4-spiro-cyclohexadienonyl-β-lactam-3-carbonitriles **57** by means of the intramolecular nucleophilic cyclization of *N*-(*p*-hydroxyphenyl)cyanoacetamides **56** with iodobenzene diacetate (IBD) as oxidant and potassium hydroxide as base (Scheme 16).[10]

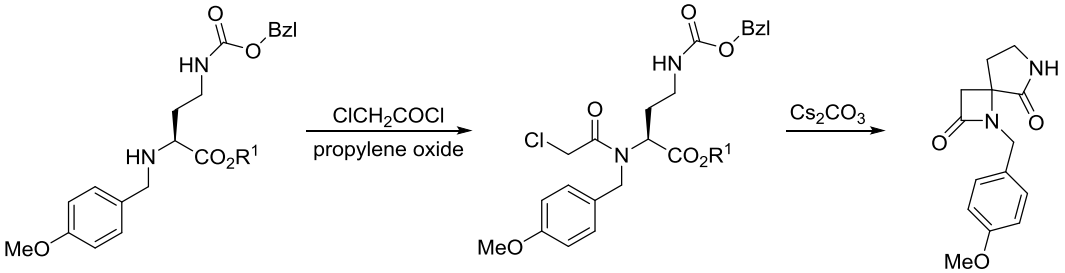


56 **57**
(57-95%)

R^1 = Bn, 4-$MeOC_6H_4CH_2$, 3-$MeOC_6H_4CH_2$, 2-$MeOC_6H_4CH_2$, 3,4-$(MeO)_2C_6H_3CH_2$, 4-$FC_6H_4CH_2$, 4-$ClC_6H_4CH_2$, 3-$ClC_6H_4CH_2$, 2-$ClC_6H_4CH_2$, 4-$BrC_6H_4CH_2$, 4-$NCC_6H_4CH_2$, 4-$NO_2C_6H_4CH_2$, $(CH_3)_2CH$,  , 

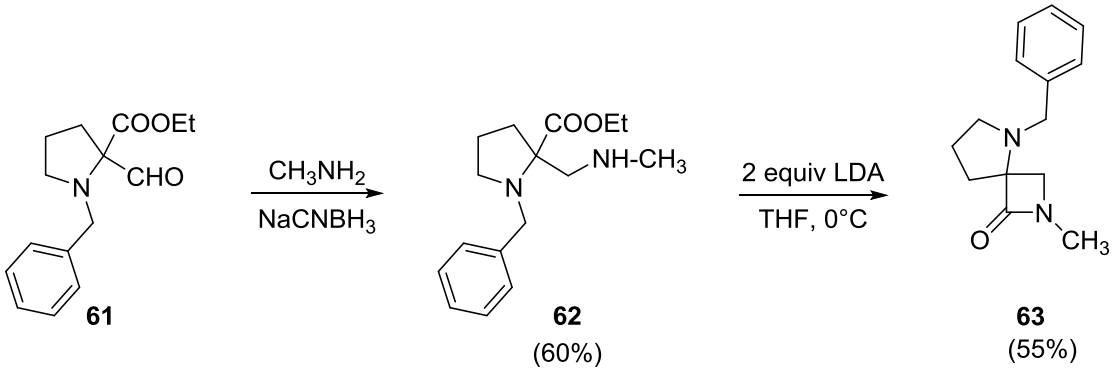
Scheme 16

The cyclization of Dab-derived (Dab = 2,4-diaminobutanoic acid) chloroacetyl compound **59**, which was obtained in a quantitative yield by treatment of compound **58** with chloroacetyl chloride in the presence of propylene oxide, gave rise to 1,6-diazaspiro[3.4]octane-2,5-dione **60** (Scheme 17). The construction of spirocylic β-lactam **60** could be explained by the concomitant formation of the β-lactam and pyrrolidinone ring, the latter due to a 5-*exo*-*trig* ring closure between the ZNH group and the carboxylic ester, followed by Z-protecting group removal.[52]



Scheme 17

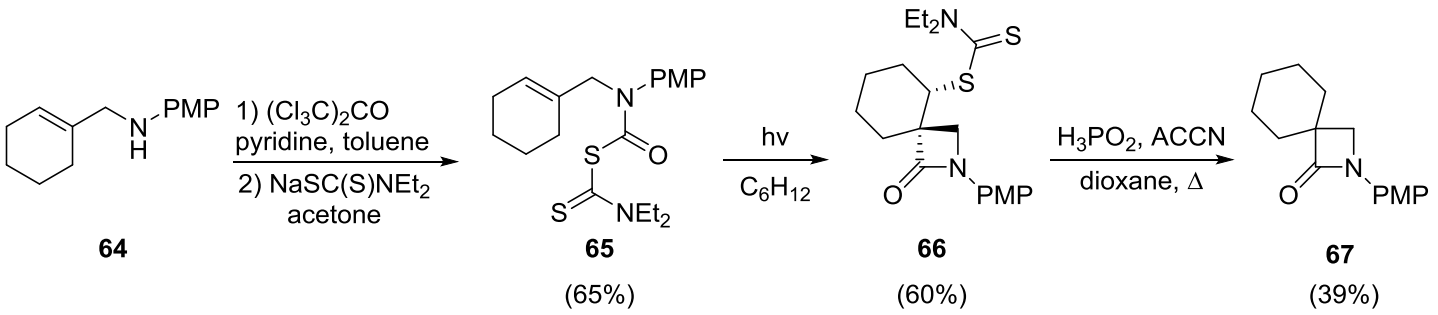
In the course of a study on proline-like compounds with potential biological interest, Ponticelli and co-workers[53] have devised an approach toward the synthesis of functionalized spiro-pyrrolidine **63** (Scheme 18). In particular, treatment of pyrrolidine aldehyde **61** with the reducing reagent $NaCNBH_3$, together with methyl-amine, gave rise to the β-amino ester **62**. Subsequently, the cyclization of compound **62** using two equivalents of the strong base LDA led to the desired spiro-β-lactam **63.**[53] In independent research, Sharada and co-workers have also described an effective synthesis of a pyrrolidine-derived spiro-β-lactam starting from natural proline.[54]



Scheme 18

The Grainger group[55] has published the preparation of a spirocyclic β-lactam by using a 4-*exo*-*trig* carbamoyl radical cyclization approach. Specifically, amine **64**, prepared in one step by reductive amination of commercially available 1-cyclohexene-1-carboxaldehyde with *p*-methoxyaniline,[11] was converted into the carbamoyl radical precursor **65** (Scheme 19). Then, irradiation of compound **65** with a 500 W halogen lamp afforded spirocyclic dithiocarbamate **66** as a single diastereomer. The stereochemistry of compound **66** was

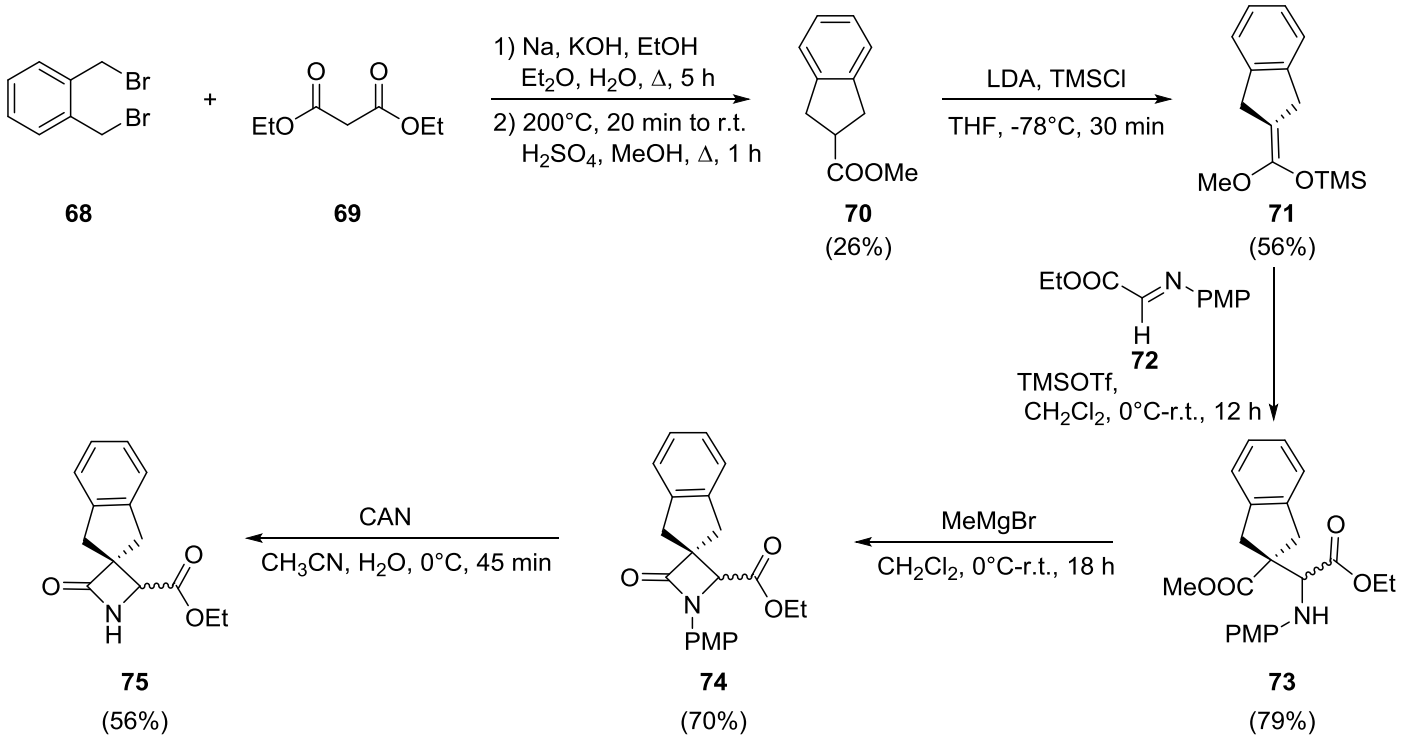
determined by NOE spectral analysis, which showed the proton adjacent to sulfur to be on the same side of the cyclohexyl ring as the methylene group of the β-lactam. The reduction of **66** with H_3PO_2-ACCN successfully gave spirocyclic β-lactam **67**.[55]



64 **65** (65%) **66** (60%) **67** (39%)

Scheme 19

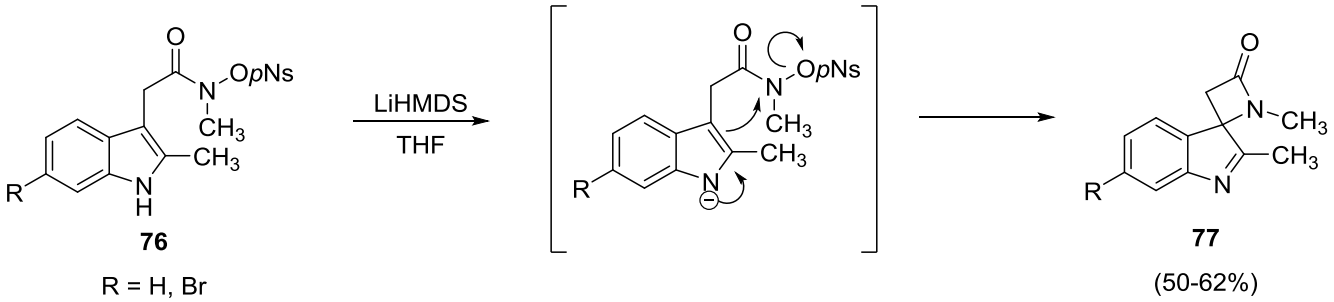
Spiro-β-lactam **75** has been synthesized as an intermediate compound in an effort to find drugs to improve hepatitis C virus (HCV) therapy (Scheme 20).[56] 1,2-Bis(bromomethyl)benzene **68** was condensed with diethyl malonate **69**, furnishing a crude diethyl malonate derivative. This derivative was reacted with sulfuric acid in the presence of methanol at 200 °C, giving methyl ester **70**. Treatment of ester **70** with LDA afforded the corresponding enolate, which was trapped with TMSCl leading to silyl enol ether **71**. Reaction of generated enol **71** with *N*-*p*-methoxyphenyl (PMP) imine **72** in the presence of TMSOTf gave compound **73** as a mixture of enantiomers. Cyclization of compound **73** with MeMgBr gave rise to spiro compound **74** in 70% yield. Removal of the PMP group of spiro-β-lactam **74** with CAN led to the desired compound **75**.[56]



68 **69** **70** (26%) **71** (56%) **72** **73** (79%) **74** (70%) **75** (56%)

Scheme 20

Indolenine β-lactams **77**, present as key moieties in the complete structure of chartellines, were synthesized by an intramolecular nucleophilic substitution initiated by indolenine derivatives **76** using LiHMDS as a base (Scheme 21).[57]



76

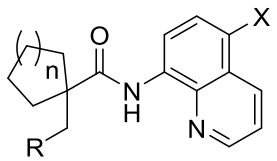
R = H, Br

77

(50-62%)

Scheme 21

A highly regioselective intramolecular amination of an sp^3 carbon in amide derivatives bearing an 8-aminoquinolinyl group as the bidentate directing group using transition metal catalysts has recently attracted considerable attention of different research groups.[58-63] The intramolecular dehydrogenative cyclization of aliphatic amides **78** afforded spiro-β-lactams **79** by utilizing a bidentate chelation and various oxidants in combination with copper, nickel and cobalt catalysts (Scheme 22). The formation of β-lactams was proposed to proceed in all cases *via* C-N bond-forming reductive elimination.[63]



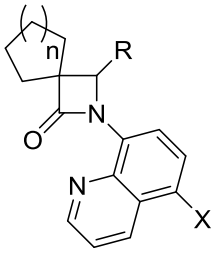
78

R = H, Ph, CH_3

X = H, Cl

n = 0, 1, 2

1) CuCl (20 mol%), 1.2 equiv duroquinone
1.5 equiv $PhCO_2Na$, *o*-xylene, air, 160°C
2) $[Cu(OAc)_2]$ (20 mol%), 3.0 equiv Ag_2CO_3
$Cl(CH_2)_2Cl$, 140°C, 24 h
3) CuI (20 mol%), O_2 (1 atm), 2 equiv Na_2CO_3
PhCN/*o*-xylene (3/2), 140°C, 34 h
4) $[Ni(dme)_2I_2]$ (10 mol%), 3 equiv TEMPO
2 equiv K_2HPO_4, 0.1 equiv TBAI,
*n*PrCN/PhCN, 150°C
5) $Ni(OTf)_2$ (10 mol%), Ag_2CO_3 (25%)
2 equiv Na_2CO_3, DMF, 140°C, 24 h
6) $Co(OAc)_2$ (10 mol%), 2.5 equiv Ag_2CO_3
0.5 equiv $PhCO_2Na$, PhCl, 150°C

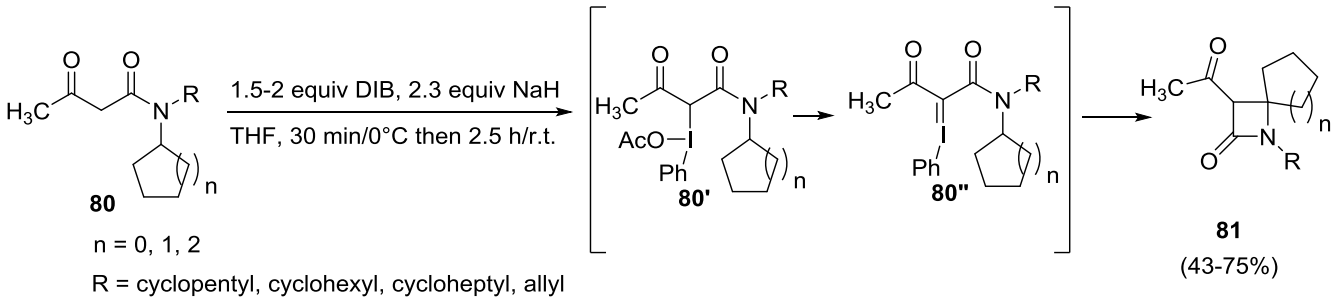


79

(27-90%)

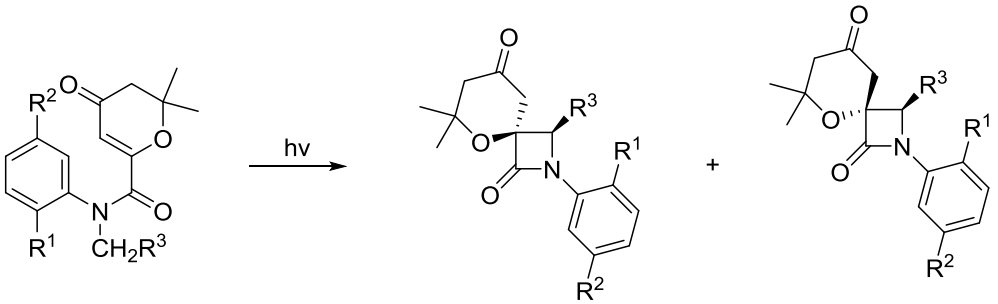
Scheme 22

The direct C-H cyclization of amides **80** bearing five-, six- and seven-membered rings proceeded via *in situ* iodonium ylide formation **80"** without the assistance of a transition metal, delivering the corresponding spiro-β-lactams **81** in a single step (Scheme 23). From a mechanistic point of view, this transformation is consistent with the facile formation of a reactive singlet carbene. However, it circumvents the classical use of diazo substrates for C-H insertion chemistry.[64]



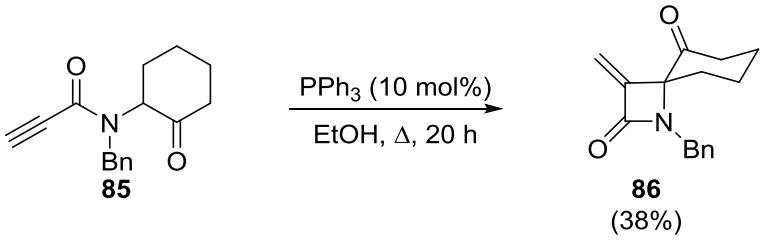
Scheme 23

Phototransformation chemistry has demonstrated a great potential for challenging building block synthesis. In that regard, the irradiation (direct excitation at ~350 nm or triplet sensitization with thioxanthone at ~420 nm) of atropisomeric enones **82** gave rise to the corresponding spiro-β-lactam photoproducts **83** (as major products) and **84** (as minor products) (Scheme 24). Computational investigation revealed that the presence of an *ortho*-*tert*-butyl substituent on atropisomeric enones **82** prevented the 6π-photocyclization to undergo an efficient hydrogen abstraction leading to atropselective spiro-β-lactam formation.[65,66]



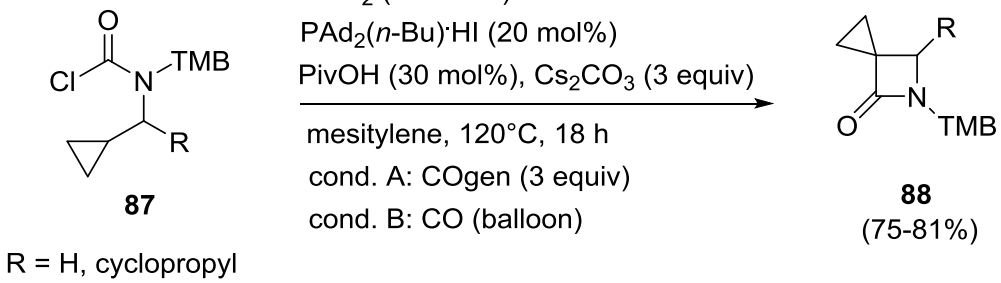
Scheme 24

Cyclization of propiolamide **85** with triphenylphosphine as a catalyst in ethanol under reflux furnished the corresponding spiro-3-methyleneazetidin-2-one **86** in a moderate yield (Scheme 25). The rather low yield of spiro-β-lactam **86** might be rationalized by the steric hindrance experienced in the 4-*exo* cyclization step.[67]



Scheme 25

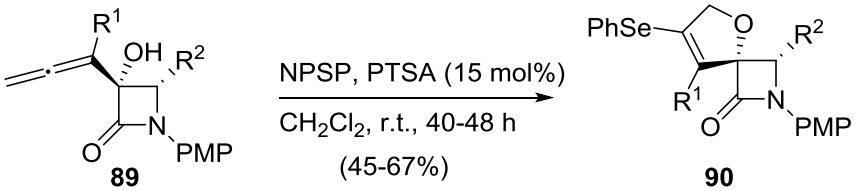
Several methods based on C(sp^3)-H activation using Pd as a catalyst have recently been introduced to access a wide variety of ring systems.[68-70] Boudoin and co-workers have described the utilization of carbamoyl chlorides **87** as appropriate substrates to construct spirocyclic β-lactams **88** through Pd-catalyzed C(sp^3)-H activation under both CO balloon and COgen (solid CO-releasing molecules) conditions (Scheme 26).[71]



Scheme 26

2.3. Transformations of substituents connected to monocyclic azetidin-2-ones

One of the most convenient methodologies for the preparation of spiro-fused β-lactams concerns the deployment of substituents on monocyclic azetidin-2-ones. In that respect, the Benito group has recently reported on the synthesis of spirocyclic seleno-β-lactams **90** from azetidin-2-one-tethered allenols **89** and the selenenylating reagent *N*-phenylselenophthalimide (NPSP) *via* ring enlargement (Scheme 27).[72]



R^1 = Ph, R^2 = (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl

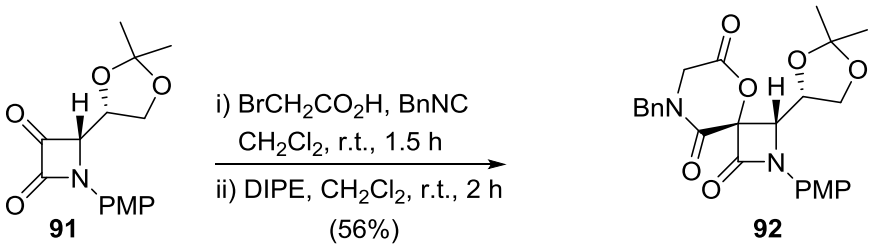
R^1 = Me, R^2 = (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl

R^1 = Me, R^2 = 4-MeC_6H_4

R^1 = Me, R^2 = (*R*)-3-methoxy-1-(4-methoxyphenyl)-2-oxoazetidinyl

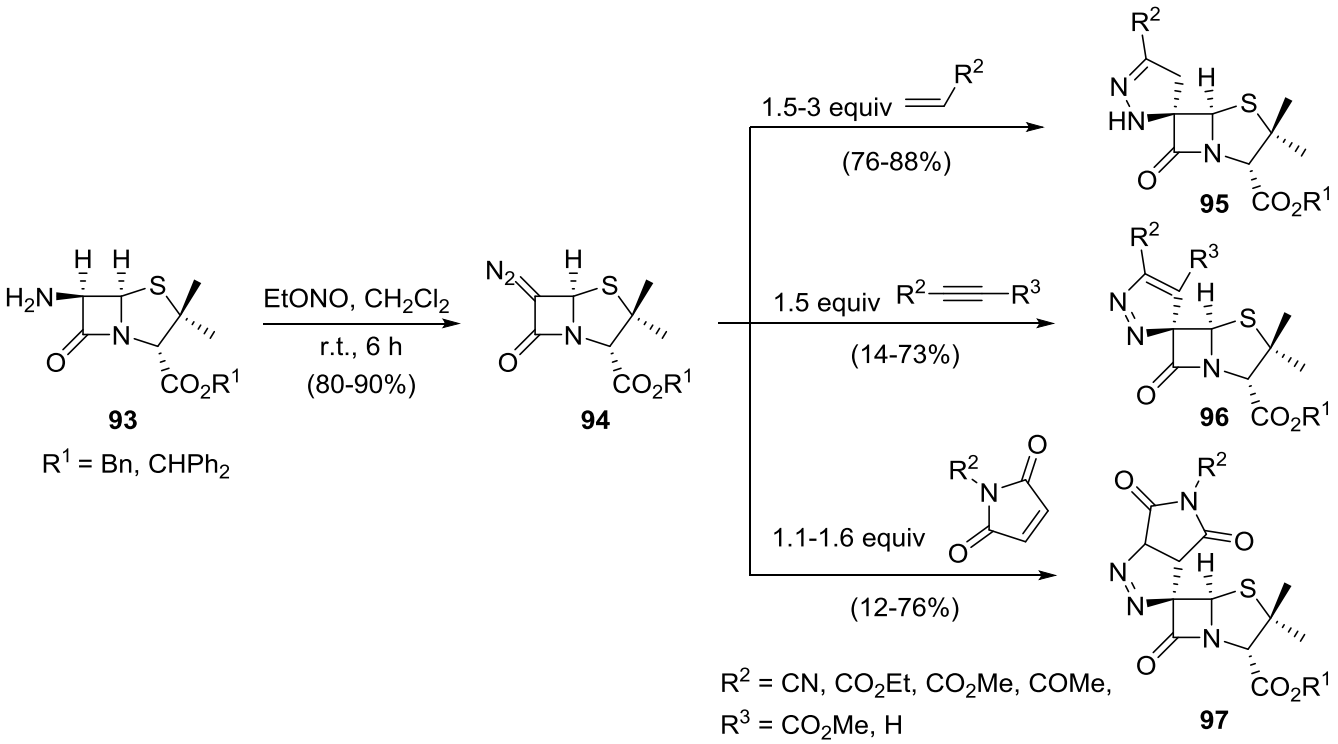
Scheme 27

In addition, this group has disclosed a diastereoselective synthesis of spirocyclic β-lactam derivative (-)-**92** starting from optically pure azetidine-2,3-dione (+)-**91** applying Passerini reaction conditions with bromoacetic acid and benzyl isocyanide, followed by the addition of the non-nucleophilic base *N*,*N*′-diisopropylethylamine (DIPEA) (Scheme 28).[73]



Scheme 28

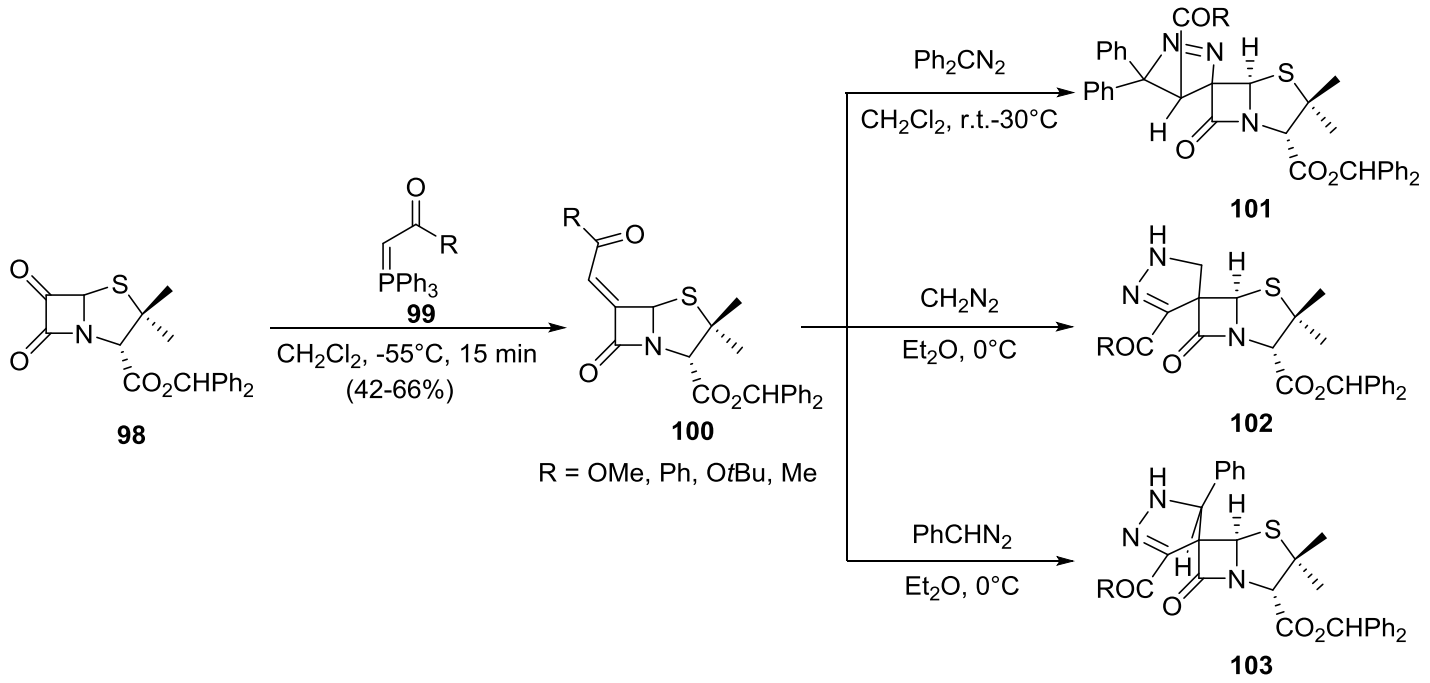
6-Diazopenicillanates **94** have been obtained in high yields by the combination of 6-β-aminopenicillanates **93** with ethyl nitrite at room temperature. Then, these 6-diazopenicillanates **94** were subjected to stereoselective 1,3-dipolar cycloaddition with acrylonitrile, acrylates and methyl vinyl ketone, giving the corresponding spiro-2-pyrazoline-β-lactam derivatives **95**, **96** and **97** as major products (Scheme 29). It should be noted that the 1,3-dipolar cycloaddition was stereoselective, the major cycloadduct being the result of the dipolarophile addition to the less sterically hindered α-side of the β-lactam.[74]



Scheme 29

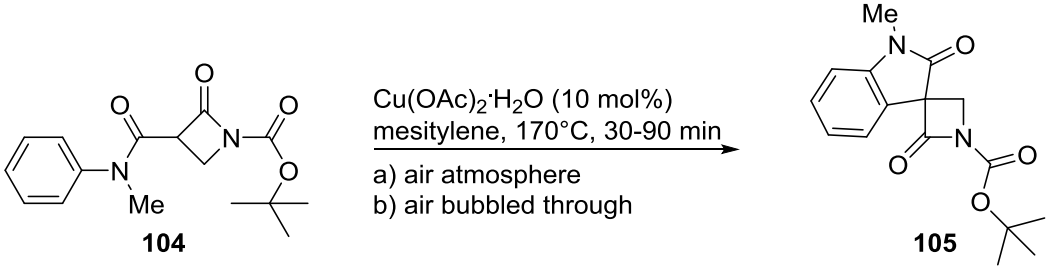
In analogy, chiral spiropyrazolinepenicillanates **101**, **102** and **103** were obtained in a stereoselective fashion *via* 1,3-dipolar cycloaddition of 6-alkylidenepenicillanates **100**, prepared through Wittig reaction of the

appropriate benzhydryl 6-oxopenicillanate **98** and phosphorus ylides **99**, with the corresponding diphenyldiazomethane, diazomethane and phenyldiazomethane (Scheme 30).[75]



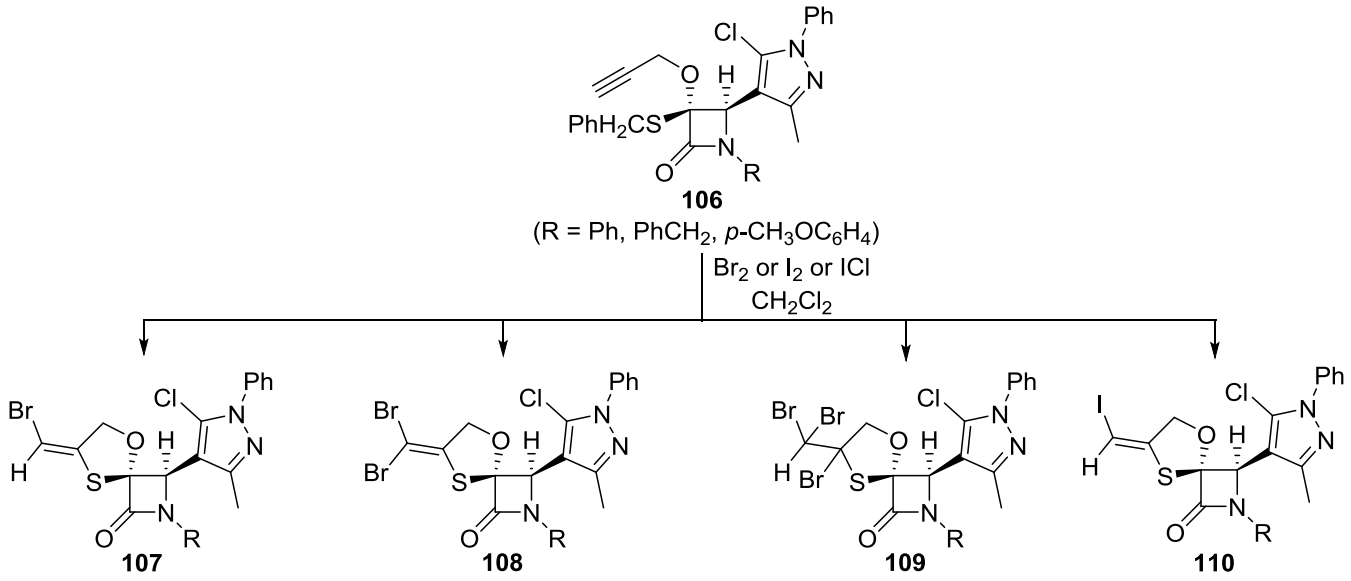
Scheme 30

In another study, the use of 10 mol% copper(II) acetate monohydrate as a catalyst and air as the stoichiometric re-oxidant enabled the synthesis of spirocyclic oxindole β-lactam **105** *via* the cyclization of precursor **104** using mesitylene as the solvent (Scheme 31).[12,76-78]



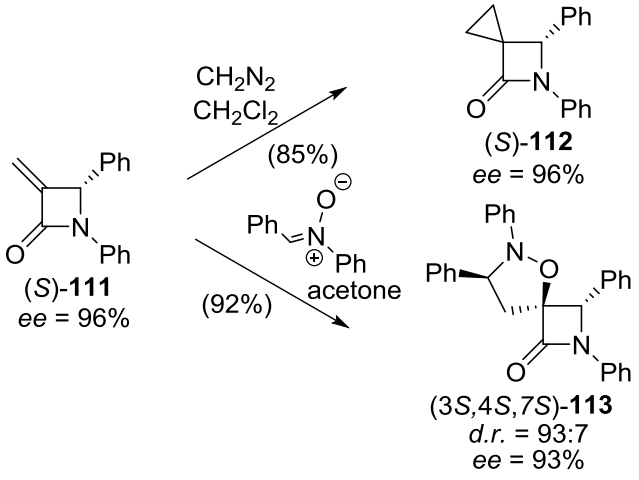
Scheme 31

Halocyclization of seleno- or thio-substituted β-lactams containing a carbon-carbon multiple bond concerns one of the pioneering methods for synthesis of halogenated 4-pyrazolyl spirocyclic-β-lactams.[79-81] Bhalla has recently reported on the synthesis of halogenated 4-pyrazolyl spirocyclic-β-lactams **107**-**110** *via* halogen-mediated intrasulfenyl cyclization of *cis*-3-propynyloxy-4-pyrazolyl-β-lactams **106** (Scheme 32). The effect of halogenating reagents and selectivity on the formation of the product has been carefully considered. These novel spiro-β-lactams **107**-**110** have been submitted for molecular docking studies and *in vitro* evaluation for biological activity.[80]



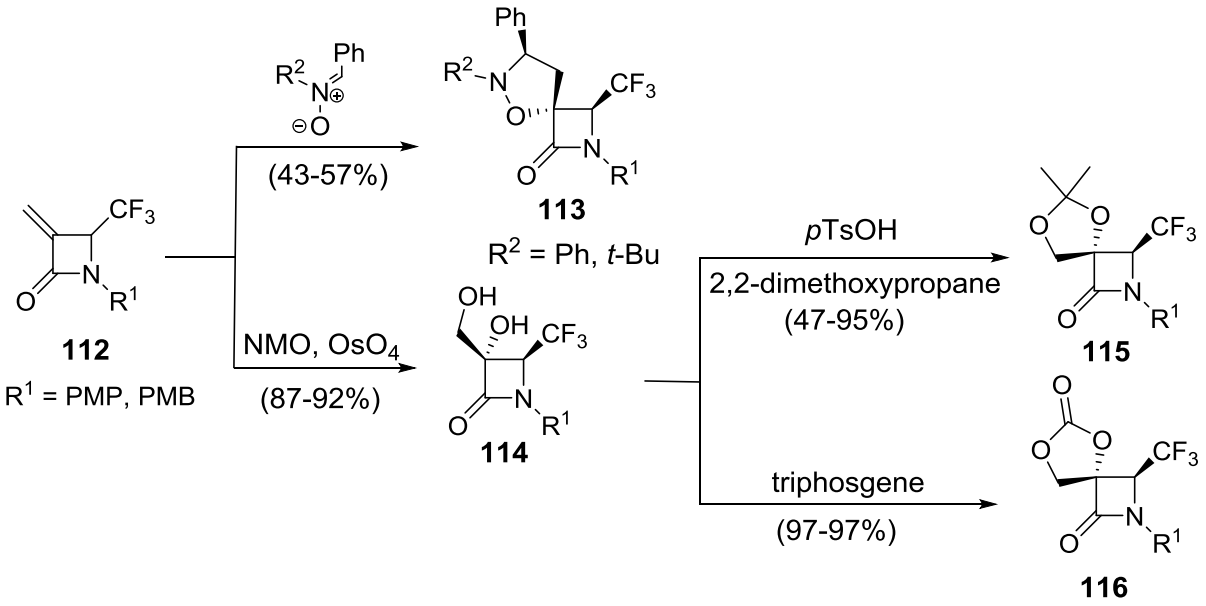
Scheme 32

The optically active α-methylene-β-lactam (*S*)-**111** has been subjected to cyclopropanation with CH_2N_2 in CH_2Cl_2 and [3+2]-cycloaddition with diphenylnitrone, giving rise to the corresponding cyclopropane derivative (*S*)-**112** in 85% yield and spiroisoxazolidine adduct (3*S*, 4*S*, 7*S*)-**113** in 92% yield, respectively (Scheme 33).[82]



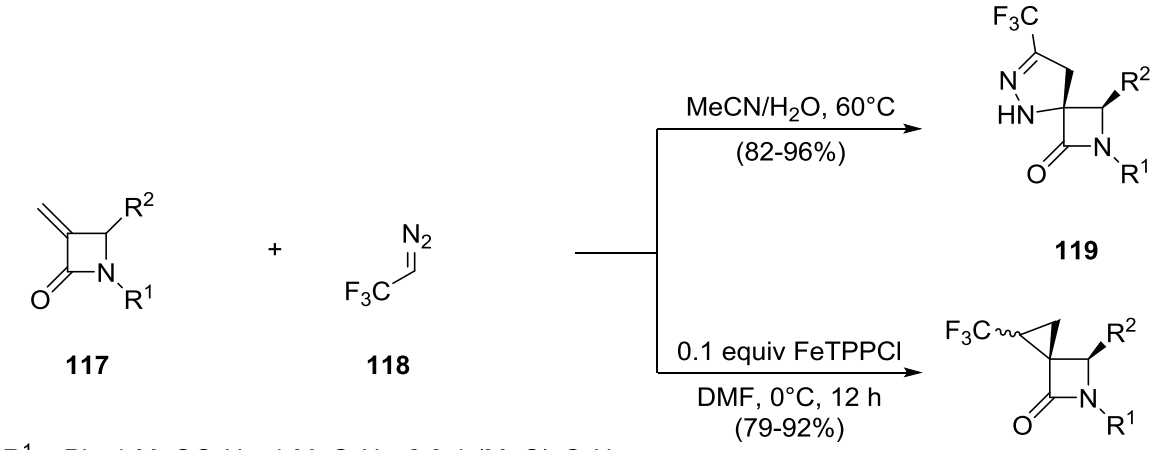
Scheme 33

Recently, the deployment of 3-methylene-4-(trifluoromethyl)azetidin-2-ones **112** as versatile building blocks allowed access to novel spiro-fused β-lactam systems. In particular, 1,3-dipolar nitrone-olefin cycloaddition of 3-methylene-β-lactams **112** with either *N*-phenyl- or *N*-*tert*-butyl-α-phenylnitrone gave 3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-ones **113** (Scheme 34). In addition, CF_3-substituted spirocycles **115** and **116** were prepared upon treatment of the corresponding diols **114**, derived from the OsO_4-mediated oxidation of 3-methylene-β-lactams **112**, with *p*TsOH in 2,2-dimethoxypropane and with triphosgene, respectively (Scheme 34).[83,84]



Scheme 34

Recently, Li and co-workers[85] have developed a facile access to a broad range of trifluoromethyl-containing spirocyclic β-lactams *via* cycloaddition of α-methylene-β-lactams **117** with CF_3CHN_2 **118**, which was generated *in situ* from 2,2,2-trifluoroethylamine hydrochloride and $NaNO_2$ (Scheme 35). Under metal-free conditions, [3+2]-cycloaddition of α-methylene-β-lactams **117** with CF_3CHN_2 led to 2-pyrazoline-containing spirocyclic β-lactams **119** as single diastereomers in good to high yields (82–96%). On the other hand, the use of an iron catalyst (FeTPPCl) gave rise to cyclopropane-containing spirocyclic β-lactams **120** with good diastereoselectivity. The resulting spirocyclic β-lactams bearing a CF_3 moiety are considered to be useful scaffolds for drug discovery and their further exploration in terms of biological activities.[85]



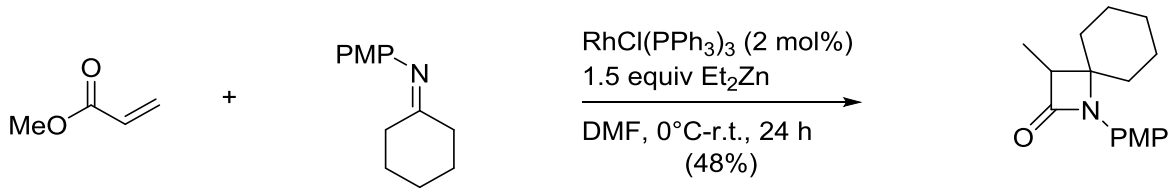
R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2,3,4-$(MeO)_3C_6H_2$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-ClC_6H_4

R^2 = Ph, 4-MeC_6H_4, 2-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-BrC_6H_4, 3-ClC_6H_4

Scheme 35

2.4. Other methods

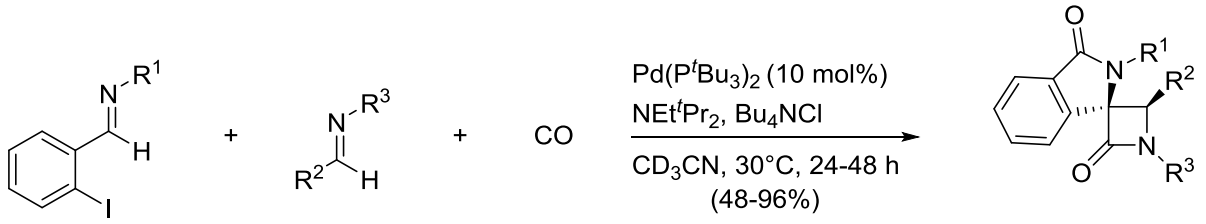
The reductive Mannich-type reaction of α,β-unsaturated ester **121** with imine **122** using a Rh catalyst and Et_2Zn provided a rapid access to spiro-β-lactam **123** (Scheme 36). A mechanism was proposed involving the formation of the rhodium−hydride complex (Rh-H) due to combination of Et_2Zn and $RhCl(PPh_3)_3$. Subsequently, this complex catalyzed the 1,4-reduction of α,β-unsaturated esters, resulting in a rhodium enolate as a Reformatsky-type reagent. In the end, this enolate reacted with imine **122**, giving rise to spiro-β-lactam **123**.[86] In addition, the Willcox group has described the synthesis of an analog of spiro-β-lactam **123** by an aliphatic amine C–H carbonylation process catalyzed by Pd.[87]



121 **122** **123**

Scheme 36

The Bruce group has recently published the synthesis of spirocyclic β-lactams **126** through a palladium-catalyzed multicomponent method, including participation of imines **125**, ortho-iodo-substituted aryl imines **124** and CO (Scheme 37). The structure of the resulting spirocyclic β-lactams, bearing a *trans* orientation of the aromatic units, was confirmed by NOE and X-ray analysis.[88]

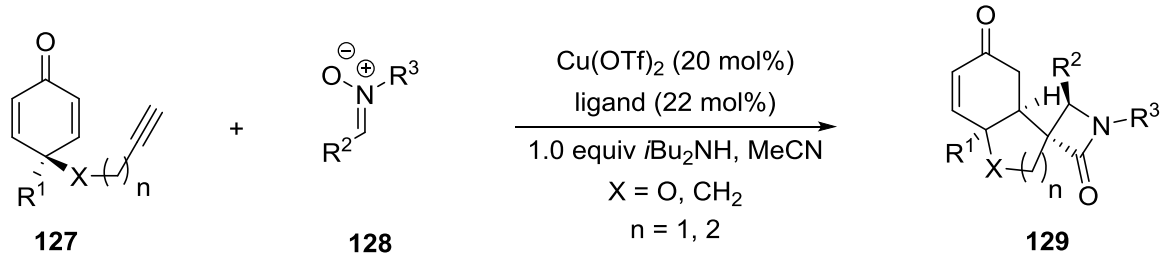


124 **125** **126**

R^1 = Bn, *i*Pr, C_6H_{13}
R^2 = 3-pyridinyl, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-FC_6H_4, PhCH=CH
R^3 = Et, Bn

Scheme 37

Recently, Enders and co-workers have investigated a novel approach utilizing a copper-catalyzed Kinugasa/Michael domino reaction of alkyne-tethered cyclohexadienones **127** and nitrones **128**, providing unprecedented spirocyclic β-lactams **129** in good yields with excellent stereoselectivities (Scheme 38).[89]



R^1 = CH_3, CH_3CH_2, Ph, *n*Pr, *n*Bu, *n*Pent, *n*Hex, OMe, 4-BrC_6H_4
R^2 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-BrC_6H_4, 4-MeC_6H_4, 2-furyl
R^3 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$

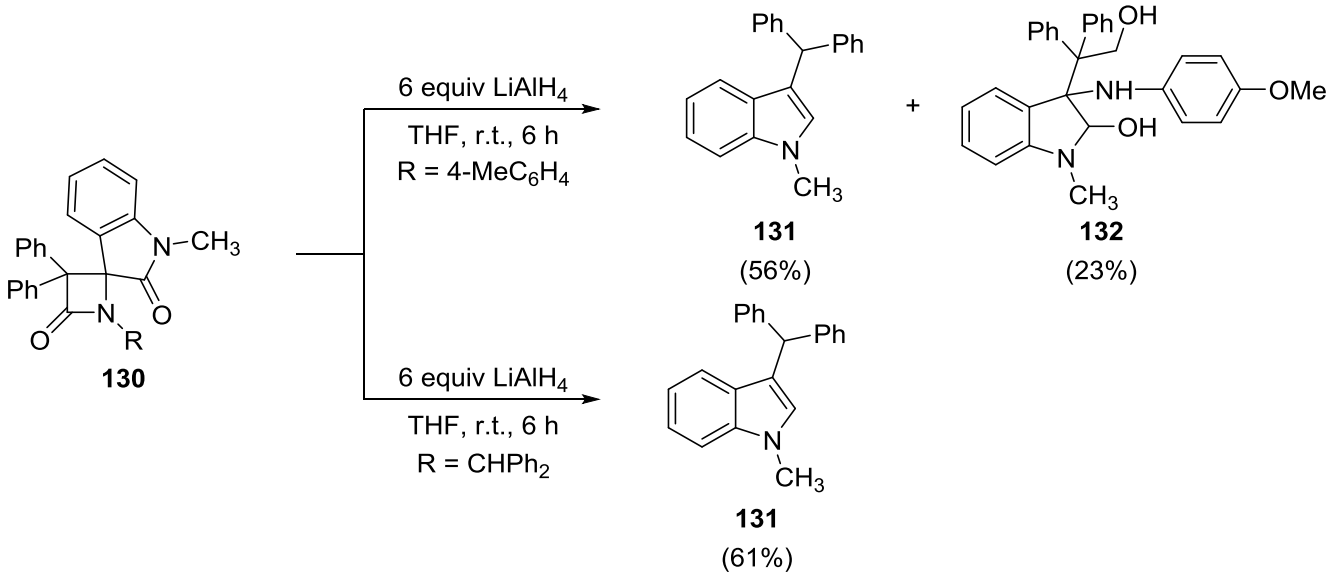
Scheme 38

3. Reactivity of Spiro-fused β-lactams

Along with efforts to improve synthetic methodologies, the deployment of spiro-fused β-lactams as interesting synthons to construct complex heterocycles has also been explored. The reactivity of spiro-fused β-lactams is related to the nature of these four-membered cyclic amides and the presence of substituents on the ring. In this section, the behavior of spiro-fused β-lactams toward ring-opening and ring-transformation reactions will be considered.

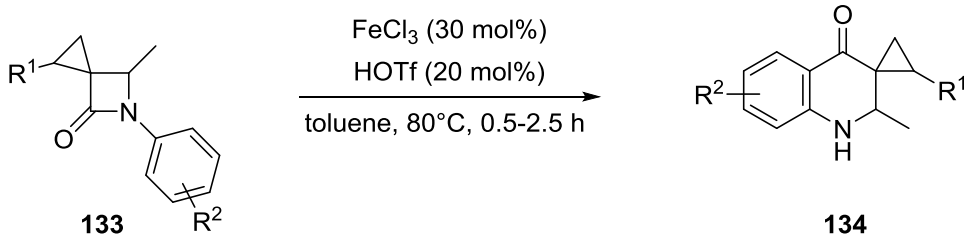
3.1. Ring-opening reactions

In general, spiro-fused azetidin-2-ones often suffer from ring-opening reactions upon treatment with various acids, bases, reducing reagents and oxidative reagents.[13] However, the treatment of 1-substituted spiro-fused β-lactams **130** with the reducing reagent $LiAlH_4$ resulted in the unanticipated 3-benzhydryl-1-methylindole **131** as the major product, accompanied by a small amount of the ring-opening product 3-(2-hydroxy-1,1-diphenylethyl)-3-(4-methoxyphenylamino)-1-methylindolin-2-ol **132** (Scheme 39). Furthermore, the cleavage of N1-C4 and C3-C4 bonds of azetidin-2-ones **130** has been investigated upon treatment with the oxidising reagent CAN.[90]



Scheme 39

The employment of a Lewis–Brønsted acid in combination with a superacid catalyst system promoted a regiospecific N1-C2 ring-opening reaction of *N*-aryl-3-spirocyclic-β-lactams **133** followed by a recyclization, providing an efficient entry to 3-spirocyclic quinolin-4(1*H*)-ones **134** in good to high yields (Scheme 40).[91]

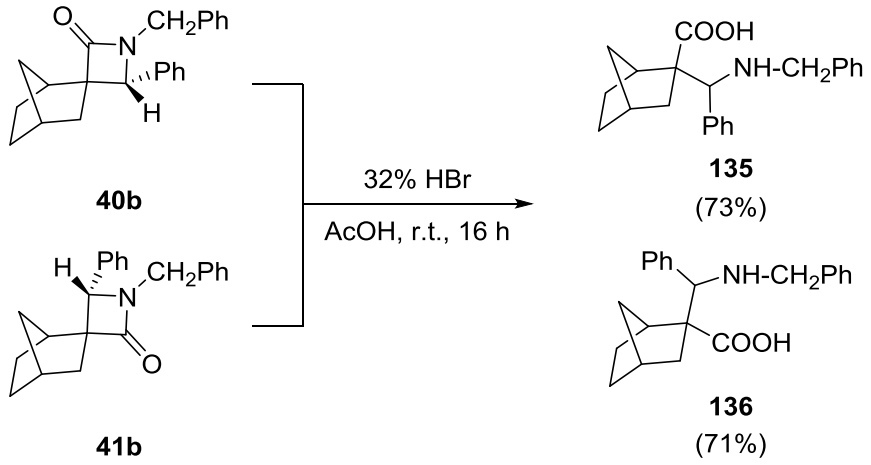


133 **134**

R^1 = H, R^2 = 2-MeO, 91%
R^1 = H, R^2 = 4-MeO, 88%
R^1 = H, R^2 = H, 92%
R^1 = H, R^2 = 2-Me, 89%
R^1 = H, R^2 = 4-Me, 90%
R^1 = H, R^2 = 2,4-diMe, 81%
R^1 = H, R^2 = 2-Cl, 87%
R^1 = H, R^2 = 1-naphthyl, 90%

Scheme 40

The norbornane-derived spiro-β-lactams **40-41b** have been subjected to acid hydrolysis (HBr), giving rise to the corresponding norbornane-derived β-amino acids **135** and **136** (Scheme 41).[45]



40b

135
(73%)

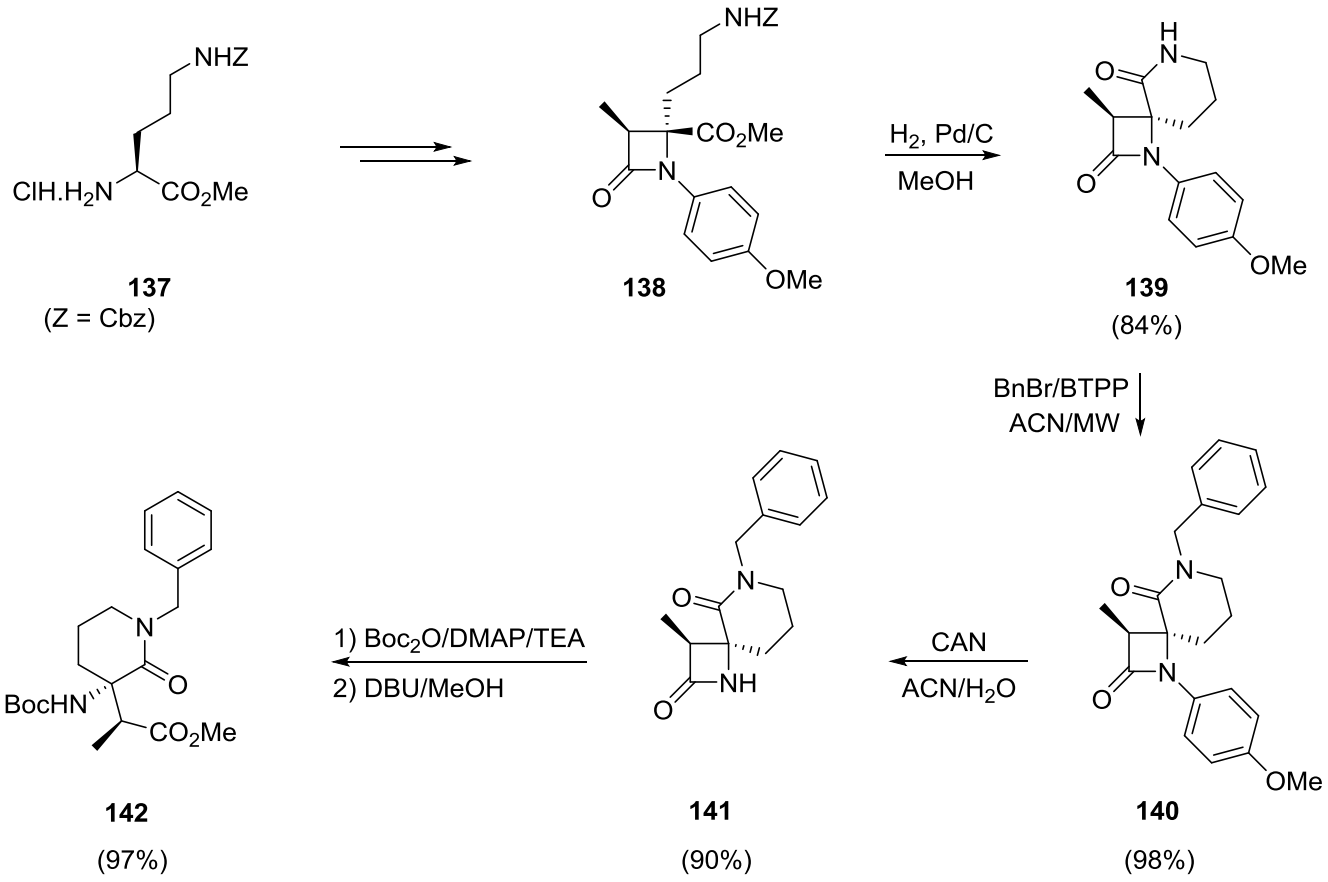
41b

136
(71%)

Scheme 41

The activation of spiro-β-lactam **141** with di-*tert*-butyl dicarbonate and subsequent intermolecular nucleophilic ring opening upon treatment with DBU/MeOH afforded 2-oxopiperidino-β-amino ester **142** in excellent yield (Scheme 42). The preparation of spiro-β-lactam **141** was performed starting from β-lactam **138**, which was synthesized from ornithine derivative **137** *via* a three-step procedure. Accordingly, the removal of the Z protecting group from **138** by catalytic hydrogenation resulted in the formation of the 3,5-spiro-derivative **139** in good yield, through a 6-*exo*-*trig* ring closure. The resulting spiro-β-lactam **139** reacted with benzyl bromide, furnishing the 1-benzyl derivative **140** in an almost quantitative yield. Treatment of

compound **140** with CAN led to the removal of the *p*-methoxyphenyl group, yielding the *N*-deprotected spiro-β-lactam **141**.[92]

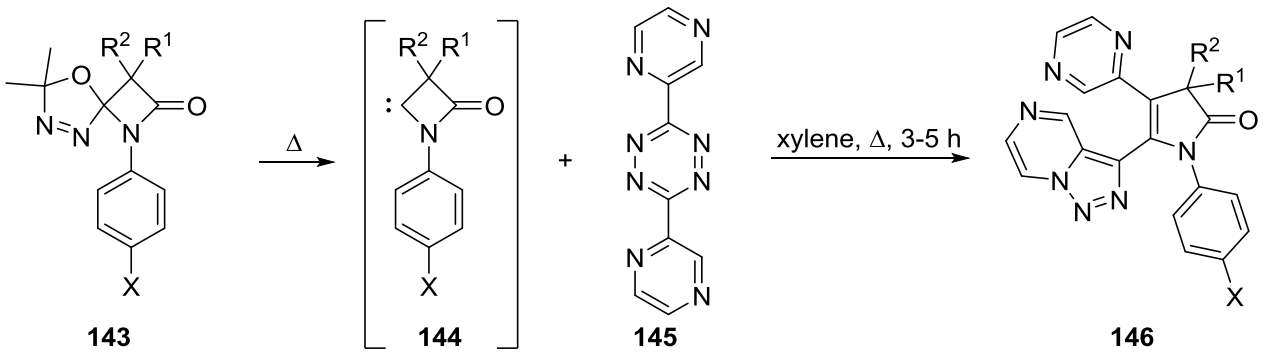


Scheme 42

Also relevant to this section is the fact that, during the course of preparing nylon-3 materials bearing diverse appended functionalities, Gellman and co-workers have recently reported the ring-opening polymerization of spiro-β-lactams generating nylon-3 homo- or co-polymers.[93]

3.2. Ring-transformation reactions of substituents attached to the ring carbon atoms

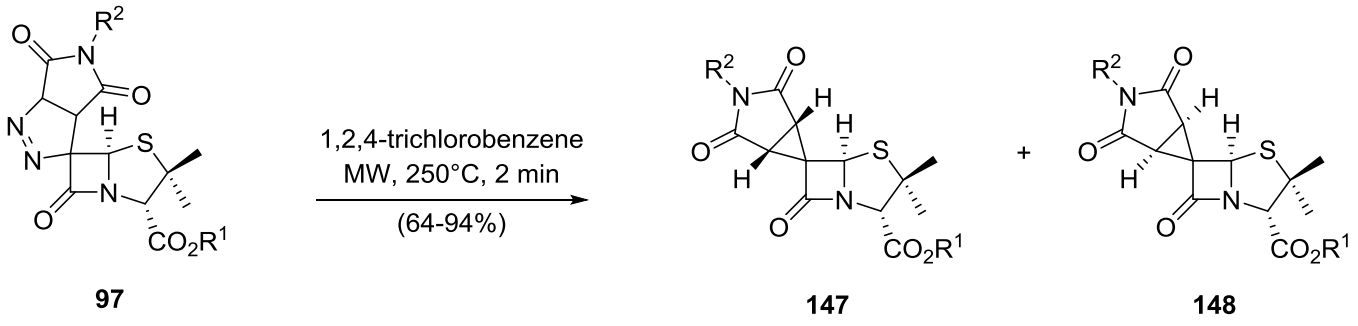
Thermolysis of spiro-β-lactam-oxadiazolines **143** to generate β-lactam carbenes **144** has attracted the attention of several research groups because of the important synthetic applications of the resulting carbenes for the construction of novel mono-, spiro- or polyheterocyclic compounds.[94] For example, the reaction of β-lactam carbenes **144** with 3,6-diphenyl-, 3,6-di(2-pyridyl)-, 3,6-di(2-thienyl)-, 3,6-di(4-pyridyl)-1,2,4,5-tetrazines and 3,6-di-(2-pyrimidinyl)tetrazines readily afforded various aryl-fused cyclopenta[*b*]pyrrol-2-one derivatives in high yields.[32,95-99] Recently, Wang has reported on the use of β-lactam carbenes **144** to produce a novel series of 5-triazolo[1,5-*a*]pyrazinepyrrol-2-ones **146** in a one-pot mechanism (Scheme 43). These 5-triazolo compounds can emit light both in solution and in a solid state, with emission peaks at 77K and in solid state, showing an obvious blue-shift.[94]



X = H, CH_3, OCH_3, Cl, Br
R^1 = CH_3, C_2H_5, -$(CH_2)_5$-
R^2 = CH_3, C_2H_5, -$(CH_2)_5$-

Scheme 43

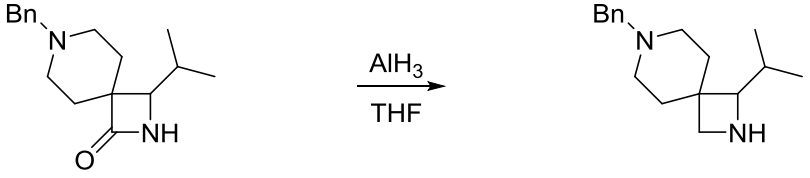
The ring contraction of spiro-1-pyrazoline-β-lactams **97** *via* microwave-induced denitrogenation gave rise to a mixture of spirocyclopropylpenicillanates **147** and **148** (Scheme 44).[74,75]



R^1 = $CHPh_2$, R^2 = Ph, **147**:**148** = 77:23
R^1 = $CHPh_2$, R^2 = CH_3, **147**:**148** = 72:28

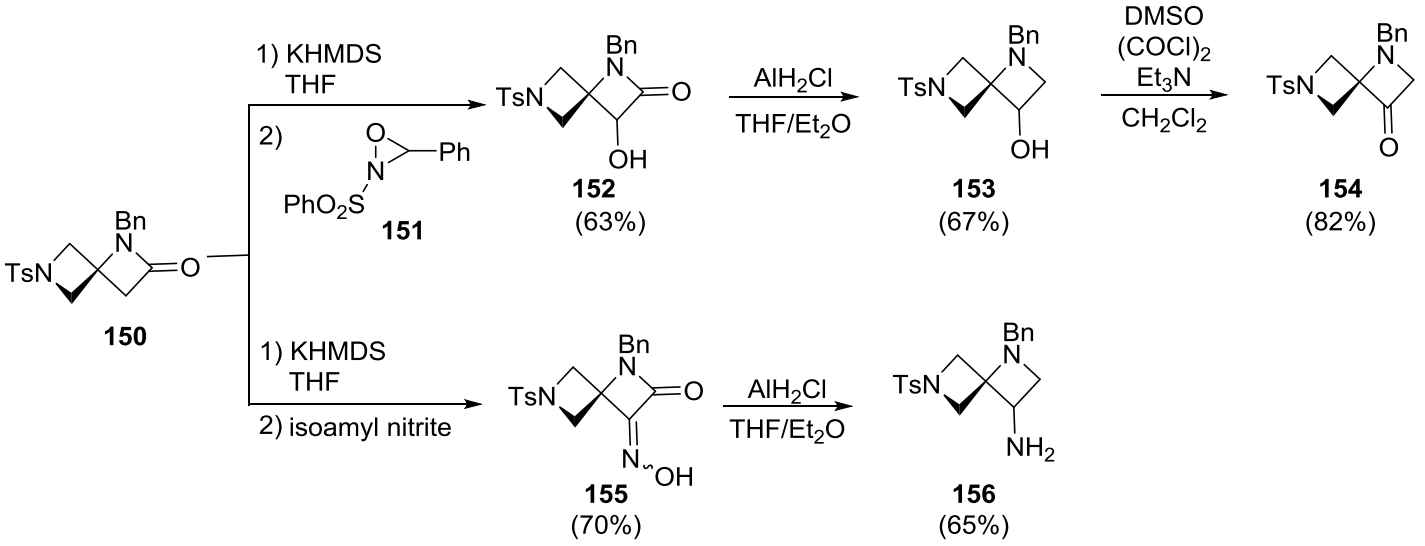
Scheme 44

The reduction of spiro-β-lactams by different reducing reagents (AlH_3, $AlClH_2$, $LiAlH_4$ …) comprises one of the most convenient methodologies to generate the corresponding spirocyclic azetidines, which have been applied in drug design.[46,48,56] For instance, the reduction of the amide group in compound **51** with AlH_3 afforded spirocyclic azetidine **149** in 92% yield (Scheme 45), which can indeed be seen as a promising building block for the preparation of complex molecules.[48] Careful monitoring of the reaction is usually required to avoid reductive β-lactam ring opening.



Scheme 45

Furthermore, spiro-β-lactam **150** has been subjected to enolization using KHMDS in THF, and subsequent treatment of the enolate with Davis oxaziridine **151** or isoamyl nitrite led to the corresponding α-hydroxy lactam **152** or oxime **155** in high yields, respectively (Scheme 46). Then, the β-lactams **152** and **155** were successfully reduced using monochloroalane to give spirocyclic azetidines **153** and **156**, respectively. The azetidin-3-ol **153** was further converted to the corresponding ketone **154** under Swern oxidation conditions.[100]



Scheme 46

4. Bioactive Spiro-fused β-lactams

Spiro-β-lactams constitute an interesting class of bioactive compounds possessing a wide spectrum of activities, such as antibacterial, antiviral and antimicrobial effects. In addition, the use of spiro-β-lactams as β-lactamase and cholesterol absorption inhibitors or synthetic intermediates for β-turn mimics and β-turn nucleators, has been documented.[11-13,74,101] In this section, a brief selection of renewed pharmacological applications of spiro-β-lactam systems will be considered.

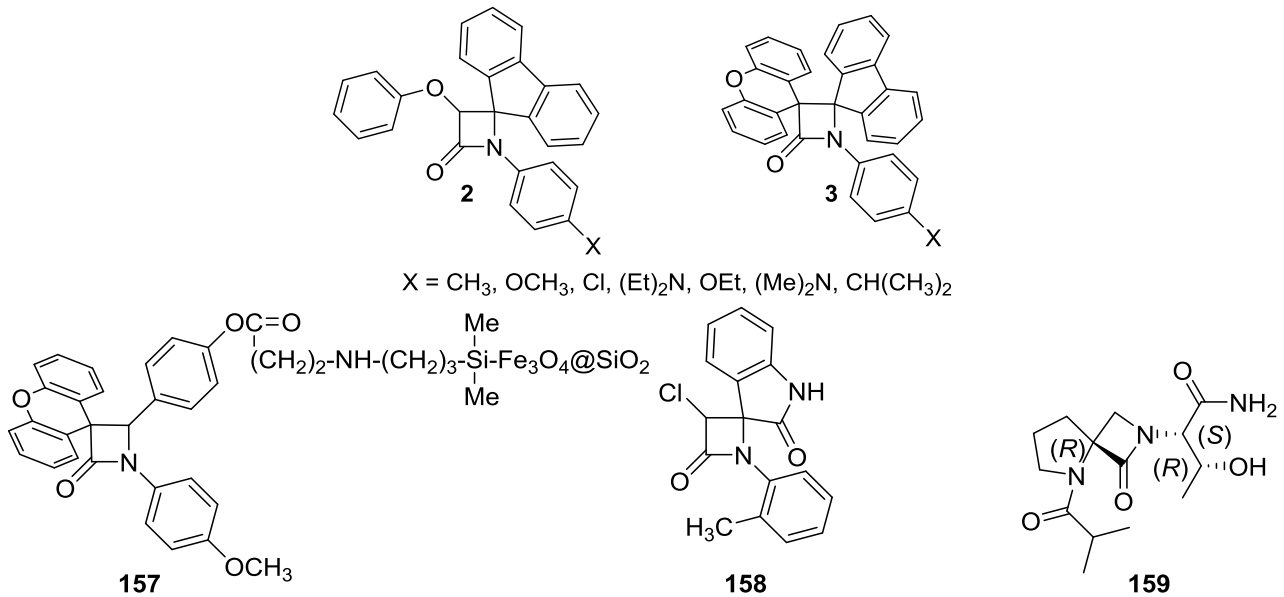


Figure 2. Bioactive spiro-fused β-lactams.

The new spiro-β-lactams **2** and dispiro-β-lactams **3** have been demonstrated to exhibit good to excellent antimalarial activities against chloroquine-resistant *Plasmodium falciparum* K14 strain with IC_{50} varying from 5 to 32.2 mM.[14] The spirocyclic β-lactam **157** (Figure 2), supported on superparamagnetic Fe_3O_4@SiO_2 nano-particles, enhanced the antibacterial activity in comparison with the corresponding spirocyclic β-lactam, which was supposed to be due to the synergic effect of the Fe_3O_4@SiO_2/β-lactam combination.[102,103]

A number of novel spiro[azetidine-2,3'-indole]-2',4(1'*H*)-dione derivatives have been tested for anti-breast cancer activity, however, only 3-chloro-1-(*o*-tolyl)spiro[azetidine-2,3'-indoline]-2',4-dione **158** (Figure 2) displayed a significant cytotoxicity (IC_{50} = 22.75-25.18 μM) for breast cancer cell lines after 48 h, which is comparable to the standard control drug doxorubicin.[104]

Recently, ((2*S*,3*R*)-3-hydroxy-2-((*R*)-5-isobutyryl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)butanamide) **159** (Figure 2) has been examined for *in vitro* and *in vivo* pharmalogical properties. This compound appeared to be a novel *N*-methyl-D-aspartate (NMDA) receptor-specific modulator that facilitates synaptic plasticity and has therapeutic potential for a variety of NMDA receptor-mediated central nervous system (CNS) disorders.[105,106]

5. Conclusions

In conclusion, the potential pharmacological activities, along with significant synthetic applications of spirocyclic β-lactams, have given a fresh impetus to synthetic chemists to design novel spiro-β-lactam structures. Synthetic approaches toward spirocyclic β-lactams, including the Staudinger ketene-imine cyclocondensation, the cyclization of β-amino acids and β-functionalised amides and transformation reactions, have been improved in recent years (*e.g.*, increase yield and stereoselectivity of reactions as well as the use of greener reaction conditions) and have been intensively discussed in this review. In view of their interesting chemical and biological properties, spirocyclic β-lactams are expected to attract considerable attention in the future as well.

Acknowledgements

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References

1 Kumar, Y.; Singh, P.; Bhargava, G. *RSC Adv.* **2016**, *6*, 99220. https://doi.org/10.1039/C6RA20973D
2 Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437. https://doi.org/10.1021/cr0307300
3 Ojima, I. *J. Org. Chem.* **2013**, *78*, 6358. https://doi.org/10.1021/jo400301u
4 Singh, G. S.; Sudheesh, S. *Arkivoc* **2014**, (*i*), 337. http://dx.doi.org/10.3998/ark.5550190.p009.524
5 Bhalla, A.; Bari, S. S.; Bhalla, J. In *Beta-Lactams: Novel Synthetic Pathways and Applications*; Banik, B. K. Ed.; Springer International Publishing: Cham, Switzerland, 2017; p 1.
6 Pitts, C. R.; Lectka, T. *Chem. Rev.* **2014**, *114*, 7930. https://doi.org/10.1021/cr4005549

7 Docquier, J.-D.; Mangani, S. *Drug Resist. Updat.* **2018**, *36*, 13. https://doi.org/10.1016/j.drup.2017.11.002

8 Van den Akker, F.; Bonomo, R. A. *Front Microbiol* **2018**, *9*.

9 Vardakas, K. Z.; Kalimeris, G. D.; Triarides, N. A.; Falagas, M. E. *Expert Opin. Drug Saf.* **2018**, *17*, 499. https://doi.org/10.1080/14740338.2018.1462334

10 Abdellaoui, H.; Xu, J. *Tetrahedron* **2014**, *70*, 4323. https://doi.org/10.1016/j.tet.2014.05.008

11 Alcaide, B.; Almendros, P. In *Heterocyclic Scaffolds I: ß-Lactams*; Banik, B. K. Eds.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2010; p 1.

12 Bari, S. S.; Bhalla, A. In *Heterocyclic Scaffolds I: ß-Lactams*; Banik, B. K. Eds.; Springer: Berlin, Heidelberg, 2010; p 49. https://doi.org/10.1007/7081_2009_8

13 Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2011**, *67*, 1989. https://doi.org/10.1016/j.tet.2011.01.013

14 Jarrahpour, A.; Ebrahimi, E.; De Clercq, E.; Sinou, V.; Latour, C.; Djouhri Bouktab, L.; Brunel, J. M. *Tetrahedron* **2011**, *67*, 8699. https://doi.org/10.1016/j.tet.2011.09.041

15 Zarei, M.; Jarrahpour, A.; Ebrahimi, E.; Aye, M.; Torabi Badrabady, S. A. *Tetrahedron* **2012**, *68*, 5505. https://doi.org/10.1016/j.tet.2012.04.088

16 Ameri Rad, J.; Jarrahpour, A.; Ersanlı, C. C.; Atioğlu, Z.; Akkurt, M.; Turos, E. *Tetrahedron* **2017**, *73*, 1135. https://doi.org/10.1016/j.tet.2017.01.009

17 Elkanzi, N. A. A. *Int. J. Org. Chem.* **2012**, *2*, 352. https://doi.org/10.4236/ijoc.2012.24048

18 Renuka, J.; Kanti, S.; Deepak, K. *J. Heterocycl. Chem.* **2013**, *50*, 315. https://doi.org/10.1002/jhet.1071

19 Zhang, H.-M.; Gao, Z.-H.; Ye, S. *Org. Lett.* **2014**, *16*, 3079. https://doi.org/10.1021/ol501205v

20 Rainoldi, G.; Faltracco, M.; Lo Presti, L.; Silvani, A.; Lesma, G. *Chem. Commun.* **2016**, *52*, 11575. https://doi.org/10.1039/C6CC05838H

21 Shah, R. J.; Modi, N. R.; Patel, M. J.; Patel, L. J.; Chauhan, B. F.; Patel, M. M. *Med. Chem. Res.* **2011**, *20*, 587. https://doi.org/10.1007/s00044-010-9354-x

22 Subba Reddy, B. V.; Karthik, G.; Rajasekaran, T.; Antony, A.; Sridhar, B. *Tetrahedron Lett.* **2012**, *53*, 2396. https://doi.org/10.1016/j.tetlet.2012.02.106

23 Kandile, N. G.; Mohamed, M. I.; Ismaeel, H. M. *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 119. https://doi.org/10.1080/14756366.2016.1238365

24 Xu, J.; Yuan, S.; Peng, J.; Miao, M.; Chen, Z.; Ren, H. *Chem. Commun.* **2017**, *53*, 3430. https://doi.org/10.1039/C7CC01232B

25 Toyoda, Y.; Ninomiya, M.; Ebihara, M.; Koketsu, M. *Org. Biomol. Chem.* **2013**, *11*, 2652. https://doi.org/10.1039/c3ob00073g

26 Lauro, F.-V.; Francisco, D.-C.; Elodia, G.-C.; Eduardo, P.-G.; Maria, L.-R.; Marcela, R.-N.; Lenin, H.-H.; Bety, S.-A. *Steroids* **2015**, *93*, 8. https://doi.org/10.1016/j.steroids.2014.09.003

27 Soleiman, H. A.; Khalafallah, A. K.; Abd-Ellatif, H. a. *Eur. J. Chem.* **2012**, *3*, 287.

https://doi.org/10.5155/eurjchem.3.3.287-292.611
28 Anand, N.; Shah, B. A.; Kapoor, M.; Parshad, R.; Sharma, R. L.; Hundal, M. S.; Pannu, A. P. S.; Bharatam, P. V.; Taneja, S. C. *J. Org. Chem.* **2011**, *76*, 5999. https://doi.org/10.1021/jo200363x
29 Song, J.-H.; Kwon, Y.-G.; Lee, H.-O.; Jung, D.-I.; Hahn, J.-T. *J. Korean Chem. Soc.* **2014**, *35*, 3651.
30 Reddy, D. R. S.; Risy, N. J. *Pharma Chemica* **2013**, *5*, 235.
31 Ali Ahmed Elkanzi, N.; Abdallah Abd El-Monem Yosef, H.; Mahmoud Morsy Mohamed, N. *Eur. J. Chem.* **2013**, *4*, 195. https://doi.org/10.5155/eurjchem.4.3.195-202.777
32 Li, Y.-J.; Yan, C.-X.; Sun, Z.-X.; Cheng, Y. *Aust. J. Chem.* **2012**, *65*, 417. https://doi.org/10.1071/CH12046
33 Allen, A. D.; Tidwell, T. T. *Chem. Rev.* **2013**, *113*, 7287. https://doi.org/10.1021/cr3005263
34 Singh, P.; Samanta, K.; Das, S. K.; Panda, G. *Org. Biomol. Chem.* **2014**, *12*, 6297. https://doi.org/10.1039/C4OB00943F
35 Heravi, M. M.; Talaei, B. In *Advances in Heterocyclic Chemistry*; Scriven, E. F. V., Ramsden, C. A. Eds.; Academic Press: Oxford, 2015; *114*, p 147.
36 Zavar, S.; Zarei, M.; Saraei, M. *Synth. Commun.* **2016**, *46*, 2031. https://doi.org/10.1080/00397911.2016.1244691
37 Zarei, M. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 360. https://doi.org/10.1246/bcsj.20110323
38 Zarei, M. *Tetrahedron* **2013**, *69*, 6620. https://doi.org/10.1016/j.tet.2013.05.121
39 Zarei, M. *Monatsh. Chem.* **2014**, *145*, 1495. https://doi.org/10.1007/s00706-014-1217-6
40 Zarei, M.; Salehinezhad, A. *J. Chem. Res.* **2015**, *39*, 698. https://doi.org/10.3184/174751915X14473416848163
41 Esmaeilpour, M.; Sardarian, A. R.; Jarrahpour, A.; Ebrahimi, E.; Javidi, J. *RSC Adv.* **2016**, *6*, 43376. https://doi.org/10.1039/C6RA03634A
42 Zarei, M.; Maaqooli, F. *Synth. Commun.* **2016**, *46*, 523. https://doi.org/10.1080/00397911.2016.1148165
43 Zavar, S.; Zarei, M.; Saraei, M. *J. Chem. Res.* **2016**, *40*, 532. https://doi.org/10.3184/174751916X14683354026584
44 Çelik, Í.; Akkurt, M.; Jarrahpour, A.; Heiran, R.; Özdemir, N. *Acta Cryst. E* **2014**, *70*, 369. https://doi.org/10.1107/S160053681400419X
45 Cremonesi, G.; Dalla Croce, P.; Forni, A.; La Rosa, C. *Tetrahedron* **2013**, *69*, 1175. https://doi.org/10.1016/j.tet.2012.11.048
46 Karlsson, S.; Bergman, R.; Löfberg, C.; Moore, P. R.; Pontén, F.; Tholander, J.; Sörensen, H. *Org. Process Res. Dev.* **2015**, *19*, 2067. https://doi.org/10.1021/acs.oprd.5b00319
47 Kirichok, A. A.; Shton, I.; Kliachyna, M.; Pishel, I.; Mykhailiuk, P. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 8865. https://doi.org/10.1002/anie.201703801
48 Kirichok, A. A.; Shton, I. O.; Pishel, I. M.; Zozulya, S. A.; Borysko, P. O.; Kubyshkin, V.; Zaporozhets, O. A.; Tolmachev, A. A.; Mykhailiuk, P. K. *Chem. Eur. J.* **2018**, *24*, 5444.

https://doi.org/10.1002/chem.201800193
49 Liang, J.; Chen, J.; Du, F.; Zeng, X.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 2820. https://doi.org/10.1021/ol901005x
50 Xu, Z.; Huang, K.; Liu, T.; Xie, M.; Zhang, H. *Chem. Commun.* **2011**, *47*, 4923. https://doi.org/10.1039/c1cc10916b
51 Xu, Z.-X.; Tan, Y.-X.; Fu, H.-R.; Liu, J.; Zhang, J. *Inorg. Chem.* **2014**, *53*, 12199. https://doi.org/10.1021/ic501849g
52 Núñez-Villanueva, D.; Bonache, M. Á.; Infantes, L.; García-López, M. T.; Martín-Martínez, M.; González-Muñiz, R. *J. Org. Chem.* **2011**, *76*, 6592.
53 Guideri, L.; Noschese, R.; Ponticelli, F. *J. Heterocycl. Chem.* **2012**, *49*, 297. https://doi.org/10.1002/jhet.823
54 Sharada, L. N.; Reddy, G. S. S.; Sammaiah, B.; Sumalatha, D. *Organic Chemistry: An Indian Journal* **2014**, *10*, 127.
55 McMaster, C.; Bream, R. N.; Grainger, R. S. *Org. Biomol. Chem.* **2012**, *10*, 4752. https://doi.org/10.1039/c2ob25434d
56 Bondada, L.; Rondla, R.; Pradere, U.; Liu, P.; Li, C.; Bobeck, D.; McBrayer, T.; Tharnish, P.; Courcambeck, J.; Halfon, P.; Whitaker, T.; Amblard, F.; Coats, S. J.; Schinazi, R. F. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6325. https://doi.org/10.1016/j.bmcl.2013.09.068
57 Nakazaki, A.; Hara, Y.; Kajii, S.; Nishikawa, T. *Heterocycles* **2013**, *87*, 611. https://doi.org/10.3987/COM-12-12657
58 Wu, X.-S.; Zhao, Y.; Zhang, G.-W.; Ge, H.-B., *Angew. Chem. Int. Ed. Engl.* **2014**, *126*, 3780. https://doi.org/10.1002/ange.201311263
59 Wu, X.-S.; Zhao, Y.; Ge, H.-B., *Chem. Eur. J.* **2014**, *20*, 9530. https://doi.org/10.1002/chem.201403356
60 Zhen, W.; Ni, J.-Z.; Yoichiro, K.; Motomu, K. *Angew. Chem. Int. Ed.* **2014**, *53*, 3496. https://doi.org/10.1002/anie.201311105
61 Wang, C.; Yang, Y.; Qin, D.; He, Z.; You, J. *J. Org. Chem.* **2015**, *80*, 8424. https://doi.org/10.1021/acs.joc.5b01302
62 Wu, X.; Yang, K.; Zhao, Y.; Sun, H.; Li, G.; Ge, H. *Nat. Commun.* **2015**, *6*, 6462. https://doi.org/10.1038/ncomms7462
63 Aihara, Y.; Chatani, N. *ACS Catal.* **2016**, *6*, 4323. https://doi.org/10.1021/acscatal.6b00964
64 Gomes F. R., L.; Veiros F., L.; Maulide, N.; Afonso A. M., C. *Chem. Eur. J.* **2015**, *21*, 1449. https://doi.org/10.1002/chem.201404990
65 Kumarasamy, E.; Ayitou, A. J.-L.; Vallavoju, N.; Raghunathan, R.; Iyer, A.; Clay, A.; Kandappa, S. K.; Sivaguru, J. *Acc. Chem. Res.* **2016**, *49*, 2713. https://doi.org/10.1021/acs.accounts.6b00357
66 Nandini, V.; Avadakkam, S.; J.-L., A. A.; Steffen, J.; B., S. R.; Jayaraman, S. *Chem. Eur. J.* **2016**, *22*, 11339.
67 Zhu, L.; Xiong, Y.; Li, C. *J. Org. Chem.* **2015**, *80*, 628. https://doi.org/10.1021/jo502265a
68 Cai, S.; Yang, K.; Wang, D. Z. *Org. Lett.* **2014**, *16*, 2606. https://doi.org/10.1021/ol501071k
69 Baudoin, O. *Acc. Chem. Res.* **2017**, *50*, 1114.

https://doi.org/10.1021/acs.accounts.7b00099
70 He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754. https://doi.org/10.1021/acs.chemrev.6b00622
71 David, D.; Ronan, R.; Olivier, B. *Angew. Chem. Int. Ed.* **2017**, *56*, 7218. https://doi.org/10.1002/anie.201703109
72 Alcaide, B.; Almendros, P.; Luna, A.; Gómez-Campillos, G.; Torres, M. R. *J. Org. Chem.* **2012**, *77*, 3549. https://doi.org/10.1021/jo202495z
73 Alcaide, B.; Almendros, P.; Aragoncillo, C.; Callejo, R.; Ruiz, M. P.; Torres, M. R. *J. Org. Chem.* **2012**, *77*, 6917. https://doi.org/10.1021/jo301113g
74 Santos, B. S.; Nunes, S. C. C.; Pais, A. A. C. C.; Pinho e Melo, T. M. V. D. *Tetrahedron* **2012**, *68*, 3729. https://doi.org/10.1016/j.tet.2012.03.022
75 Santos, B. S.; Gomes, C. S. B.; Pinho e Melo, T. M. V. D. *Tetrahedron* **2014**, *70*, 3812. https://doi.org/10.1016/j.tet.2014.03.109
76 Aman, B.; Paloth, V.; Bari, S. S. *Eur. J. Org. Chem.* **2006**, *2006*, 4943.
77 Bhalla, A.; Venugopalan, P.; Bhasin, K. K.; Bari, S. S. *Tetrahedron* **2007**, *63*, 3195. https://doi.org/10.1016/j.tet.2007.02.001
78 Moody, C. L.; Franckevičius, V.; Drouhin, P.; Klein, J. E. M. N.; Taylor, R. J. K. *Tetrahedron Lett.* **2012**, *53*, 1897. https://doi.org/10.1016/j.tetlet.2012.01.120
79 Reshma; Arora, R.; Hundal, G.; Bhalla, A.; Bari, S. S. *J. Chem. Sci.* **2015**, *127*, 1957.
80 Bhalla, A.; Bari, S. S.; Bhalla, J.; Khullar, S.; Mandal, S. *Tetrahedron Lett.* **2016**, *57*, 2822. https://doi.org/10.1016/j.tetlet.2016.05.047
81 Narula, D.; Bari, S. S.; Banik, B. K.; Bhalla, A. *Asian J Chem* **2017**, *29*, 2582. https://doi.org/10.14233/ajchem.2017.20673
82 Wang, X.-M.; Meng, F.-Y.; Yan, W.; Han, Z.-B.; Chen, Y.-J.; Liu, L.; Wang, Z.; Ding, K.L. *Angew. Chem. Int. Ed.* **2012**, *51*, 9276. https://doi.org/10.1002/anie.201204925
83 Dao Thi, H.; Danneels, B.; Desmet, T.; Van Hecke, K.; Van Nguyen, T.; D'hooghe, M. *Asian J. Org. Chem.* **2016**, *5*, 1480. https://doi.org/10.1002/ajoc.201600387
84 Dao Thi, H.; Van Nguyen, T.; D'hooghe, M. *Monatsh. Chem.* **2018**, *149*, 687. https://doi.org/10.1007/s00706-017-2134-2
85 Li, S.; Cao, W.-J.; Ma, J.-A. *Synlett* **2017**, *28*, 673.
86 Isoda, M.; Sato, K.; Funakoshi, M.; Omura, K.; Tarui, A.; Omote, M.; Ando, A. *J. Org. Chem.* **2015**, *80*, 8398. https://doi.org/10.1021/acs.joc.5b01233
87 Willcox, D.; Chappell, B. G. N.; Hogg, K. F.; Calleja, J.; Smalley, A. P.; Gaunt, M. J. *Science* **2016**, *354*, 851. https://doi.org/10.1126/science.aaf9621
88 Torres, G. M.; De La Higuera Macias, M.; Quesnel, J. S.; Williams, O. P.; Yempally, V.; Bengali, A. A.; Arndtsen, B. A. *J. Org. Chem.* **2016**, *81*, 12106. https://doi.org/10.1021/acs.joc.6b02405
89 Shu, T.; Zhao, L.; Li, S.; Chen, X.-Y.; von Essen, C.; Rissanen, K.; Enders, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 10985.

https://doi.org/10.1002/anie.201806931
90 Singh, G. S.; Luntha, P. M. *J. Heterocycl. Chem.* **2011**, *48*, 1312. https://doi.org/10.1002/jhet.731
91 Hu, Y.; Fu, X.; Barry, B.-D.; Bi, X.; Dong, D. *Chem. Commun.* **2012**, *48*, 690. https://doi.org/10.1039/C1CC15881C
92 Nunez-Villanueva, D.; Garcia-Lopez, M. T.; Martin-Martinez, M.; Gonzalez-Muniz, R. *Org. Biomol. Chem.* **2015**, *13*, 5195. https://doi.org/10.1039/C5OB00429B
93 Zhang, J.; Markiewicz, M. J.; Weisblum, B.; Stahl, S. S.; Gellman, S. H. *ACS Macro Lett.* **2012**, *1*, 714. https://doi.org/10.1021/mz300172y
94 Miao, X.; Yingkai, S.; Yan, Z.; Sanxiao, Z.; Jie, J.; Xiaorong, W. *ChemistrySelect* **2017**, *2*, 1370. https://doi.org/10.1002/slct.201601503
95 Shao, N.; Pang, G.-X.; Yan, C.-X.; Shi, G.-F.; Cheng, Y. *J. Org. Chem.* **2011**, *76*, 7458. https://doi.org/10.1021/jo201273p
96 Xing, J.; Wang, X.-R.; Yan, C.-X.; Cheng, Y. *J. Org. Chem.* **2011**, *76*, 4746. https://doi.org/10.1021/jo200499u
97 Wang, X.-R.; Xing, J.; Yan, C.-X.; Cheng, Y. *Org. Biomol. Chem.* **2012**, *10*, 970. https://doi.org/10.1039/C1OB06595E
98 Yan, C.-X.; Zhao, Y.; Wang, X.-R.; Cheng, Y. *Tetrahedron* **2013**, *69*, 10279. https://doi.org/10.1016/j.tet.2013.10.034
99 Yao, X.; Wang, X. *Arkivoc* **2016**, (*iii*), 352. http://dx.doi.org/10.3998/ark.5550190.p009.524
100 Burkhard, J. A.; Guérot, C.; Knust, H.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 66. https://doi.org/10.1021/ol2028459
101 Bhattacharya, B.; Turos, E. *Tetrahedron* **2012**, *68*, 10665. https://doi.org/10.1016/j.tet.2012.06.012
102 Esmaeilpour, M.; Sardarian, A. R.; Jarrahpour, A.; Ebrahimi, E.; Javidi, J. *RSC Advances* **2016**, *6*, 43376. https://doi.org/10.1039/C6RA03634A
103 Bhalla, A.; Modi, G.; Bari, S. S.; Kumari, A.; Berry, S.; Hundal, G. *Tetrahedron Lett.* **2017**, *58*, 1160. https://doi.org/10.1016/j.tetlet.2017.02.011
104 Sukhramani, P. S.; Sukhramani, P. S.; Tirthani, S. R.; Desai, S. A.; Suthar, M. P. *Pharmacia Lettre* **2011**, *3*, 236.
105 Bittermann, H.; Gmeiner, P. *J. Org. Chem.* **2006**, *71*, 97. https://doi.org/10.1021/jo0517287
106 Amin, K. M.; Houck, D. R.; Gross, A. L.; Zhang, X.-l.; Cearley, C.; Madsen, T. M.; Kroes, R. A.; Stanton, P. K.; Burgdorf, J.; Moskal, J. R. *Int. J. Neuropsychopharmacol.* **2018**, *21*, 242. https://doi.org/10.1093/ijnp/pyx096

Authors' Biographies

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Matthias D'hooghe was born in Kortrijk, Belgium, in 1978. He received a Master degree in 2001 (Master of Science in Bioscience Engineering: Chemistry) and a PhD degree in 2006 (Doctor in Applied Biological Sciences: Chemistry), both from Ghent University, Belgium, with Prof. N. De Kimpe as promoter. In 2007, he became postdoctoral assistant at the Department of Green Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, and in 2009 he performed a short postdoctoral stay with Prof. D. Vogt at Eindhoven University of Technology (The Netherlands) in the field of homogeneous catalysis. In October 2010, he was promoted to Professor (Research Professor) at the Department of Green Chemistry and Technology (Ghent University), and he was granted tenure in 2015. His main research interests include the chemistry of small-ring azaheterocycles, with a special focus on aziridines, azetidines and β-lactams, and the synthesis of different classes of bioactive heterocyclic compounds. Prof. D'hooghe has been elected as a laureate of the DSM Science & Technology Awards 2007, finalist of the European Young Chemist Award 2012 and recipient of the Thieme Chemistry Journal Award 2013. He is the author of >150 publications in international peer-reviewed journals.

