Novel Aspects on the Preparation of Spirocyclic and Fused Unusual β-Lactams

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Abstract β-Lactam antibiotics have occupied a central role in the fight against pathogenic bacteria and the subsequent rise in quality of life for the world population as a whole. However, the extensive use of common β-lactam antibiotics such as penicillins and cephalosporins in medicine has resulted in an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer. The resistance of bacteria to the classical β-lactam antibiotics can be overcome, *e.g.*, by using novel β-lactam moieties in drugs which show much higher stability towards these resistance bacteria. In addition, there are many important nonantibiotic uses of 2-azetidinones in fields ranging from enzyme inhibition to gene activation. These biological activities, combined with the use of these products as starting materials to prepare α- and β-amino acids, alkaloids, heterocycles, taxoids, and other types of compounds of biological and medicinal interest, provide the motivation to explore new methodologies for the synthesis of substances based on the β-lactam core. The aim of this chapter is to provide a survey of the types of reactions used to prepare non-conventional spirocyclic and fused β-lactams, concentrating on the advances that have been made in the last decade, and in particular in the last five years. We will draw special attention to radical cyclizations, cycloaddition reactions, and transition metal-catalyzed reactions.

1

1

Introduction

Since the advent of penicillin, the β-lactam antibiotics have been the subject of much discussion and investigation, within both the scientific and public sectors [1]. β-Lactam antibiotics have occupied a central role in the fight against pathogenic bacteria and the subsequent rise in quality of life for the world population as a whole. However, the extensive use of common β-lactam antibiotics such as penicillins and cephalosporins (Fig. 1) in medicine has resulted in an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer. It is well known that bacterial resistance to β-lactam antibiotics stems from the expression of a β-lactamase that catalyzes the hydrolytic cleavage of the substrate amide bond. β-Lactamases can be classified into four different classes (A–D) according to structure. Class A, C, and D β-lactamases are serine enzymes, the serine residue acting as the nucleophile in the hydrolysis reaction. Class A β-lactamases are also known as "penicillinases" on account of the ease with which they can hydrolyse penicillins, and class C β-lactamases as "cephalosporinases" by virtue of their increased activity against cephalosporins. Of the four structural classes of this enzyme, metallo-β-lactamases (class B) contain zinc and other divalent cations as cofactors.

Figure 1

Two main therapeutic strategies have been adopted to counteract bacterial resistance to β-lactam antibiotics. One strategy consists of modifying the structure of the β-lactam antibiotic, aiming to render it insensitive to the β-lactamase attack. Recently, trinems antibiotics (depicted in Fig. 2) have been the subject of considerable study owing to their broad spectrum of antibacterial activity, resistance to β-lactamases and stability to renal dehydropeptidases [2]. As a result of their impressive biological activity, tricyclic β-lactams have become interesting targets for synthesis. A second approach uses a reagent, typically a β-lactam derivative, which incapacitates the β-lactamase, in synergy with the β-lactam antibiotic. Clavulanic acid (depicted in Fig. 2) is the archetipe of β-lactamase

inhibitors [3]: in synergistic mixture with amoxicillin (depicted in Fig. 2), under the name "augmentin", it arrived to the practice some years ago. Both approaches have produced results and a new generation of antibiotics has been developed.
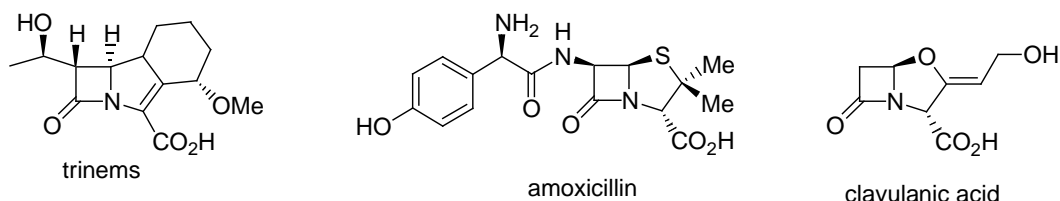

trinems

amoxicillin

clavulanic acid

Figure 2

In addition, there are many important nonantibiotic uses of 2-azetidinones in fields ranging from enzyme inhibition [4] to gene activation [5]. Systems containing one carbon atom common to two rings, spirocyclic compounds, represent an important structural organization. Spirocyclic β-lactams (Fig. 3) behave as β-turn mimetics [6], as well as enzyme inhibitors [7], they are precursors of α,α-disubstituted β-amino acids [8], and the spiranic β-lactam moiety is present in chartellines and chartelamides [9], a family of marine natural products. Synthetic studies and biosynthetic speculation inspired by an unexpected reaction on the marine alkaloid chartelline C have been described [9f].
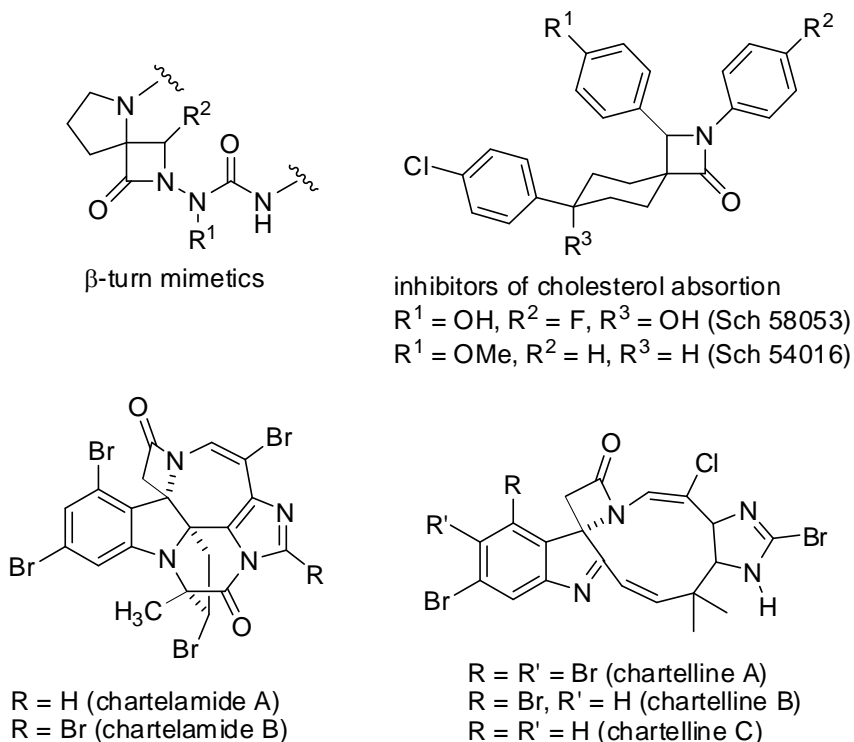

β-turn mimetics

inhibitors of cholesterol absorption
R^1 = OH, R^2 = F, R^3 = OH (Sch 58053)
R^1 = OMe, R^2 = H, R^3 = H (Sch 54016)

R = H (chartelamide A)
R = Br (chartelamide B)

R = R' = Br (chartelline A)
R = Br, R' = H (chartelline B)
R = R' = H (chartelline C)

Figure 3

These biological activities, combined with the use of these products as starting materials to prepare α- and β-amino acids, alkaloids, heterocycles, taxoids, and other types of compounds of biological and medicinal interest [10],

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provide the motivation to explore new methodologies for the synthesis of substances based on the β-lactam core.

The cyclic 2-azetidinone skeleton has been extensively used as a template on which to build the carbo(hetero)cyclic structure joined to the four-membered ring, using the chirality and functionalization of the β-lactam ring as a stereocontrolling element. This review embraces the gamut of unusual β-lactams, including spiranic and fused 2-azetidinones. Without a doubt this contribution does not include every report of unusual β-lactams, nor does it fully summarize all aspects of the cited references. Instead, examples have been chosen based on their demonstrated and potential usefulness, in the opinion of the authors. The aim of this review is to provide practicing and aspirant β-lactam chemists with a survey and flavor of the types of reactions used to prepare non-conventional β-lactams, and insight into why certain methodologies are advantageous under particular circumstances, concentrating on the advances that have been made in the last decade, and in particular in the last five years. We will draw special attention to radical cyclizations, cycloaddition reactions, and transition metal-catalyzed reactions.

2
Preparation of Spirocyclic-β-lactams with Non-Classical Structure

2.1
Using Cycloaddition Reactions

It has been reported the synthesis of pyrrolidine and tetrahydrofuran spiro-β-lactams by a Staudinger-type process [11]. The β-lactams **4** and **5** were prepared by reaction of either 2-tetrahydrofuroyl chloride **2** or 3-tetrahydrofuroyl chloride **3** with imines **1** (Scheme 1). The acid chloride was added to a stirred, refluxing solution of the imine and triethylamine in toluene. After refluxing of the solution overnight and aqueous work-up, a mixture of *cis*- and *trans*-spiro-β-lactams **4** or **5** was obtained in good to moderate yields. When other solvents such as dichloromethane and lower temperatures were used, the starting materials were always recovered. The β-lactams **4** and **5** are the expected products of the [2+2] cycloaddition reaction of imines with the corresponding cyclic ketenes. In all cases, the diastereomeric mixtures of spiro-β-lactams **4** and **5** were separated by

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column chromatography. The relative configuration in the stereogenic centres of the azetidinone ring was established by nuclear overhauser effect (NOE) difference NMR experiments.


2 X = O
3 X = NCbz
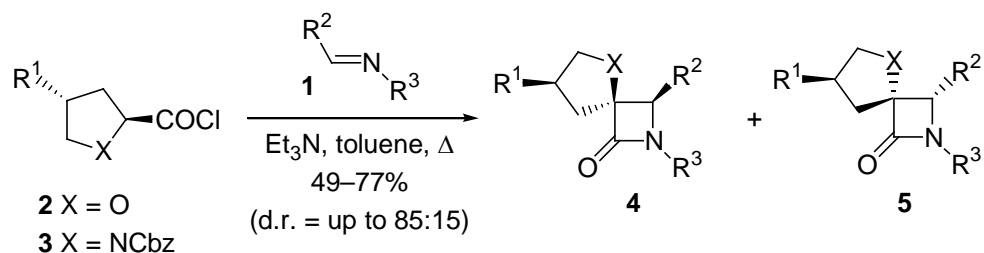
Scheme 1

This protocol was also apply to diazepam derivatives **6** [12]. When these compounds were treated with *N*-benzyloxycarbonyl-L-proline acid chloride and tetrahydrofuroyl chloride, the expected spirocyclic systems **7** (Scheme 2) were obtained in good yields. In the case of the *N*- benzyloxycarbonyl-L-proline acid chloride, the reaction was carried out at room temperature, while the process involving the tetrahydrofuroyl chloride needed to be performed in refluxing toluene. This higher temperature was the likely cause of the loss of selectivity observed in the latter case, in which a 10:1 mixture of diastereoisomers was obtained.


X = NCbz, O
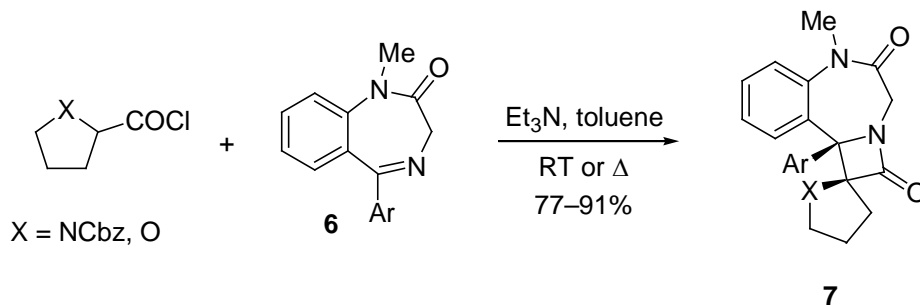
Scheme 2

Staudinger reaction of imine **8** derived from 7-oxanorbornenone with 2-alkoxyacetyl chlorides in the presence of Et₃N (toluene, RT), afforded β-lactams **9** (Scheme 3). These were obtained as single diastereomers, and no traces of the corresponding isomeric *exo*-β-lactams were detected in the crude reaction products [13]. It is worth mentioning that this stereochemical outcome of β-lactam formation with acid chlorides under Staudinger reaction conditions was opposite to the one expected from a *simple* [2+2]-cycloaddition reaction, which should have taken place from the *exo* face of compound **8**.
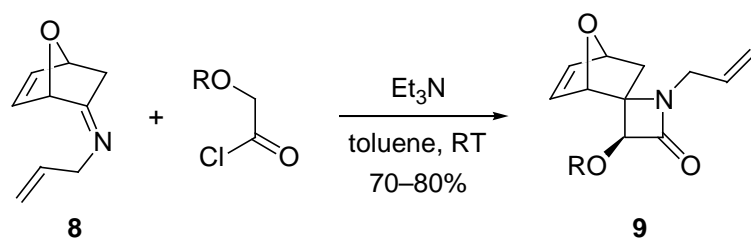
Scheme 3

Optically active α-methylene-β-lactam **10** was synthesized and submitted to 1,3-dipolar cycloadditions with diazomethane, 4-methoxybenzonitrile oxide, and diphenylnitrone [14]. All cycloadditions proceed with complete regioselectivity giving products **11–13** in an *anti*-fashion with respect to the substituent at the C4-position of the starting β-lactam in diastereomeric ratios of about 85:15 (Scheme 4). Pure optically active compounds could be obtained in almost all cases after chromatography. Unambiguous structure elucidation could be achieved by X-ray crystal analysis and NOE investigations.
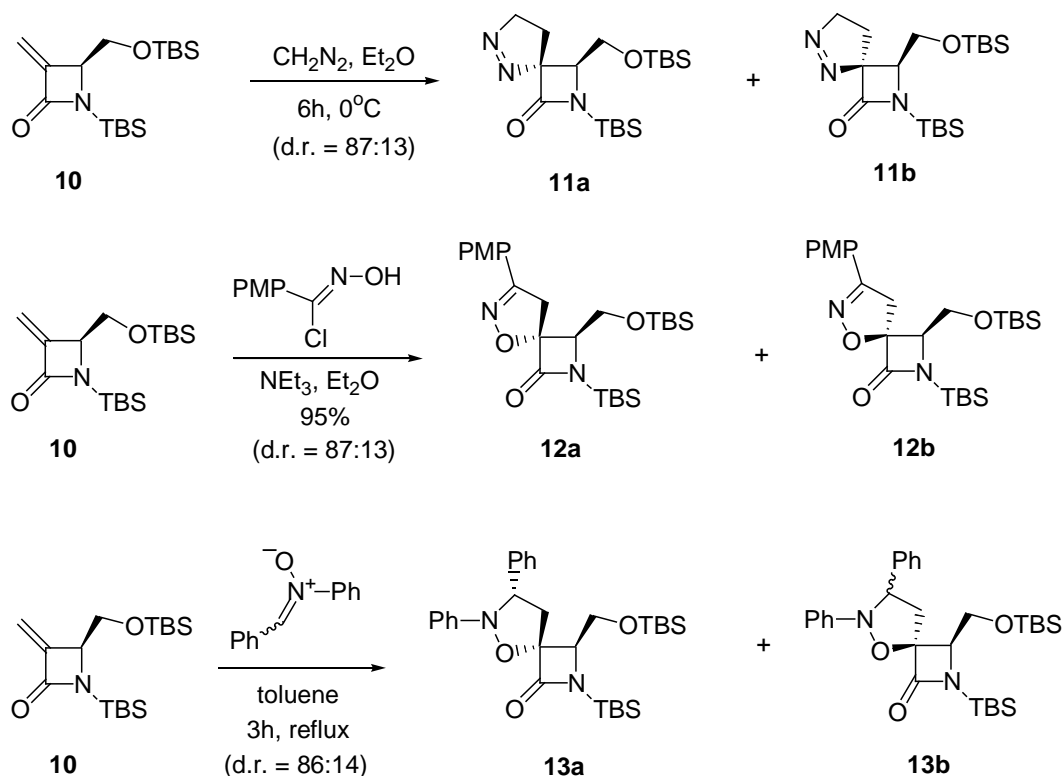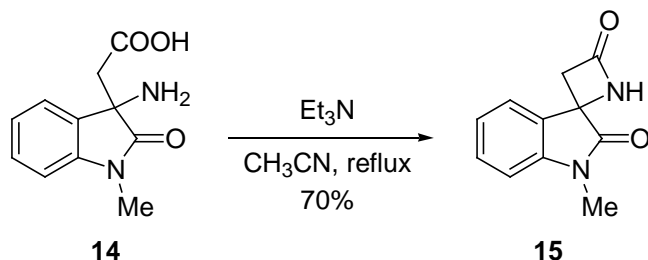

Scheme 4

2.2
Using Cyclization and Rearrangement Reactions

A model compound **15** containing an indole β-lactam moiety in chartellines was synthesized from the Mannich reaction of isatin imine with ketene silyl acetal, followed by β-lactam formation through cyclization of the resulting β-amino acid

14 (Scheme 5) [15]. L-Proline-catalyzed direct asymmetric Mannich reactions of *N*-PMP protected α-imino ethyl glyoxylate with various α, α-disubstituted aldehydes affords quaternary β-formyl α-amino acid derivatives with excellent yields and enantioselectivities. The Mannich products are further converted to the corresponding spiranic β-lactams [16].
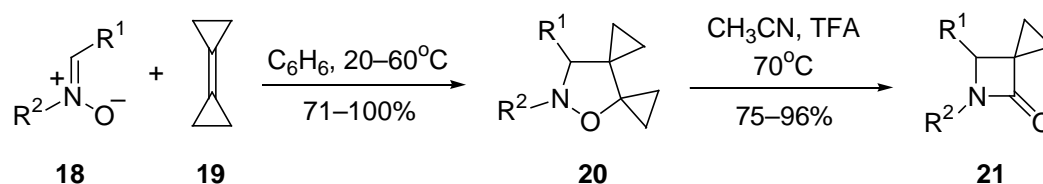

Scheme 5

The synthesis of spiro-linked β-lactam-dihydropyridines **17** through the cyclization of lithiated pyridine carboxamides **16** has been achieved (Scheme 6) [17]. Thus, treatment of **16** with LDA at –40 °C and addition of methyl chloroformate led to the formation of the corresponding dearomatized product in 91% yield. Other acylating agents, namely, benzyl chloroformate and benzoyl chloride, were equally effective at promoting this new type of cyclization as was methyl triflate. Methyl iodide gave significantly lower yields, and no dearomatized product was obtained on quenching with ammonium chloride, a good indication that electrophilic attack at the pyridine nitrogen is needed to promote the cyclization. It is presumed that the electrophile attacks the lithiated amide at the pyridine nitrogen rather than the considerably more basic organolithium center, presumably for steric reasons. The resulting pyridinium system is activated toward attack at C4, and the spirocyclic β-lactam results.
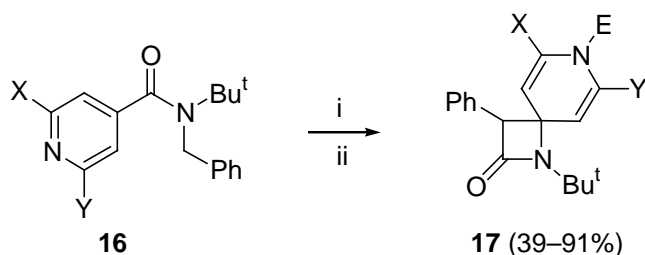
Scheme 6 i) LDA, –40 °C; ii) E–Cl.

1,3-Dipolar cycloaddition of nitrones **18** to bicyclopropylidene **19** gave the corresponding cycloadducts **20**. Treatment of these bis-spirocyclopropanated isoxazolidines with trifluoroacetic acid in acetonitrile furnished the corresponding 3-spirocyclopropanated β-lactams **21** in good yields. The structure of the β-lactam derived from *N*-benzyl-*C*-(methoxycarbonyl)nitrone was proved by X-ray crystal structure analysis. Thus, this new method furnishes compounds with a 5-azaspiro[2.3]hexan-4-one skeleton in 68–94% overall yield in two simple steps

(Scheme 7) [18]. The one-pot three-component reaction for the direct conversion of certain alkylhydroxylamine hydrochlorides (alkyl = benzyl, *p*-methoxybenzyl, benzhydryl, *tert*-butyl), formaldehyde or an alkyl glyoxylate and bicyclopropylidene **19** to furnish the 3-spirocyclopropanated 2-azetidinones related to **21** has also been developed. Microwave heating of mixtures of the three components in the presence of sodium acetate in ethanol for 15–120 min furnished the spirocyclic β-lactams in 49–78% yield (7 examples) [19].

R^1 = CO$_2$Me, Ph, CN, 2-Py; R^2 = Bn, PMB, Me

Scheme 7

Oxaciclopropane formation has been observed to give the highly strained oxiranyl-β-lactam **23**, possessing a spirocyclic structure by treatment of a 3-[bromo(nitro)methyl] 3-hydroxy-β-lactam **22** with bases (Scheme 8) [20]. The structure of the spirocycle **23** was proved by X-ray crystal structure analysis.
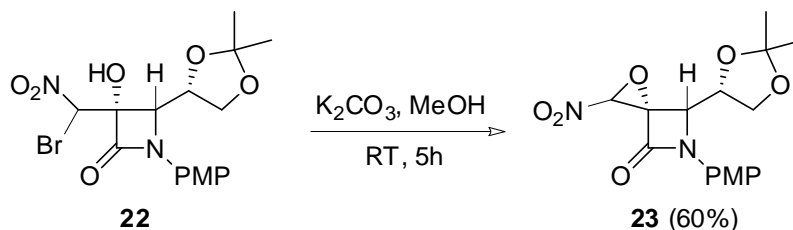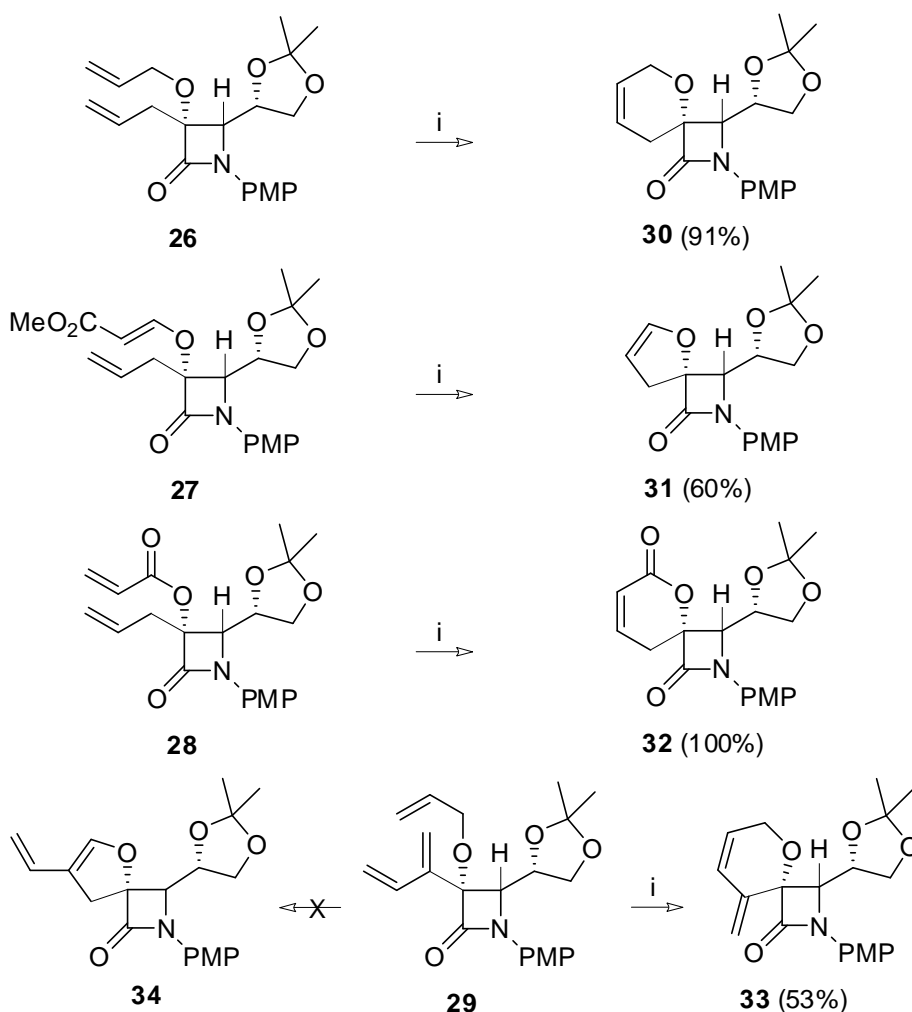

Scheme 8

Treatment of bicyclic lactone **24** with benzylamine in dioxane afforded an open chain triflate amide, which was stirred in THF in the presence of potassium carbonate to cyclizate to the spirocyclic β-lactam **25** (Scheme 9) [21].
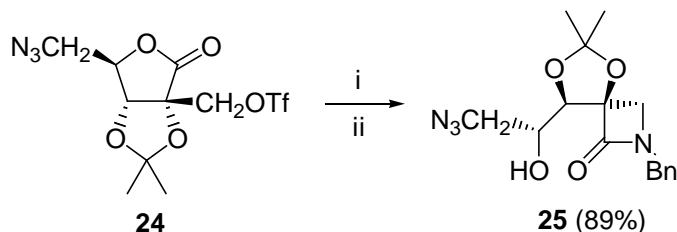
**Scheme 9** i) BnNH$_2$, 1,4-dioxane, RT; ii) K$_2$CO$_3$, THF, RT, 8 days.

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2.3
Using Metal-Mediated Reactions

The synthesis of oxaspiro-β-lactam structures containing five- and six-membered rings was explored through RCM reaction. Unfortunately, dienes **26–29** having a quaternary center proved to be resistant to ring closure mediated by Ru-based first generation Grubbs' carbene under smooth reaction conditions (5 mol%, CH$_2$Cl$_2$, 25 ^{o}C). The majority of the reaction mixture was composed of unreacted dienes. It was found that dienic substrates **26–29** require more vigorous conditions for ring closure. Spiro ring-closing metathesis was achieved upon heating at reflux temperature in a toluene solution. Under optimized conditions (5 mol% Grubbs' carbene, toluene 0.03 M, 110 ^{o}C), good yields of unusual β-lactams **30–32** containing dihydrofuran, dyhydropyran and dyhydropyranone spiranic rings were obtained (Scheme 10). The six-membered spiro compound **33** which bears an exocyclic methylene was achieved when the spirocyclization taked place on triene **29**. No traces of the five-membered regioisomer **34** could be detected, because only the least substituted double bond of the 1,3-diene system reacted (Scheme 10) [22].


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Scheme 10 i) [Cl$_2$(PCy$_3$)$_2$Ru=CHPh], toluene, reflux.

Treatment of enynes **35** and **36** with first generation Grubbs' carbene under the above diene ring-closing metathesis conditions, did not furnished the desired spirocycles. Next trials of cyclization were attempted by using its imidazolidinylidene analogue, the more active second generation Grubbs' carbene. In this way, the spirocyclization was effective on enyne-β-lactams **35** and **36** to afford the inner-outer-ring dienes (cyclic dienes in which one of the double bonds is *endo*-cyclic) **37** and **38** (Scheme 11) [23].
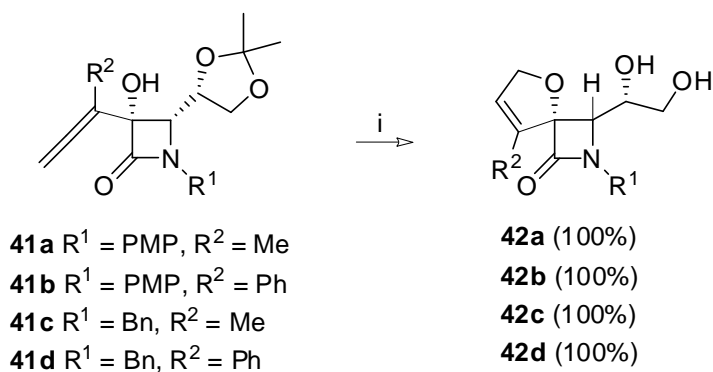

35 → **37** (35%)

36 → **38** (44%)
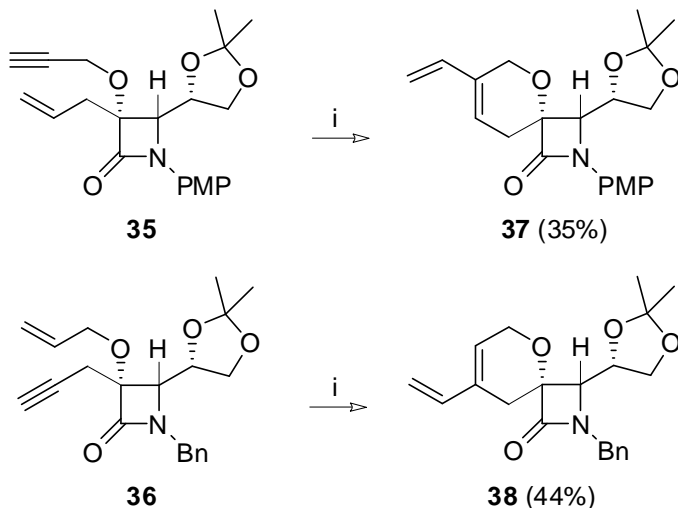
Scheme 11 i) [Cl$_2$(Im)(Cy$_3$P)Ru=CHPh], toluene, reflux.

Palladium-catalyzed reaction of bromo dienes **39** was complete after a few hours, and afforded spirocycles **40a** and **40b** as single regio- and stereoisomers (Scheme 12). The Heck spirocyclization reaction is regioselective, giving five-membered heterocycles. In addition, it is stereoselective because the Heck adducts were obtained as single geometric isomers [23].

39a R = PMP
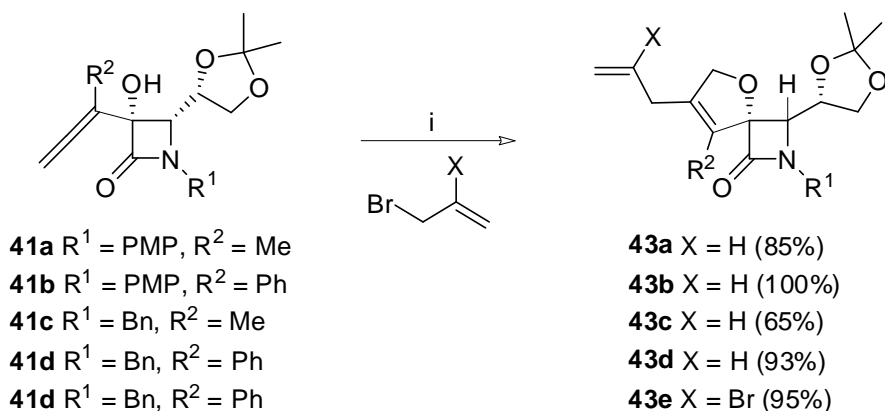**39b** R = Bn

40a R = PMP (47%)
40b R = Bn (50%)
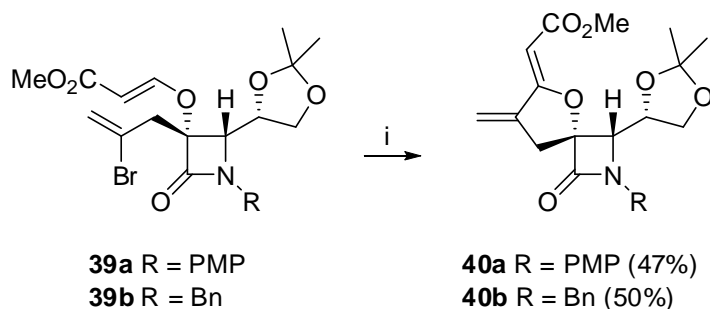
Scheme 12 ii) Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, DMF, 105 $^\circ$C.

The AgNO$_3$-induced reaction of β-lactam-tethered α-allenic alcohols **41** gave, with concomitant acetonide cleavage, the spirocyclic dihydrofurans **42** in quantitative yields (Scheme 13) [22].

41a R^1 = PMP, R^2 = Me
41b R^1 = PMP, R^2 = Ph
41c R^1 = Bn, R^2 = Me
41d R^1 = Bn, R^2 = Ph

42a (100%)
42b (100%)
42c (100%)
42d (100%)

Scheme 13 ii) AgNO$_3$ (1 equiv), acetone–H$_2$O (1:1), reflux.

The palladium-catalyzed cyclizative coupling reaction of α-allenols **41** with alkenyl halides was also explored. The transformation of allenols **41** into spirocyclic disubstituted dihydrofuran β-lactams **43** was readily achieved in high yields, by treatment with allyl bromide or 2,3-dibromopropene in the presence of palladium(II) chloride (5 mol%) (Scheme 14) [23].


41a R^1 = PMP, R^2 = Me
41b R^1 = PMP, R^2 = Ph
41c R^1 = Bn, R^2 = Me
41d R^1 = Bn, R^2 = Ph
41d R^1 = Bn, R^2 = Ph

43a X = H (85%)
43b X = H (100%)
43c X = H (65%)
43d X = H (93%)
43e X = Br (95%)

Scheme 14 i) 5 mol % PdCl$_2$, DMF, RT.

The formation of spirocyclic azetidinones **43** could be explained following a Pd(II)-catalyzed mechanism. Initial Pd(II)-coordination gave an allenepalladium complex **44**. Species **44** suffers an intramolecular cycloetherification reaction to give the palladadihydrofuran **45**. Intermediate **45** reacted with the appropriate allyl bromide to form intermediates **46**, which after dehalopalladation generated spiro-β-lactams **43** with concomitant regeneration of the Pd(II) species (Scheme 15) [23].
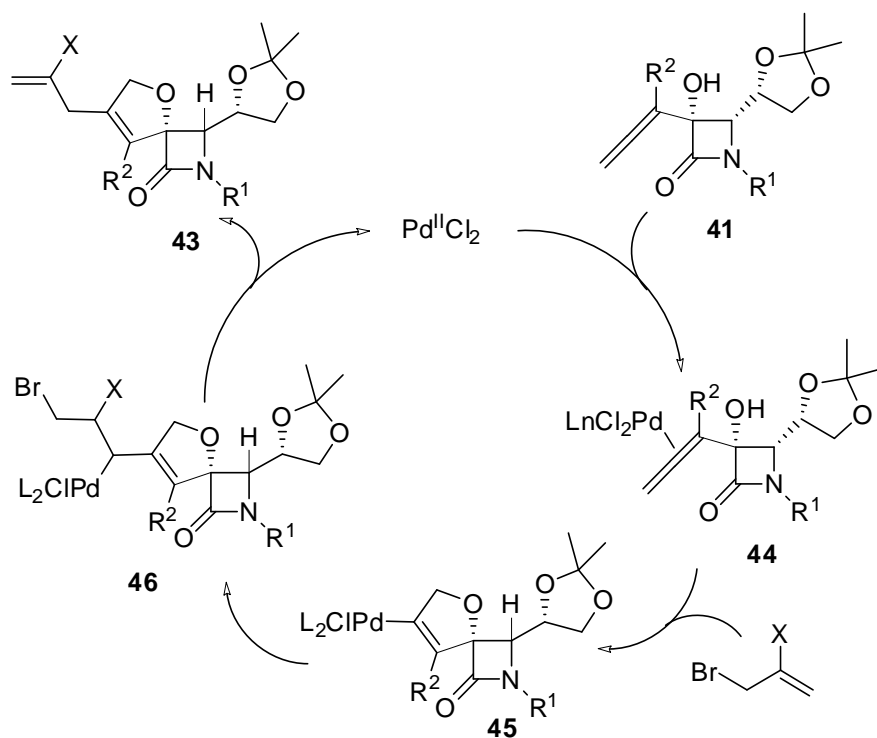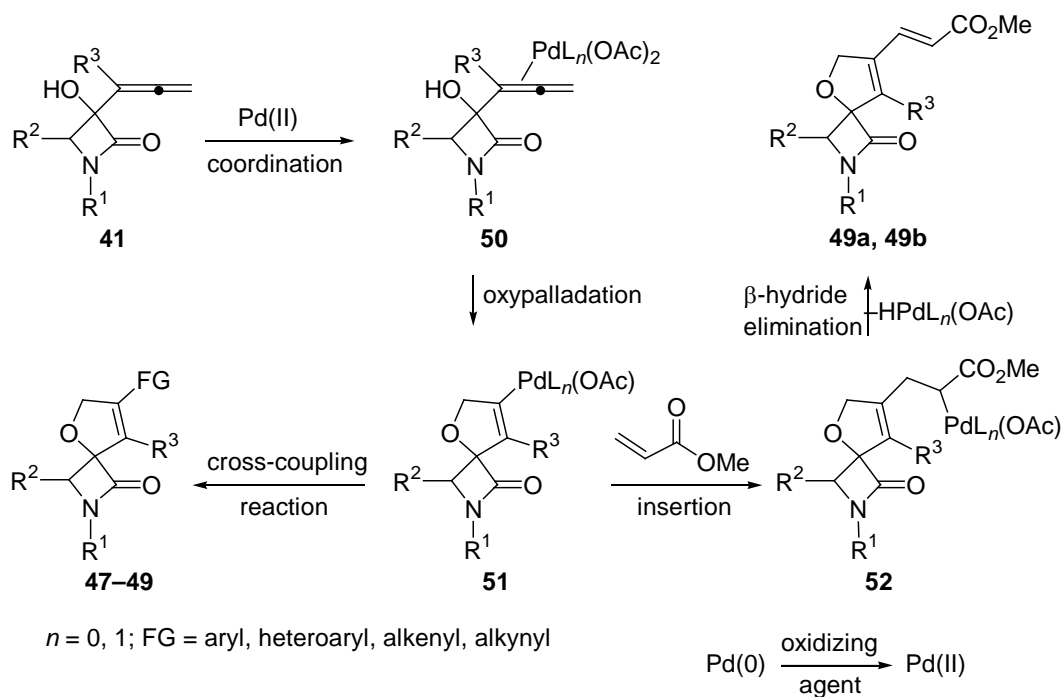
Scheme 15

Using a single catalytic system it has been successfully accomplished a domino cyclization of α-allenols–cross coupling (Heck, Sonogashira, and Suzuki) reaction sequence for the synthesis of spiro-β-lactams [24]. Treatment of enantiopure α-allenols **41** with the appropriate coupling partner under optimized conditions, led to formation of the desired products **47–49** as single isomers (Scheme 16). Similarly, the heterocyclizative cross-coupling between 2-azetidinone-tethered allenols and α-allenic acetates has resulted in the achievement of β-lactam–dihydrofuran hybrids in good yields [25].
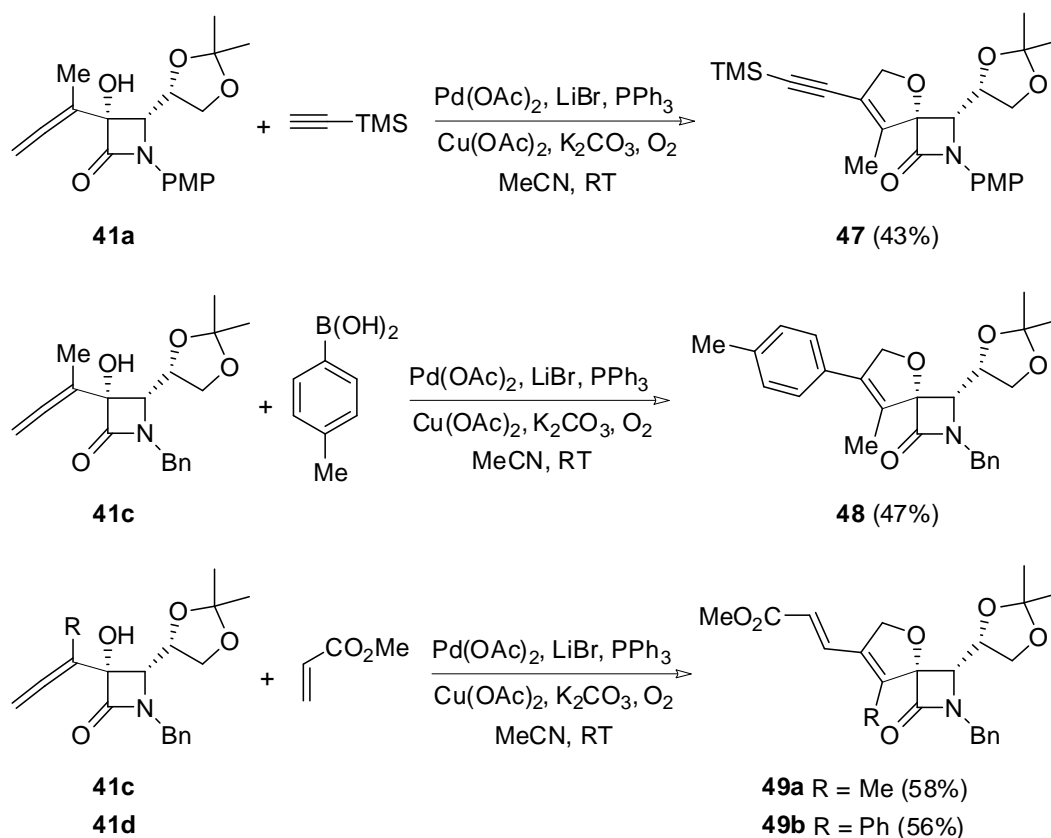
Scheme 16

The formation of spirolactams **47–49** could be rationalized in terms of a sequence domino cyclization of α-allenols–cross coupling reactions. A palladium(II)-catalyzed mechanism for the domino sequence leading to spiranic adducts **47–49** is proposed in Scheme 17. It could be presumed that the initially formed allenepalladium complex **50** undergoes an intramolecular attack by the hydroxyl group (oxypalladation), giving rise to the spirocyclic vinylic palladium species **51**. Next, palladadihydrofuran intermediate **51** is trapped by the cross-coupling reagents leading to compounds **47–49**. For example, the palladium species **51** can then form the intermediate **52** in a subsequent Heck reaction with acrylate, which leads to the final spirocycles **49a** and **49b** and Pd(0) in a β-hydride elimination [24]. It is necessary for the catalytic cycle that Pd(0) is reoxidized to Pd(II); this is achieved by the addition of Cu(OAc)$_2$, which does not interfere with the course of the reaction.
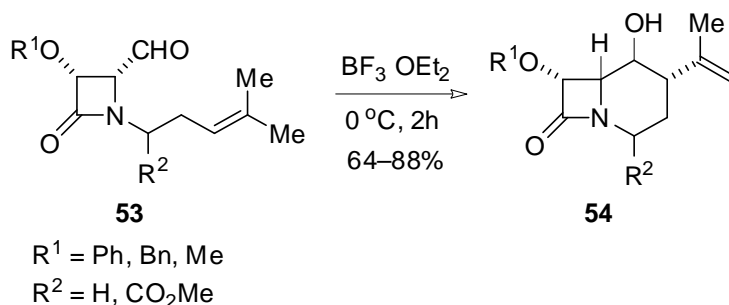
13

Scheme 17

3
Preparation of Fused β-Lactams with Non-Classical Structure

3.1
Using Cycloaddition Reactions

Enantiopure carbacepham derivatives **54** have been prepared in good yields via Lewis acid promoted carbonyl-ene cyclization of the corresponding 2-azetidinone-tethered alkenylaldehydes **53** (Scheme 18) [26].

R^1 = Ph, Bn, Me
R^2 = H, CO$_2$Me

Scheme 18

Starting from some of the above 1-hydroxycarbacephams **54**, the synthesis of inner-outer-ring 2-[*tert*-butyldimethylsilyloxy]dienes **55** with a carbacepham structure and their totally π-facial *endo* selective Diels–Alder reactions to structurally novel polycyclic β-lactams **56** have been reported (Scheme 19) [27].
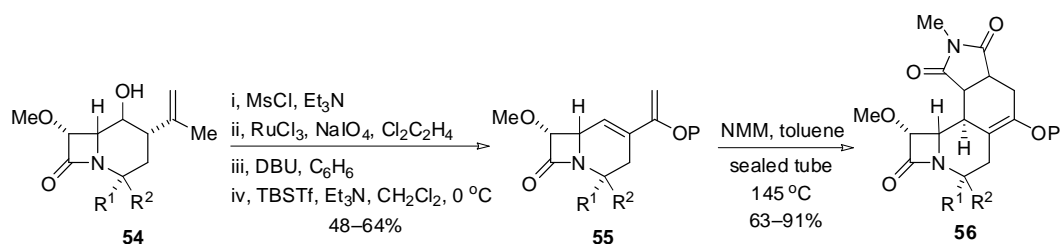
Scheme 19

It has been shown that the combination of ring-closing metathesis and Diels–Alder reaction sequences is a useful synthetic tool for the asymmetric synthesis of novel polycyclic carbacephem derivatives [28]. Thus, enyne metathesis of monocyclic 2-azetidinone **57** afforded bicyclic compound **58**. This diene was then engaged in a Diels–Alder reaction with dimethyl acetylenedicarboxylate as dienophile to obtain tricyclic β-lactam **59** in high yield (Scheme 20).
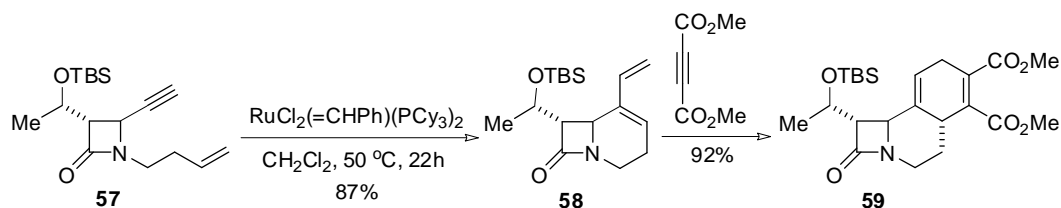
Scheme 20

It has been demonstrated that the intramolecular Diels–Alder reaction is a simple and efficient entry to different tricyclic 2-azetidinones, with a six-membered ring fused to the β-lactam nucleus. Homoallylic mesylate **60** was used for the stereoselective preparation of fused tricyclic 2-azetidinone **61** through a tandem one-pot elimination-intramolecular Diels–Alder reaction (Scheme 21) [29]. In similar way, starting from mesylate **62**, elimination and intramolecular Diels–Alder reaction have allowed the preparation of enantiopure fused tetracyclic β-lactam **63** (Scheme 22) [30]. 1,4-Cyclohexadiene **63** is prone to undergo aromatization to afford the tetracyclic β-lactam **64** containing a benzene ring, as illustrated in Scheme 22.
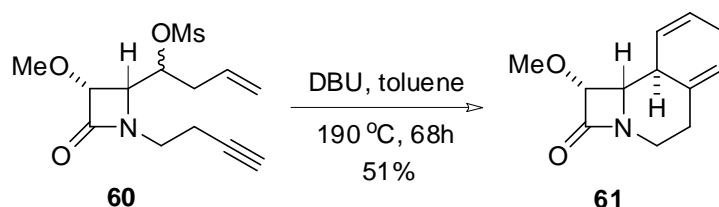
Scheme 21
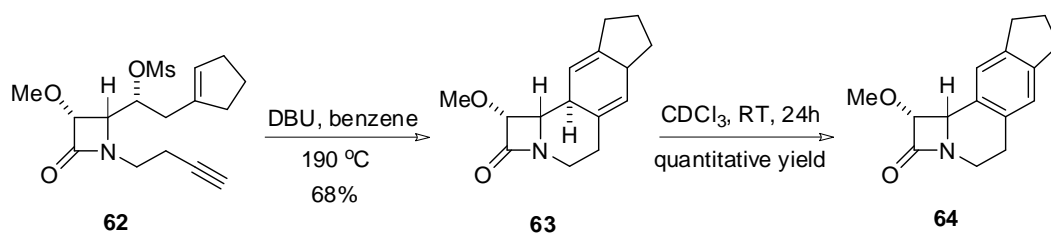
Scheme 22

Reaction of enallenes **65** or allenynes **66** in the presence of methanesulfonyl chloride at 190 °C provided tricyclic azetidinones **67** or **68**. These tricycles have been obtained from monocyclic allenols, masked functionalized dienes, via a domino allenol transposition/intramolecular Diels–Alder reaction process (Scheme 23) [31]. The mechanism of the one-pot allenol-diene transformation is depicted in Scheme 24. The extremely high selectivity observed in the formation of dienes may point to a pericyclic reaction pathway. Accordingly, the allenol component reacts with methanesulfonyl chloride resulting in a methanesulfonate intermediate. Next, the in situ generated α-allenic methanesulfonate **69** suffers a [3,3]-sigmatropic rearrangement, involving the six-membered cyclic transition structure **70**, to give the corresponding mesyloxy-diene counterpart **71**.

65a → i / 43% → **67a** (100:0)

65b → i / 54% → **67b** (95:5)

65c → i / 47% → **67c** (100:0)

66a → i / 45% → **68a** (100:0)

66b → i / 58% → **68b** (85:15)

66c → i / 52% → **68c** (100:0)

Scheme 23 i) CH$_3$SO$_2$Cl, Et$_3$N, toluene, sealed tube, 190 $^{\circ}$C.
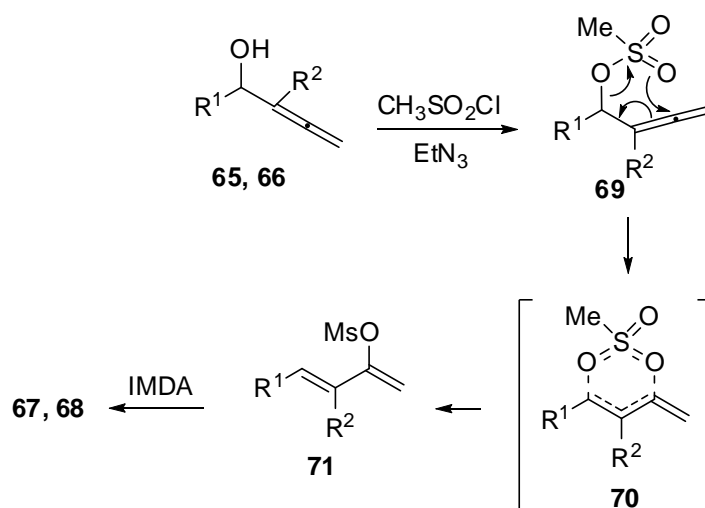
R^1 = 2-azetidinone-tethered alkene(alKyne); R^2 = Me or Ph

Scheme 24

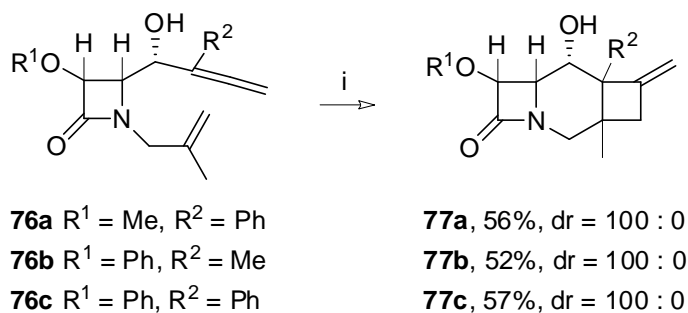A convenient metal-free methodology for the preparation of structurally novel strained tricyclic β-lactams containing a cyclobutane ring has been developed. The first examples accounting for the intramolecular [2+2] cycloaddition reaction in β-lactams have been achieved via the thermolysis of 2-azetidinone-tethered enallenols **72** and **74** [32]. As shown in Scheme 25, enallenes **72** and **74** undergo efficiently [2+2] thermal cyclization to afford the corresponding strained tricycles **73** and **75**. The tricyclic ring structures **73** and **75** arises from a formal [2+2] cycloaddition of the alkene with the distal bond of the allene, most likely via a diradical intermediate. Exposure of *N*-methallyl allenols **76** to the above thermal treatment afforded methylenecyclobutane 2-azetidinones **77** as the only products (Scheme 26). Notably, the presence of an internal substituent on the alkene moiety switched the regioselectivity. The successful reversal of regioselectivity in the allene component just by a subtle variation in the substitution at the alkene moiety, is an important development. In the current case, it allowed the preparation of a diverse array of structurally novel strained tricyclic β-lactams. For example, enantiopure compounds **77** are remarkable since they bear two quaternary stereogenic centers.

72d R = Me   **73a**, 56%, dr = 100 : 0
72e R = Ph   **73b**, 58%, dr = 100 : 0
72f R = H   **73c**, 40%, dr = 100 : 0

74a R = Me   **75a**, 45%, dr = 100 : 0
74b R = Ph   **75b**, 57%, dr = 100 : 0
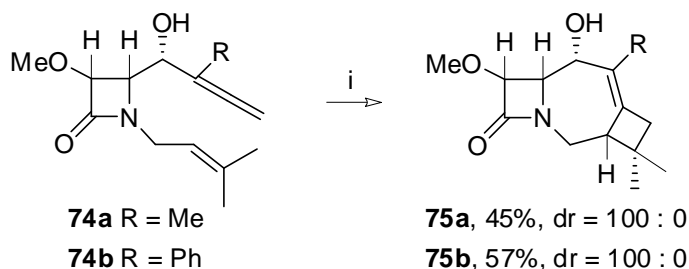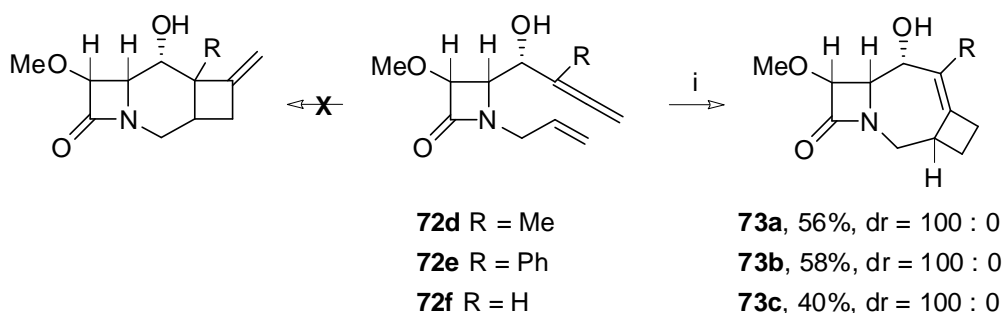
Scheme 25 i) Toluene, sealed tube, 220 ºC.

76a R^1 = Me, R^2 = Ph   **77a**, 56%, dr = 100 : 0
76b R^1 = Ph, R^2 = Me   **77b**, 52%, dr = 100 : 0
**76c** R^1 = Ph, R^2 = Ph   **77c**, 57%, dr = 100 : 0

Scheme 26 i Toluene, sealed tube, 220 ºC.

The formation of fused strained tricycles **73** and **75** can be rationalized by a mechanism which includes an exocyclic diradical intermediate **78** through an initial carbon–carbon bond formation, involving the central allene carbon and the proximal alkene carbon atom (path *A*, Scheme 27). An alternative mechanism for the thermal reaction leading to tricyclic 2-azetidinones **73** and **75** is proposed in path *B* (Scheme 27). This pathway involves an endocyclic diradical intermediate **79** arising from the initial attack of the terminal olefinic carbon onto the distal allene carbon. For both pathways, the final step must be a rapid ring-closure of the diradical intermediates which takes place before bond rotation can occur.

72, 74   path A   **78**   →   **73, 75**

72, 74   path B   **79**   →   **73, 75**
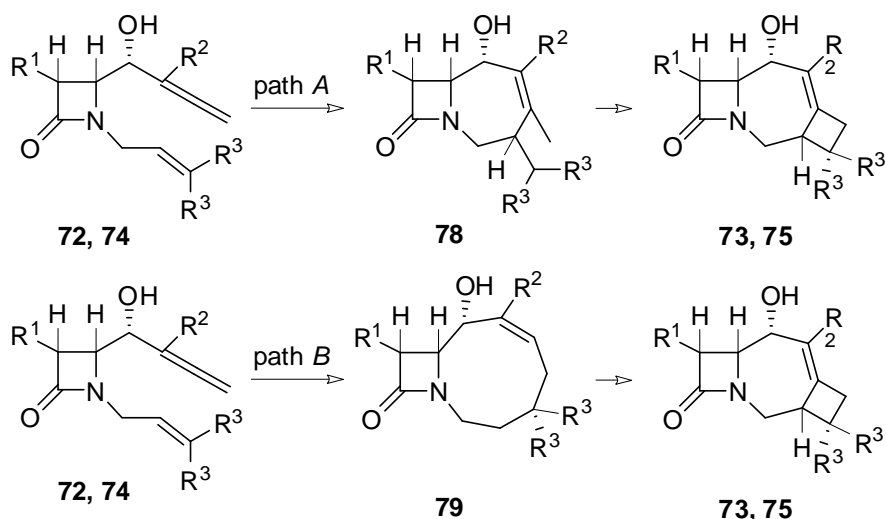
Scheme 27

Analogously, the thermal formation of fused strained tricycles **77** can be rationalized by a mechanism which includes an exocyclic diradical intermediate **80** through an initial carbon–carbon bond formation, involving the proximal allene carbon and the internal alkene carbon atom (path *C*, Scheme 28). The alternative pathway leading to tricyclic 2-azetidinones **77** is proposed in path *D* (Scheme 28). This proposal involves an endocyclic diradical intermediate **81** arising from the initial attack of the terminal olefinic carbon onto the central allene carbon. The final ring-closure step of the diradical intermediates account for the cyclobutane formation.

76   path C   **80**   →   **77**

76   path D   **81**   →   **77**
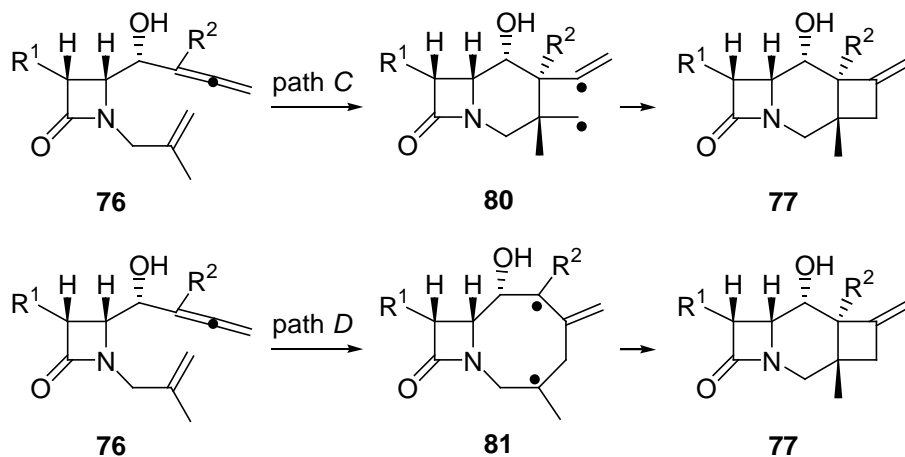
Scheme 28

It seems that the regioselectivity in this type of [2+2] cycloaddition reactions is determined by the presence or absence of an alkyl substituent at the internal alkene carbon atom, as the enallenes **72** and **74** lacking a methyl group exclusively gave addition at the β,γ-double bond, while the enallenes **76** bearing a methyl group at the internal olefinic carbon underwent a formal [2+2] cycloaddition reaction at the α,β-double bond. The pathway *A* proposed in

Scheme 27 looks valid for the formation of products **73** and **75**, where when R^3 = Me makes the exocyclic diradical most stable and the presence of the double bond makes the allylic radical **78** favored over the alternate endocyclic vinylic radical **79** in path *B*. However, it could be presumed that for the formation of compounds **77** the pathway *D* proposed in Scheme 28 is more reasonable. The simultaneous stabilization of the endocyclic diradical **81** for the presence of the methyl substituent as well as the allylic stabilization makes this radical favored over the exocyclic diradical **80**.

The intramolecular nitrone-alkene cycloaddition reaction using 2-azetidinone-tethered alkenyl(alkynyl)aldehydes **82–85** as starting materials has been introduced as an efficient route to prepare fused tricyclic aziridine-, isoxazoline- and isoxazolidine-β-lactams **86–89** [33]. The regioselectivity of this cycloaddition deserves special mention, because depending of the alkene(alkyne) substituent position at the tethered alkenyl(alkynyl)aldehyde, the regioselectivity was tuned from bridged (**86**) to fused (**87–89**) tricyclic compounds (Scheme 29). When the alkene substituent was moved from C3 to N1 in the 1,4-tethered alkenylaldehyde, the bridged *N*,*O*-heterocycles **86** were formed as the exclusive products. Formation of the bridged-ring products **86** is worthy of note because only fused-ring products have been found in the intramolecular nitrone-alkene cycloaddition reactions of related *N*-alkenyl-2-prolinaldehyde and related cyclic-bridged alkenylaldehydes. It is possible that, because of the rigid angular disposition imparted by the planar lactam group, the fused-ring transition state increases in energy thereby becoming uncompetitive with the usually unfavored bridged-ring transition state. The aziridine carbaldehyde **88** may arise by thermal sigmatropic rearrangement.
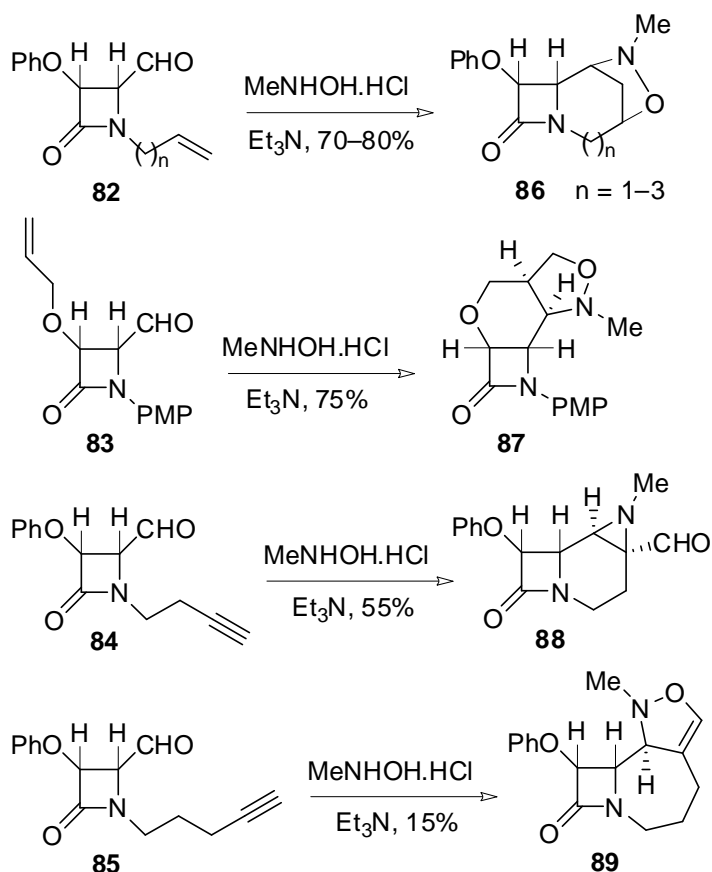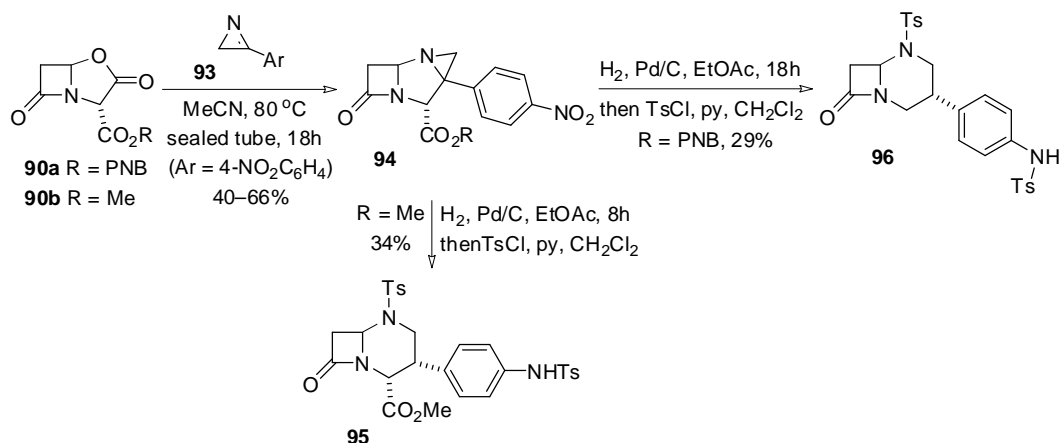
Scheme 29

The reactivity of 2*H*-azirines **91** and **93** as 1,3-dipolarophiles towards β-lactam based azomethine ylides derived from oxazolidinones **90** has been investigated [34]. The reaction of 3-(4-methoxyphenyl)-2*H*-azirine **91** with oxazolidinone **90** did not afford the expected cycloadduct. However, compound **92** was isolated as the major product in 41% yield (Scheme 30). In contrast, by using a nitroaryl moiety at the 3-position of the azirine ring, the initial cycloadducts **94** were prevented from further fragmentation (Scheme 31). Subsequent release (by nitro group reduction and protection) of the corresponding anilide then triggers the desired C–N bond cleavage. It has also been demonstrated that depending on the nature of the ester-protecting group (**94a** *vs.* **94b**) these conditions lead to either **95** or **96**, both of which are novel azacepham derivatives.
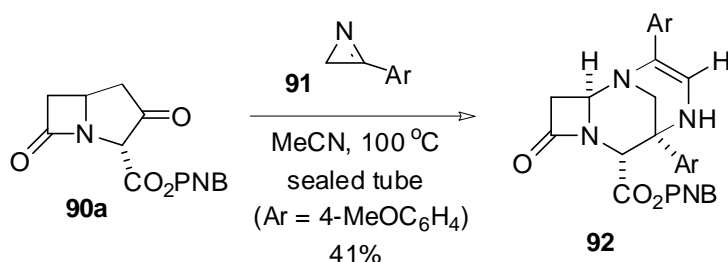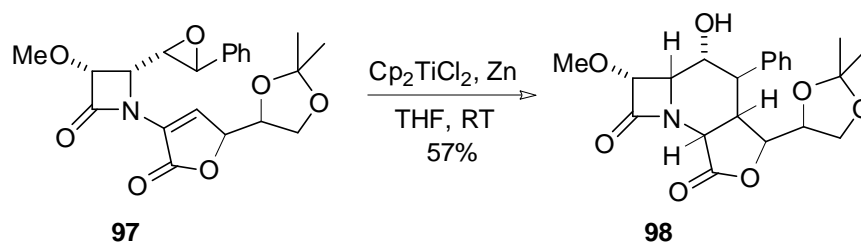

Scheme 30

Scheme 31

3.2
Using Radical Reactions

The reductive opening of epoxy-β-lactam **97** with titanocene(III) chloride gives rise to a benzyl radical that can be trapped by intramolecular π systems to give the tricyclic 2-azetidinone **98** (Scheme 32) [35].

Scheme 32

An approach (racemic and asymmetric) to benzofused tricyclic β-lactams including benzocarbapenems as well as benzocarbacephems, through intramolecular aryl radical cyclization of 2-azetidinone-tethered haloarenes has been reported [36]. Haloaryl β-lactams **99–103** were reacted with tributyltin hydride and AIBN in benzene at reflux to give the expected benzocarbapenems **104** and **106** and benzocarbacephems **105**, **107** and **108** in good yields as single diastereomers after chromatographic purification (Scheme 33, Table 1). These intramolecular radical reactions were carried out under standard dilution conditions, and did not require the use of high dilution techniques. Removal of the organotin halides by a solution of KF in water is essential for an appropriate chromatographic purification of compounds **104–108**. With the exception of the reaction of **101b**, neither cyclization products different from **104–108** nor reduction products were detected in the ¹H-NMR spectra of the crude reaction mixtures. The full stereoselectivity of the radical cyclisation is particularly

attractive, being independent of the substitution at C3 or N1 on the β-lactam ring. In addition, 2-azetidinones bearing styryl or carboxymethyl substituents at C4 underwent 5(or 6)-*exo-trig* radical cyclization to benzocarbapenems and benzocarbacephems **104–108** in a totally regioselective fashion, as expected when the radical acceptor has a radical-stabilizing moiety at the β-position. The radical reaction of the crotonaldehyde-imine derived β-lactam **101b**, lacking a radical-stabilizing moiety, deserves special mention. Haloalkenyl β-lactam **101b** formed, along with benzocarbapenem **106b** benzocarbacephem **109** (Scheme 34).
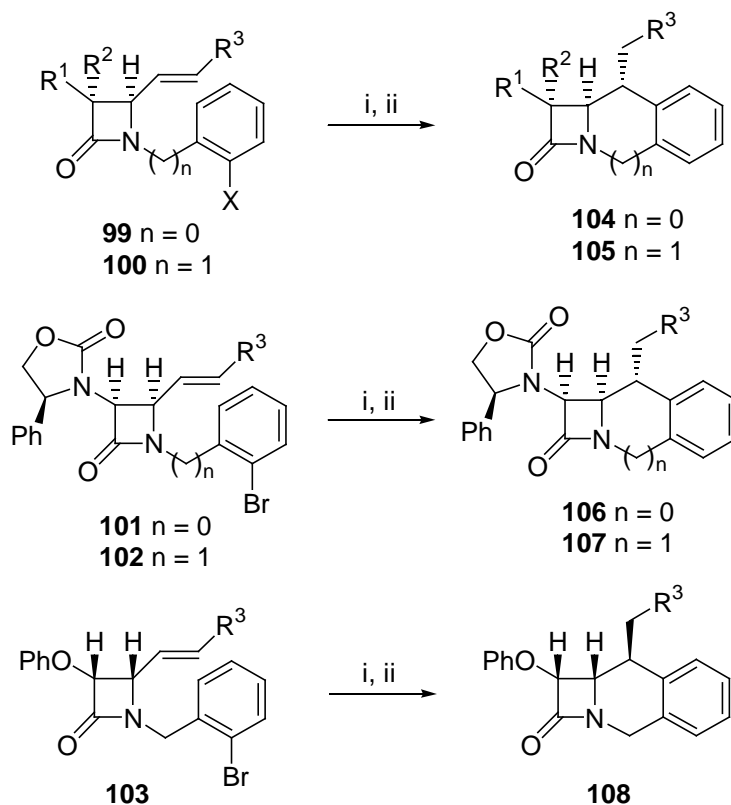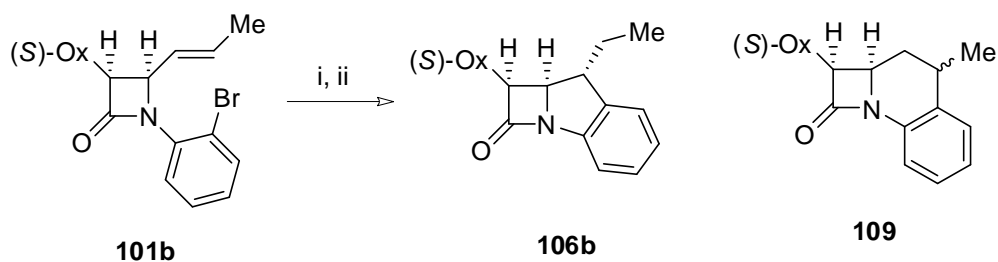

Scheme 33 i) Bu$_3$SnH (1.2 eq), AIBN (0.1 eq), benzene, reflux, 1-2 h; ii 10% aqueous KF, 30 min.

Table 1. Preparation of Fused Tricyclic β-Lactams **104–108**

substrate[a]	R^1	R^2	R^3	X	n	product[a]	yield (%)[b]
99a	Me	Me	Ph	Br	0	**104a**	65
99b	PhO	H	Ph	Br	0	**104b**	66
cis-**99c**	BnO	H	Ph	I	0	*cis*-**104c**	60
trans-**99c**	BnO	H	Ph	I	0	*trans*-**104c**	65
100a	PhO	H	Ph	Br	1	**105a**	50
100b	BnO	H	Ph	Br	1	**105b**	61
101a			Ph		0	**106a**	70
101b			Me		0	**106b**	30
102			Ph		1	**107**	57
103a			CO$_2$Me			**108a**	64
103b			Me			**108b**	47

[a]Compounds **99**, **100**, **104** and **105** are racemic. [b]Yield of pure, isolated product with correct analytical and spectral data.

101b　　　**106b**　　　**109**

(*S*)-Ox = *(S)*-4-phenyl-2-oxo-1,3-oxazolidin-3-yl

Scheme 34 i) Bu$_3$SnH (1.2 eq), AIBN (0.1 eq), benzene, reflux, 1.5 h; ii 10% aqueous KF, 30 min.

A mechanistic explanation for tricyclic β-lactams **104–109** is depicted in Scheme 35. The complete selectivity observed in the formation of benzocarbapenems **104** and **106** and benzocarbacephems **105**, **107** and **108** must be due to the preference of the radical intermediates for the conformation depicted in Scheme 36 for these cyclizations.
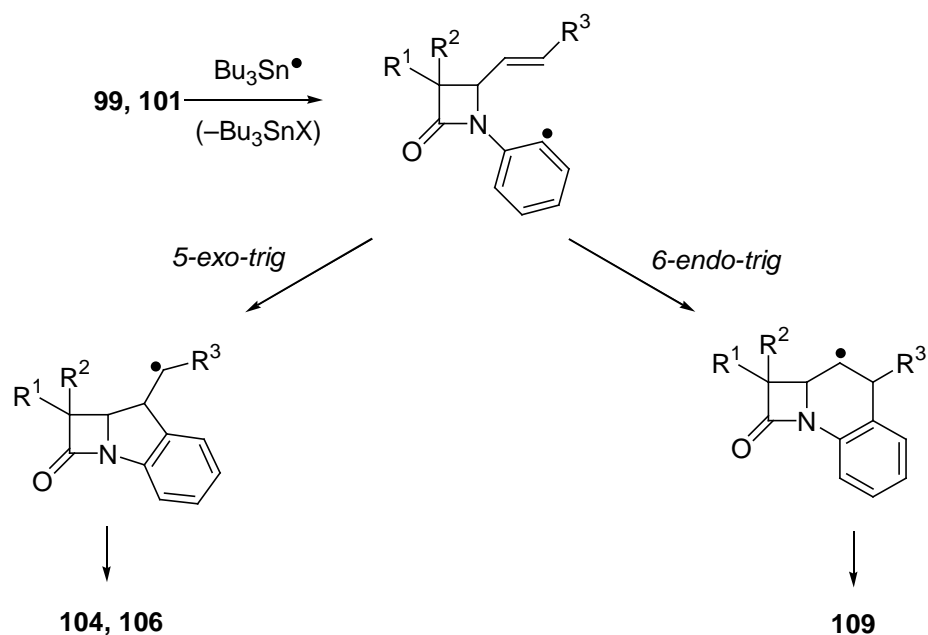
Scheme 35
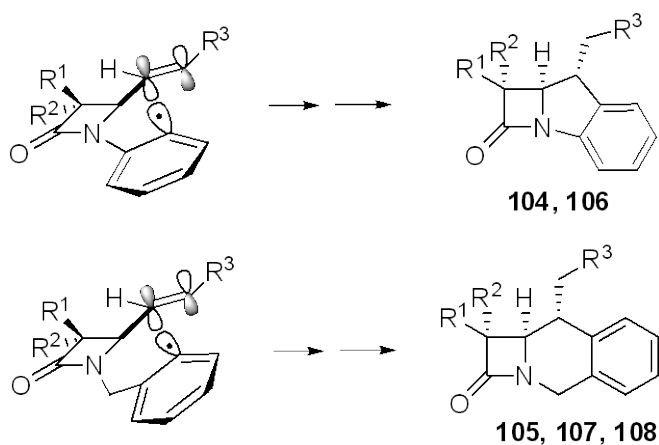
Scheme 36

The extension of the above radical intramolecular cyclization of *N*-haloaryl-β-lactams to 2-azetidinones bearing the proradical center at C3 was also explored. The treatment of haloarenes **109a–c** under similar conditions for the preparation of benzocarbapenems and benzocarbacephems **104–108** gave the fused tricyclic β-lactams **110a–c** (Scheme 37, Table 2). Compounds **110a** and **110b** were obtained as mixtures of diastereomers, which are epimers at the newly formed C5 stereocenter, while the amino derivative **110c** could be prepared as a single isomer.
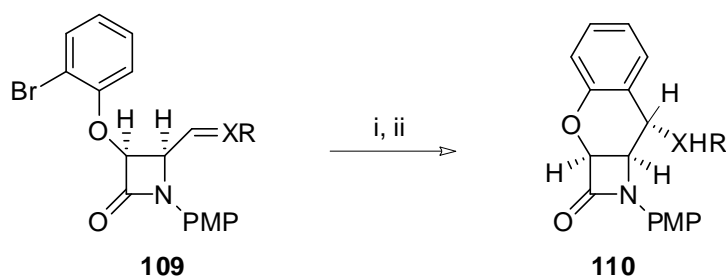
Scheme 37 i) Bu$_3$SnH (1.2 eq), AIBN (0.1 eq), benzene, reflux, 1 h; ii) 10% aqueous KF, 30 min.

**Table 2**. Preparation of Fused Tricyclic β-Lactams **110**

| substrate[a]	R	X	d.r.[c]	product[a]	yield (%)[b]
109a	Ph	CH	85:15	**110a**	69
109b	CO$_2$Me	CH	70:30	**110b**	56
109c	Bn	N	>95:5	**110c**	60

[a]PMP = 4-MeOC$_6$H$_4$. [b]Compounds **109** and **110** are racemic. [c]The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra of the crude reaction mixtures before purification. [d]Yield of pure product (mixture of isomers).

The formation of rings with more than seven atoms have unfavorable rates because the addition step is often too slow to allow it to compete successfully with other pathways open to the radical intermediate. In stannane based chemistry for example, premature hydrogen abstraction from the organotin hydride is difficult to avoid. However, Baylis-Hillman adducts **111** derived from enantiopure 1-alkenyl (or alkynyl)-4-azetidinone-2-carbaldehydes are used for the stereoselective and divergent preparation of highly functionalized bicycles **112** and **113** fused to medium-sized heterocycles (Scheme 38) [37]. The Baylis-Hillman reaction using non-racemic protected α-amino aldehydes has been attempted with limited success, due to partial racemization of the chiral aldehyde by DABCO after prolongate exposure times. However, this is not the case of 4-oxoazetidine-2-carbaldehydes, because on reacting with various activated vinyl systems the corresponding adducts can be prepared almost as single diastereoisomers. The diastereofacial preference of this addition reaction for *syn*-addition to the aldehyde moiety was interpreted by the Felkin-Anh model. Formation of *N*-fused bicyclic β-lactams **112** and **113** can be explained in terms of a competition between a tandem radical Michael addition/*endo*-cyclisation and a tandem radical addition/Michael addition, depending on the electronic nature of the radical promoter (Scheme 39). It is known that nucleophilic radicals react more rapidly with electron poor alkenes than with electron rich alkenes or alkynes, and conversely, electrophilic radicals react more rapidly with electron rich alkenes than electron poor alkenes. In the above case, Baylis-Hillman adducts may react through two different pathways to give the bicyclic systems. The more

nucleophilic benzylic radical would favor formation of compounds **112**, while the more electrophilic radicals, such as PhS· and Ph$_3$Sn·, should promote formation of compounds **113**. Alternatively, the differences in reactivity between the benzylic and the thiyl and stannyl radicals, respectively, could be explained by other considerations. Thus, for the thiyl and stannyl radicals the initial addition to the double bond is fast but reversible. Since the cyclization is a slow reaction, it can not compete with fragmentation. However, the addition to the triple bond is irreversible and therefore only products deriving from addition to the triple bond are isolated. Addition of the benzylic radical to the double bond of course is not reversible.
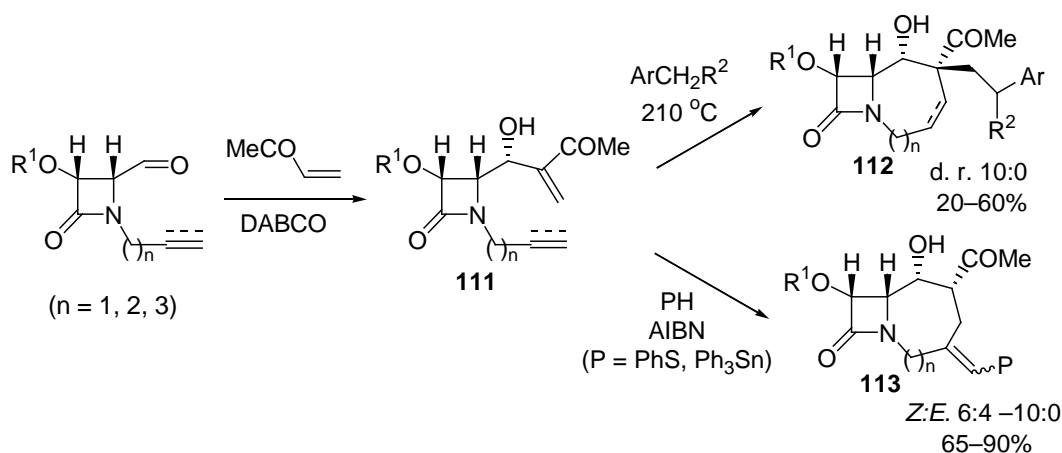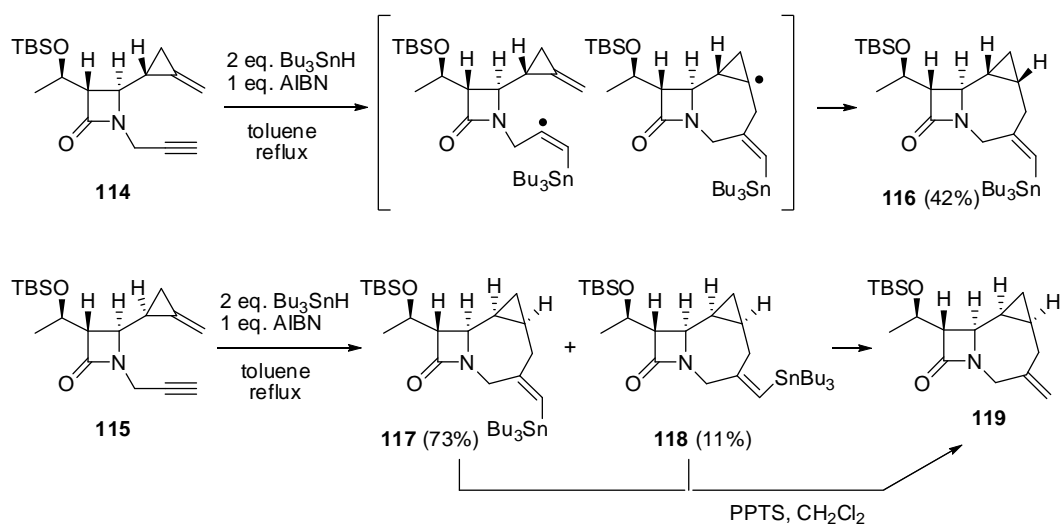

Scheme 38
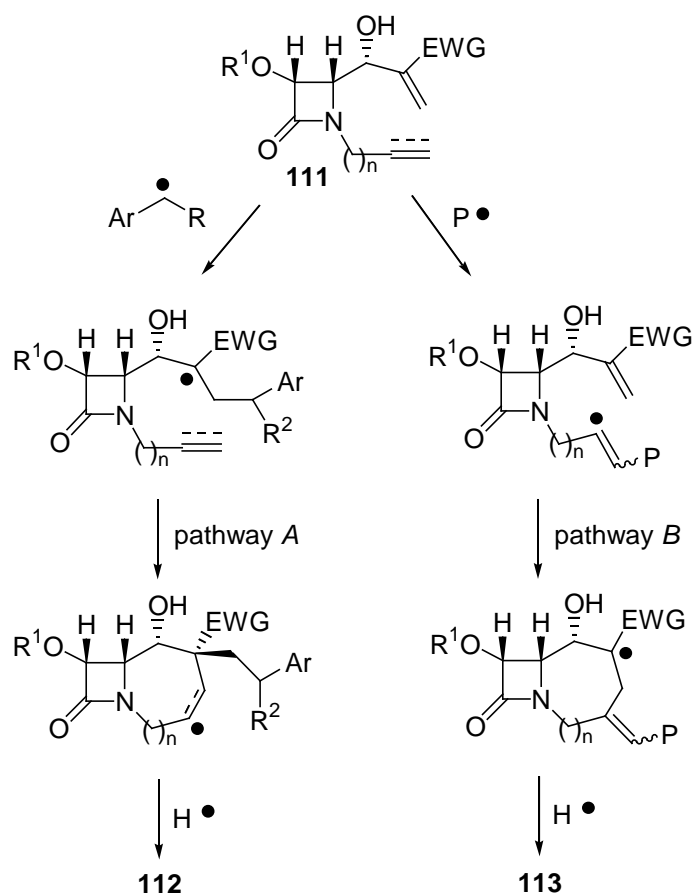
Scheme 39

The synthesis of *N*-fused tricyclic β-lactams involving a radical cascade sequence in enyne 2-azetidinones **114** and **115** bearing a methylenecyclopropane unit has been reported [38]. Slow addition of Bu₃SnH/AIBN to a refluxing solution of **114** gave tricyclic vinylstannane **116** as a single stereoisomer in 42% yield, whereas cyclization of **115** under identical conditions gave fused heterocycles **117** and **118** in 73 and 11% yield, respectively, in all three cases via a *7-endo* cyclization. Treatment of vinyl stannanes **117** and **118** with PPTS in dichloromethane yielded a common tricyclic product **119** (Scheme 40).

Scheme 40

A different report provided the access to a highly strained tetracyclic [3.6.6.4] ring system containing a fused tetrahydropyran-β-lactam moiety [39]. The radical precursors **120** were easily accessible via cycloaddition reaction of the appropriate imines with a chiral chloride derived from enantiomerically pure (+)-3-carene. When compounds **120** were subjected to radical cyclization conditions, fused tetracyclic β-lactams **121** were achieved as a single diastereomer (Scheme 41). The high stereoselectivity in this 6-*exo-trig* cyclization was rationalized by invoking a six-membered transition state mode. The conformational constraint within the rigid bicyclic system and β-lactam framework with a flexible oxygen tether does not allow the system to go through the generally favored 6-*exo*-chair transition state, and now an energetically favored six-membered boat-like transition state seems to be involved.
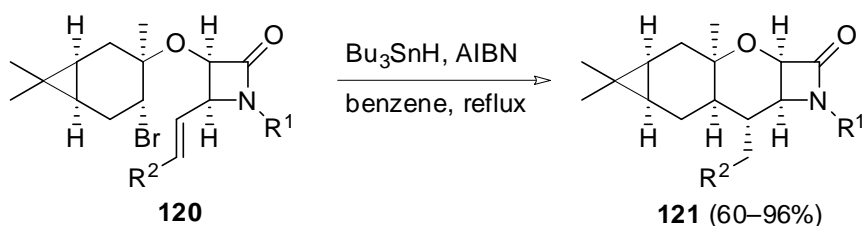
Scheme 41

Six-, seven-, or eight-membered bicyclic 2-azetidinones have been prepared through triphenyltin hydride-promoted intramolecular free radical cyclization reaction of β-lactam-tethered bromodienes (Scheme 42) [40]. The tin-promoted radical reaction of bromodienic alcohol **122a** gave the eight-membered ring fused-β-lactam **123** together with the homoallylic alcohol **124**. The free radical cyclization proceeded elegantly in bromodiene **122b** to provide the desired non-conventional bicyclic β-lactam **125** as single isomer. The 1-vinyl-3-hydroxy-6-hexenyl radical (radical numbering) derived from bromide **122c** afforded the

seven-membered ring fused bicycle **126** prevailing over the isomeric product **127** containing a six-membered ring. Triphenyltin hydride-promoted cyclization of bromodiene **122d** afforded the expected fused 2-azetidinone **128** as a single isomer in fair yield.
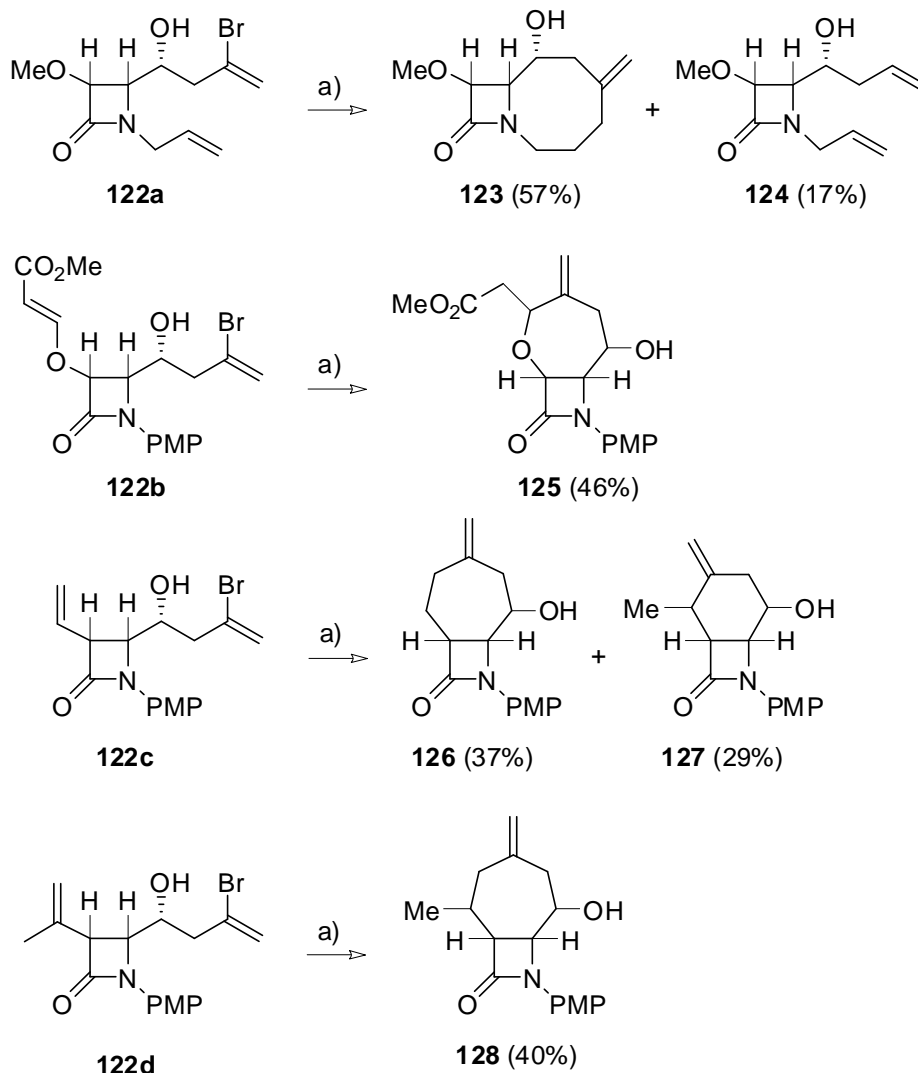
Scheme 42 a) Ph$_3$SnH (1.2 eq), AIBN (0.1 eq), benzene, reflux.

The synthesis of eight- and nine-membered rings fused to 2-azetidinones has been investigated using radical chemistry in β-lactam ene adducts bearing an extra alkyne tether [30]. The tin-promoted radical cyclization proceeded in enynes **129a** and **129b** to provide the desired non-conventional bicyclic β-lactams as single isomers in moderate yields (Scheme 43). Treatment of vinylic stannane **130a** with PTSA in CH$_2$Cl$_2$ yielded the destannilated eight-membered fused adduct **131**.

129a n = 1
129b n = 2

PTSA
CH₂Cl₂

130a n = 1, P = SnPh₃, 46%
130b n = 2, P = SnPh₃, 36%
131 n = 1, P = H, 100%
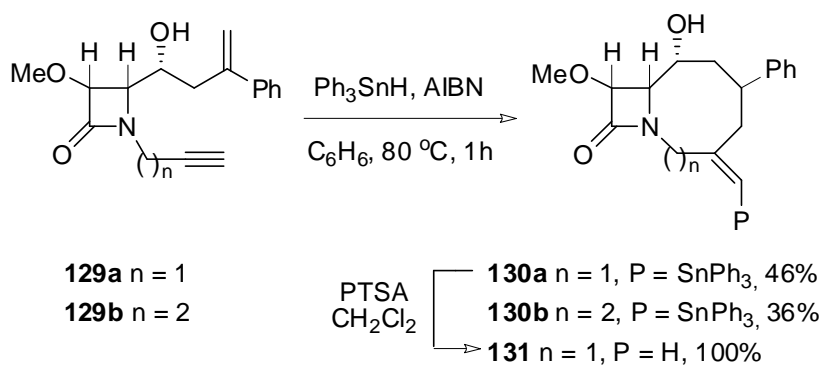
Scheme 43

A novel approach to racemic and enantiopure non-conventional fused bi- and tricyclic β-lactams has been developed by using regio- and stereocontrolled intramolecular free radical reactions in monocyclic 2-azetidinone-tethered allenynes and haloallenes [41]. In an initial study, we found that allenynol **132a** when heated in the presence of triphenyltin hydride and AIBN in benzene solution, gave the bicyclic β-lactam **133a** in 64% yield as a single regio- and *Z*-isomer. Tin-promoted cyclization of allenynol **132b** afforded the expected 2-azetidinone **133b** containing a medium-sized ring. Allenynol *anti*-**132c** having the alkynyl side chain at C3 instead of N1 underwent cyclization to afford the C3–C4 fused β-lactam **133c**. Similar behavior was observed for the free radical cyclization of allenynone **132d**, which afforded the heterobicyclic ketone **133d**. Interestingly, only bicycles **133** were found as a consequence of a totally regioselective radical cyclization onto the central carbon (Scheme 44). Neither the *endo*-cyclized product nor the *exo*-cyclized product was detected.

132a R = Me
132b R = Ph

133a R = Me (64%, *Z:E* = 100:0)
133b R = Ph (49%, *Z:E* = 100:0)

***anti*-132c**

133c (47%, *Z:E* = 0:100)

132d

133d (44%, *Z:E* = 100:0)
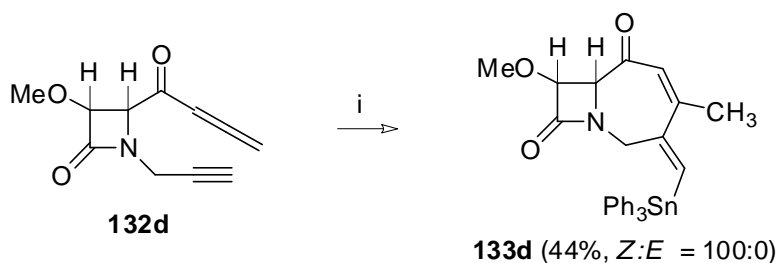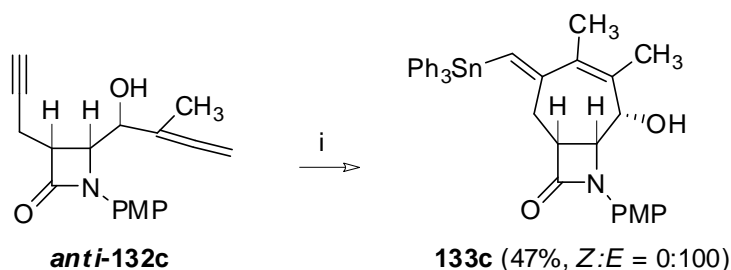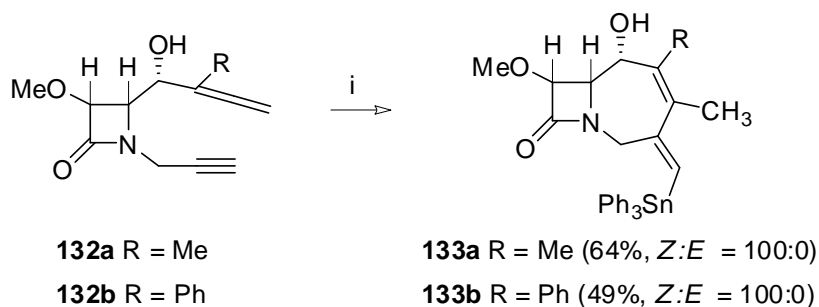
Scheme 44 i) Ph$_3$SnH (1.2 eq), AIBN (0.1 eq), benzene, reflux.

The extension of the above radical cyclization of 2-azetidinone-tethered allenynes to bromovinyl and haloaryl allenes bearing the proradical center at N1 was explored. The tin-promoted radical reaction was also useful in the conversion of the β-lactam allenes **134a** and **134b** with a bromopropenyl group substituted at the nitrogen atom, into the corresponding bicyclic systems **135a** and **135b** with similar efficiency and selectivity (Scheme 45). The treatment of β-lactam allenes **136a–d** having a bromo- or iodophenyl group (*N*-tethered) under similar conditions for the preparation of bicycles **133** and **135** gave the fused tricyclic β-lactams **137a–c** containing a central seven-membered ring (Scheme 46). Benzofused β-lactams **137** can be considered as superior cyclohomologous of benzocarbapenems and benzocarbacephems, which have been designed as suicide inactivators of β-lactamases.

134a R = Me
134b R = Ph

135a R = Me (67%)
135b R = Ph (61%)
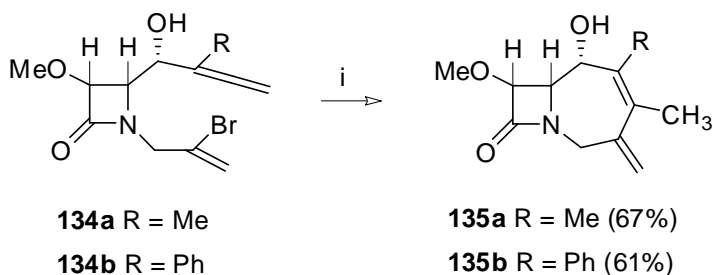
Scheme 45 i) Ph$_3$SnH (1.2 eq), AIBN (0.1 eq), benzene, reflux.
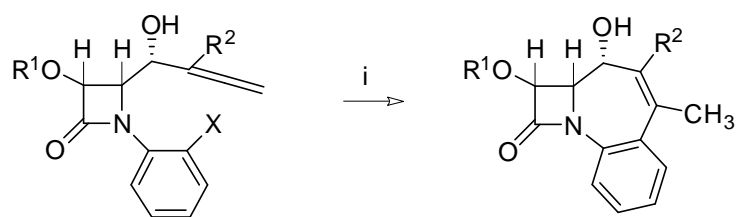
136a R^1 = Me, R^2 = Me, X = Br   **137a** (52%)
136b R^1 = Me, R^2 = Ph, X = Br   **137b** (46%)
136c R^1 = Me, R^2 = Me, X = I   **137a** (50%)
136d R^1 = Ph, R^2 = Me, X = I   **137c** (41%)
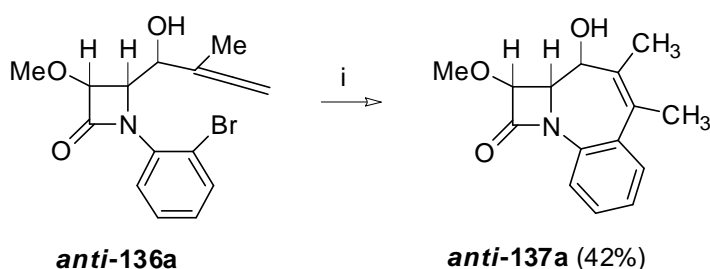
anti-**136a**   *anti*-**137a** (42%)

Scheme 46 i Ph$_3$SnH (1.2 eq), AIBN (0.1 eq), benzene, reflux.

It is presumed that the stannyl radical, by addition to the terminal position of the triple bond in allenynes **132**, or through bromine abstraction in bromovinyl and haloaryl allenes **134** and **136** gives the vinylic radical intermediates **138** and **142** in the propagation step, followed by cyclization toward the central carbon bond of the allene moiety to give in a total regio- and stereoselective fashion fused cycles **133**, **135** and **136** via allylic radical intermediates **139** and **143**. While both *endo-* and *exo*-cyclizations of radical intermediates **138** and **142** would give vinylic radicals **140**, **144** and **141**, **145**, respectively, *central*-cyclization would lead to the energetically more favored allylic radicals **139** and **143** (Schemes 47 and 48).

132   **138**   **140**   *endo* adduct

133   **139**   **141**   *exo* adduct
central adduct

Scheme 47

34

134, 136 → **142** → **144** → *endo* adduct

135, 137
central adduct

143

145 → *exo* adduct
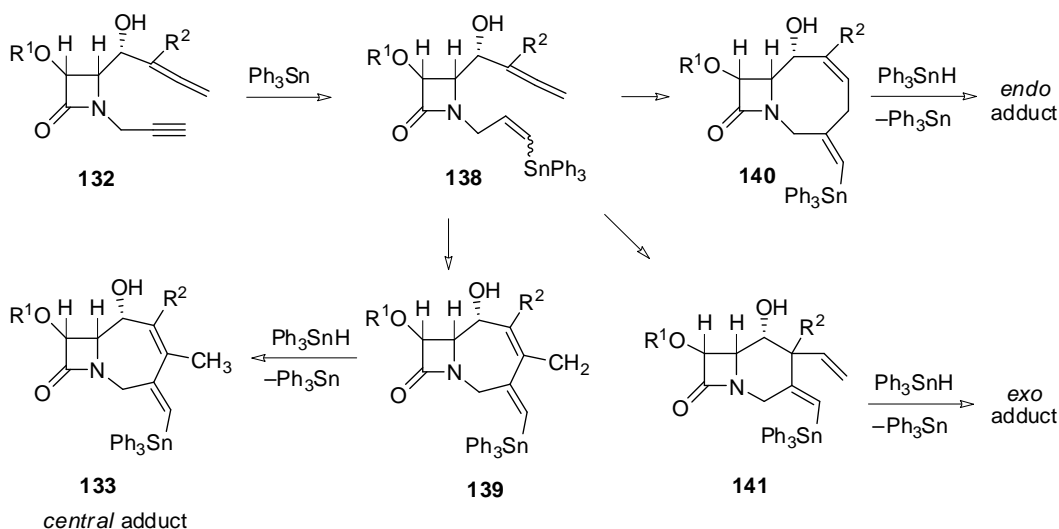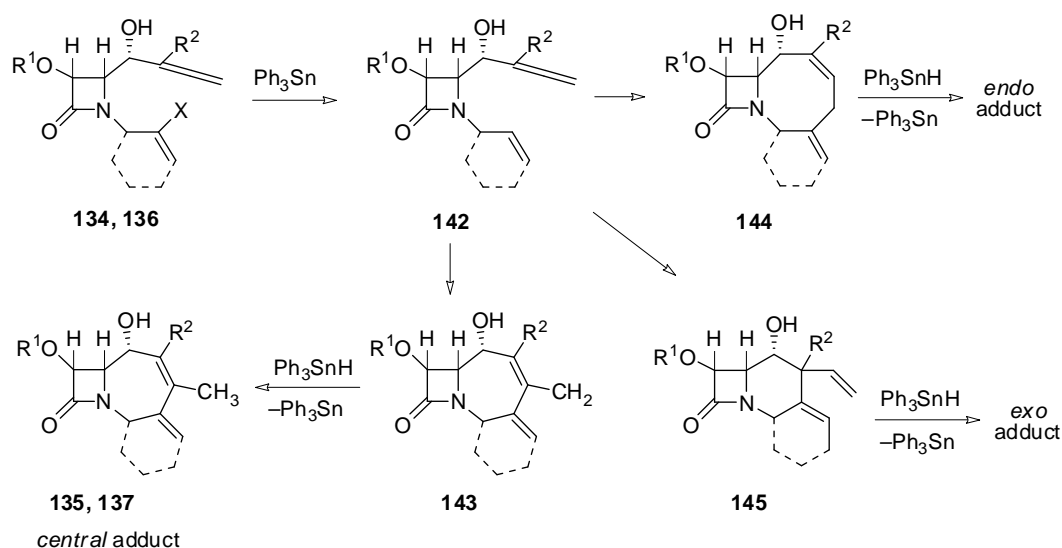
Scheme 48

Aryl-2-azetidinone-tethered haloarenes were used for the regiocontrolled preparation of fused tetracyclic biaryl-2-azetidinones which can be considered as β-lactam-biaryl hybrids via aryl-aryl radical cyclization [42]. Treatment of *trans*-β-lactams **146** with tributyltin hydride and AIBN in benzene at reflux under high dilution conditions (215 mL per mmol of starting 2-azetidinone) smoothly formed the corresponding condensed tetracyclic biaryl-2-azetidinones **147** in good yields as single *trans*-diastereomers after chromatographic purification (Scheme 49) together with small amounts of reduced starting material.

146

$\xrightarrow[\text{C}_6\text{H}_6 \,/\, \Delta]{\text{HSnBu}_3 \,/\, \text{AIBN}}$

147 (60–72%)
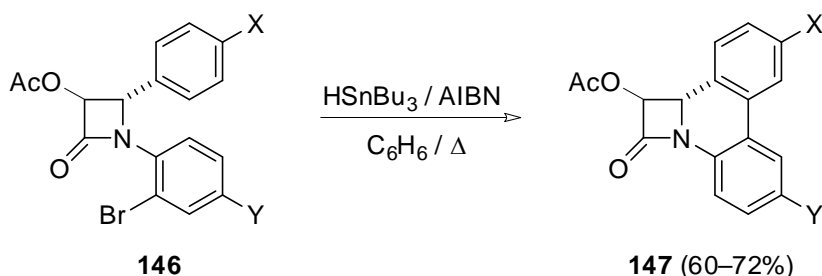
X = MeO, H; Y = H, Me

Scheme 49

3.3
Using Metal-Mediated Reactions

It has been reported the ring-closing metathesis (RCM) of 1,4-bis(ene)-substituted 2-azetidinones **148**, allowing synthetically rapid access to a wealth of novel, potentially biologically active, bicyclic β-lactam arrays, **149** (Scheme 50) [43]. The ring-closing metathesis runs were performed using either a molybdenum catalyst (Schrock catalyst) or a ruthenium catalyst (Grubbs' carbene), depending on the requirements of the reaction. Seven-membered ring closure to a

35

homooxacephem derivative was achieved in an excellent isolated yield of 84%, clearly demonstrating the synthetic utility of this method in these systems. Closure of bicyclic β-lactams with increasing ring sizes was possible, albeit progressively less successful. The eight-membered ring system was produced in 52% yield using 5% mol of Schrock catalys and in an improved 76% yield using 10% mol of the molybdenum catalyst. The nine-membered fused system was isolated in only 12% yield under the same conditions but could be optimized to 23% using 20% mol of Schrock catalyst. The ten-membered ring was produced in 3% yield using 5 mol % of the molybdenum catalyst and in 10% yield under high dilution and a higher catalyst loading.


148 n = 1–4   **149** (10–92%)

X = O, NTs, S, CH$_2$
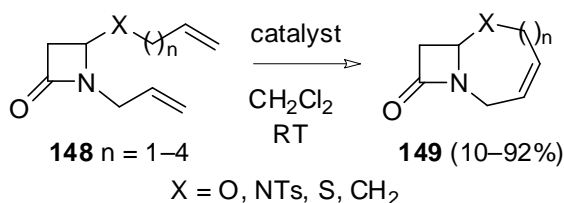
Scheme 50

While these results clearly established that polyfunctional β-lactam dienes were excellent substrates for metathesis, the reactions were not appropriate for the synthesis of bioactive β-lactam carboxylic acids. In order to find utility for this metathetic approach in the generation of novel drug candidates, a carboxylic acid motif adjacent to the lactam nitrogen was installed. The requisite framework was incorporated via Ireland–Claisen rearrangement of silyl ketene acetals derived from allyl ethers **150**. The silyl ketene acetals underwent smooth rearrangement affording the corresponding carboxylic acids in excellent yields, but as inseparable 1:1 mixtures of diastereoisomers. The above carboxylic acids had only limited solubility in the normal solvents for metathesis, and were directly converted into the corresponding ethyl or *p*-nitrobenzyl esters **151**. Treatment of monocyclic dienes **151** with Schrock or Grubbs carbenes resulted in cyclization to provide bicyclic β-lactams **152** (Scheme 51) [44].

150   **151**   **152** (50–98%)

X = O, NTs, S, CH$_2$

R = PNB, Et

n = 0–1
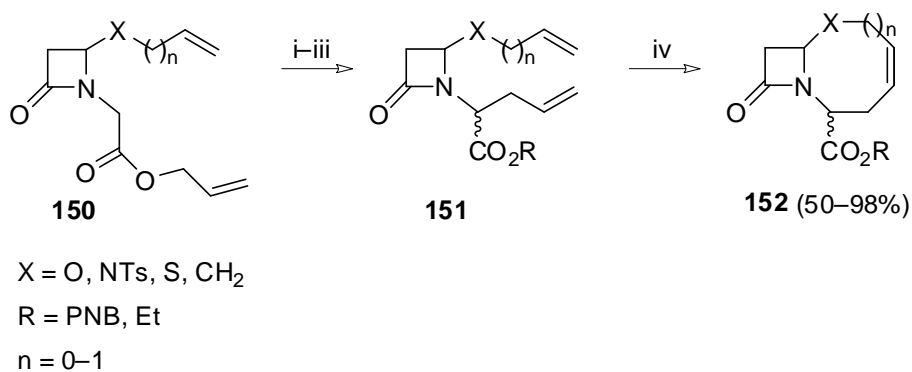
Scheme 51 i) LiHMDS, THF; ii TMSCl, Δ; iii RBr, K$_2$CO$_3$, DMF; iv catalyst, CH$_2$Cl$_2$, RT.

The synthesis of bicyclic 2-azetidinones **154** has been accomplished by ring-closing metathesis reaction of monocyclic diene- and enyne-β-lactams. The enyne metathesis of compounds **153** afforded bicycles **154** in good yields (Scheme 52) [45].
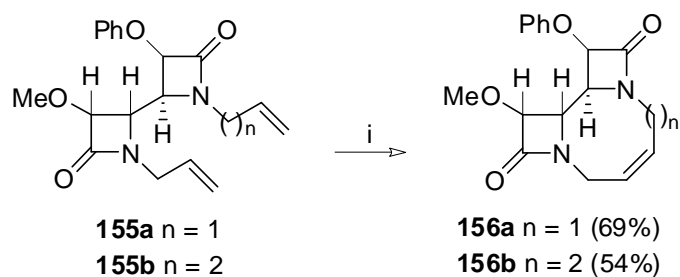

153

154 (72–100%)

$R^1 = H$, OTBS ; $R^2 = H$, OTBS
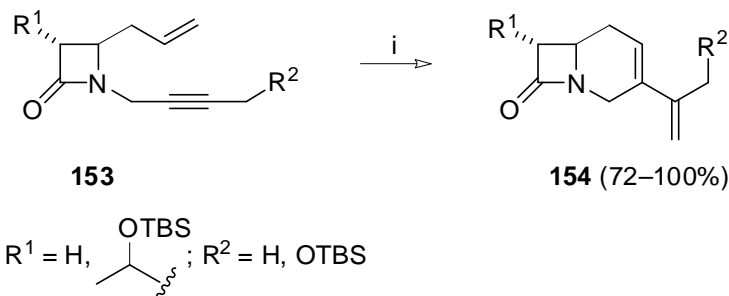
Scheme 52 i) [Cl$_2$(PCy$_3$)$_2$Ru=CHPh], CH$_2$Cl$_2$, RT.
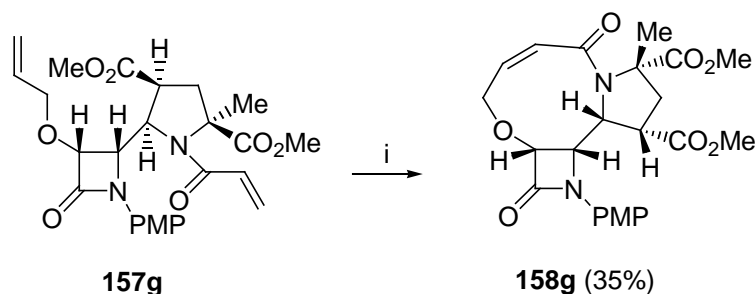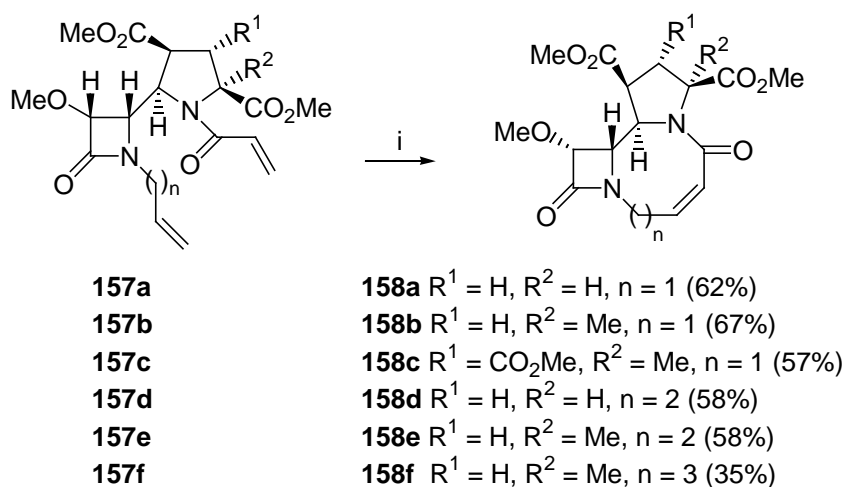
It has been reported that conveniently substituted bis-β-lactams, pyrrolidinyl-β-lactams and piperidinyl-β-lactams undergo ring-closing methatesis using Grubbs' carbene, Cl$_2$(Cy$_3$P)$_2$Ru=CHPh, to give medium-sized rings fused to bis-2-azetidinone, pyrrolidinyl-2-azetidinone or piperidinyl-2-azetidinone systems [46]. The diolefinic cyclization precursors were obtained from optically pure 4-oxoazetidine-2-carbaldehydes bearing an extra alkene tether at position 1 or 3 of the β-lactam ring via [2+2] cycloaddition of imino 2-azetidinones, *N*-metalated azometine ylide [3+2] cycloaddition and subsequent *N*-acylation of the pyrrolidinyl nitrogen atom, or through aza Diels–Alder of 2-azetidinone-tethered imines. Under standard reaction conditions, the combination of cycloaddition reactions of 2-azetidinone-tethered imines with ring-closing methatesis offers an asymmetric entry to a variety of unusual fused tricyclic 2-azetidinones bearing two bridgehead nitrogen atoms.

Treatment of dienes **155**, **157**, and **159** with Grubbs' catalyst under smooth ring-closing metathesis conditions (5 mol%, CH$_2$Cl$_2$, 25 °C), analogous to those described for bicyclic β-lactams, did not furnished the desired tricycles. The majority of the reaction mixture was composed of unreacted dienes. It was found that dienic substrates **155**, **157**, and **159** require more vigorous conditions for ring closure. Among the various solvents and conditions tested, it was found that toluene at reflux temperature gave the best yields of tricyclic-β-lactams containing medium-sized central rings. Exposure of dienes **155**, **157**, and **159** to the ruthenium catalyst Cl$_2$(Cy$_3$P)$_2$Ru=CHPh under optimized cyclization conditions (5 mol% catalyst, 0.03 M, toluene, 110 °C) resulted in clean formation of tricycles **156**, **158**, and **160** in moderate to good yields (31–69%) (Schemes 53–55). It should be mentioned that for a successful RCM a structural condition must be satisfied in the starting dienes, namely, a relative *anti*-stereochemistry at the single bond connecting the two heterocyclic rings. Interestingly, in the Grubbs'

carbene promoted reaction of compounds **159b** and **159c** together with the RCM products **160b** and **160c** *N*-deallylation products were also isolated.

155a n = 1
155b n = 2

156a n = 1 (69%)
156b n = 2 (54%)

Scheme 53 i) [Cl$_2$(PCy$_3$)$_2$Ru=CHPh], toluene, reflux.

157a
157b
157c
157d
157e
157f

158a R^1 = H, R^2 = H, n = 1 (62%)
158b R^1 = H, R^2 = Me, n = 1 (67%)
158c R^1 = CO$_2$Me, R^2 = Me, n = 1 (57%)
158d R^1 = H, R^2 = H, n = 2 (58%)
158e R^1 = H, R^2 = Me, n = 2 (58%)
158f R^1 = H, R^2 = Me, n = 3 (35%)

157g

158g (35%)

Scheme 54 i) [Cl$_2$(PCy$_3$)$_2$Ru=CHPh], toluene, reflux.

159a
159b
159c

160a n = 1 (53%)
160b n = 2 (31%)
160c n = 3 (33%)
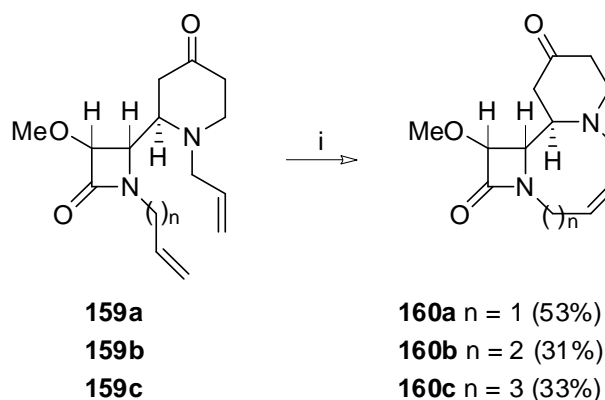
Scheme 55 i) [Cl$_2$(PCy$_3$)$_2$Ru=CHPh], toluene, reflux.

The synthesis of tricyclic β-lactams via palladium-catalyzed cyclization of iodoaryl β-lactams using a catalyst system comprising 10 mol% Pd(AcO)$_2$, 20 mol% PPh$_3$, and Tl$_2$CO$_3$ (2 mol) has been afforded [47]. The methallyl β-lactam **161** underwent *7-endo-trig* cyclization to give a 8:1 mixture of double bonds isomers **162** and **163** (Scheme 54).
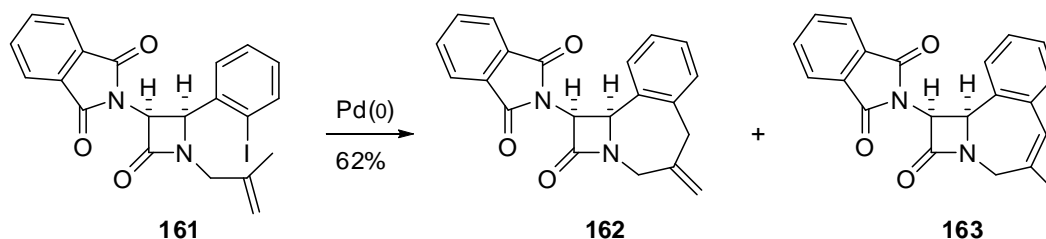
Scheme 56

It has been shown that combination of bromoallylation reaction and Heck cyclization is an useful methodology for the preparation of a variety of fused bicyclic β-lactams of non-conventional structure [48]. Starting from acetates **164** and using palladium acetate as the palladium source, DMF as solvent, potassium carbonate as base and triphenylphosphine the reaction occurred. The reaction conditions were further optimized and typical results for the preparation of bicyclic β-lactams **165–168** are summarized in Scheme 57.
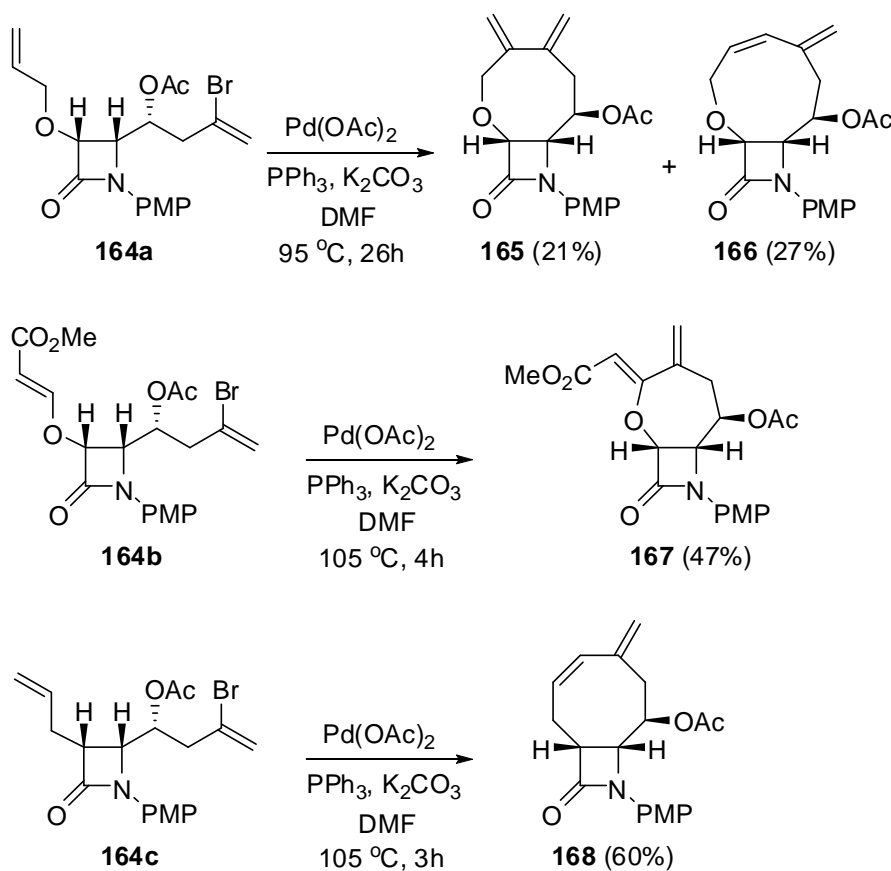
Scheme 57

Special mention deserves the Heck reaction of acetate **164d**. Substitution pattern on bromodiene **164d** should direct the regiochemical outcome of the cyclization to the six-membered or seven-membered ring formation. Interestingly, we found that the reaction produced the five-membered fused bicycle **169a** as the only isomer. As a result of steric congestion, the stereocontrolled construction of carbon atoms having four carbon ligands is a formidable challenge for chemical synthesis. Compound **169a** is remarkable since it bears a quaternary stereocenter. Adduct **169a** presumably arises from the Pd-catalyzed 5-*exo* cyclization of the initially formed α,β-unsaturated carbonyl compound **170a**. A similar reaction pattern was observed on reacting bromodienes *syn*-**164e** and *anti*-**164e**. Thus, bicyclic β-lactams **169b** and **169c** were also prepared through essentially the same procedure (Scheme 58).

164d R = H
syn-**164e** R = Me

Pd(OAc)$_2$, PPh$_3$
K$_2$CO$_3$, DMF

170a, **170b**

169a (60%; 150 °C, 1 h)
169b (65%; 105 °C, 0.5 h)

anti-**164e**

Pd(OAc)$_2$, PPh$_3$
K$_2$CO$_3$, DMF
105 °C, 0.5 h

169c (60%)
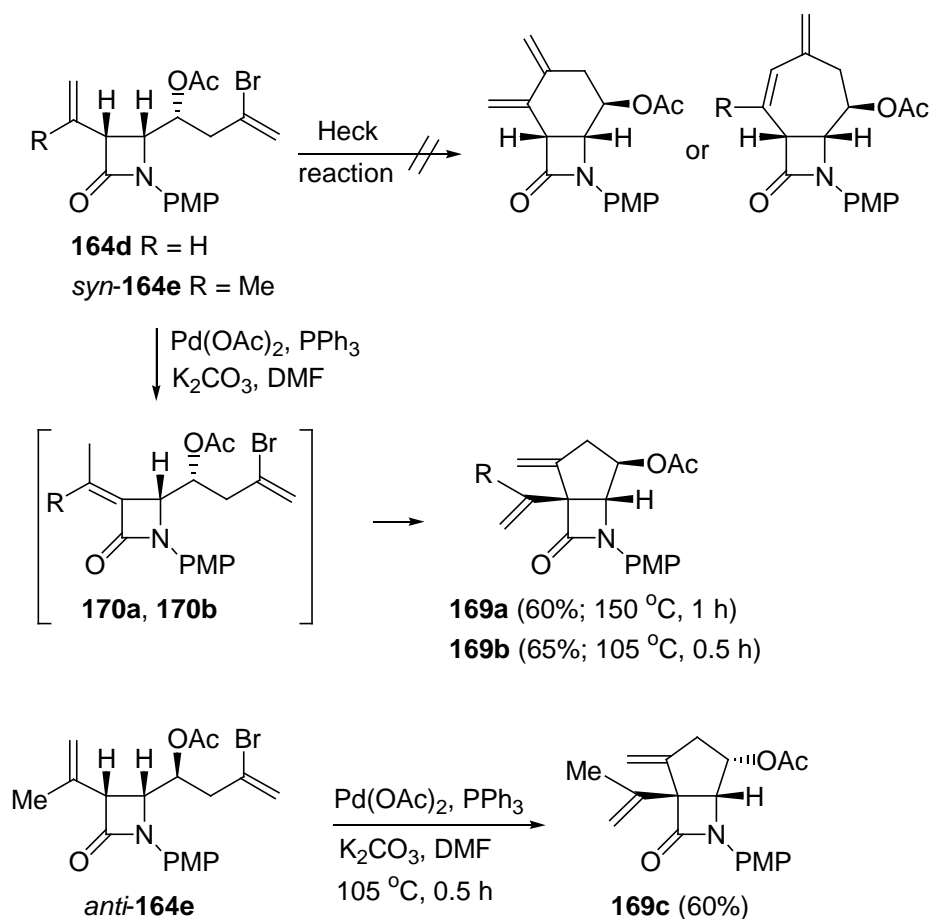
Scheme 58

The above hypothesis was probed showing that the intermediate **170** could be obtained from **164**, and that this new bromodiene does give the corresponding fused β-lactam **169** under Heck conditions. This mechanistically informative result was provided by the treatment of the bromohomoallylic acetate **164d** with potassium carbonate in acetonitrile to give a separable mixture of isomeric bromodienes *E*-**170a** and *Z*-**170a**, which under palladium catalysis afforded the

expected bicycle **169a**. The two-step synthesis of compound **169a** from diene **164d** is depicted in Scheme 59.
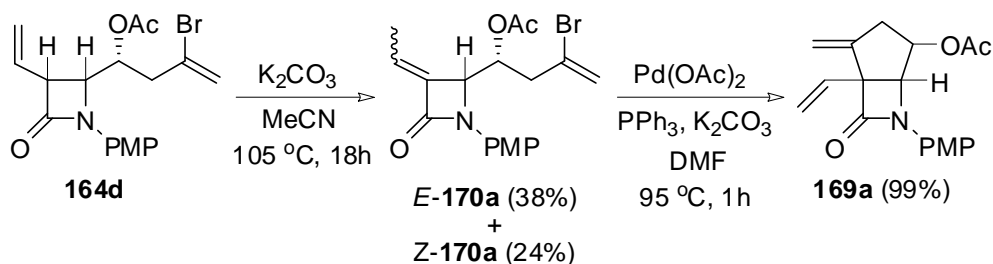
Scheme 59

The allene moiety represents a versatile and useful building block in organic synthesis. However, selectivity problems are significant. Intramolecularization of the reactions, usually by placing the group at such distance that five- or six-membered rings are formed, automatically should solve the positional selectivity problems because larger rings are unfavored. The less exploited allenic variant of the Pauson–Khand type cycloaddition was explored in allenynes **171** [49]. Substitution patterns on allenynes **171** were selected in order to direct the regiochemical outcome of the cycloaddition to the six-membered central ring formation because the intramolecular variant of the Pauson–Khand reaction has been largely restricted to the construction of bicyclo[3.3.0]octenones and bicyclo[4.3.0]nonenones. However, it was found that the [2+2+1] cycloaddition produced tricycles **173** bearing a central seven-membered ring as the only isomer. Cycloadducts **173** presumably arises from the isomerization of the initially formed adducts **172** (Scheme 60). Conjugation of the dienone moiety with the lone pair of the nitrogen atom is believed to promote the formation of compounds **173**.
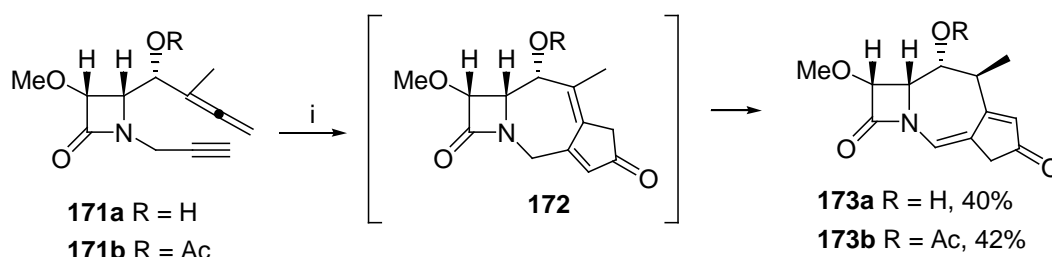
Scheme 60 i) Co$_2$(CO)$_8$, Me$_3$NO, CH$_2$Cl$_2$, RT.

The 1,2-functionalization of the allene moiety in 2-azetidinone-tethered allenynol derivatives has also been explored [49]. Carbamate **174** was selected as the starting material for the palladium(II)-catalyzed reaction. The above carbamate was prepared from the α-allenic alcohol **171a** by treatment with tosyl isocyanate. Reaction of compound **174** was carried out at room temperature in acetonitrile in the presence of 10 mol% of Pd(OAc)$_2$, 5 equiv of LiBr, 2 equiv of Cu(OAc)$_2$ and

1.2 equiv of K$_2$CO$_3$ under an atmospheric pressure of oxygen. The ^{1}H-NMR spectrum of the crude material displayed neither signal corresponding to the allene or alkyne moieties. To our delight, the resulting product was identified after purification as the tricycle **175** (Scheme 61). Compound **175** was isolated in moderate yield as the only isomer, indicating that both the regio- and stereoselectivity are extremely high.
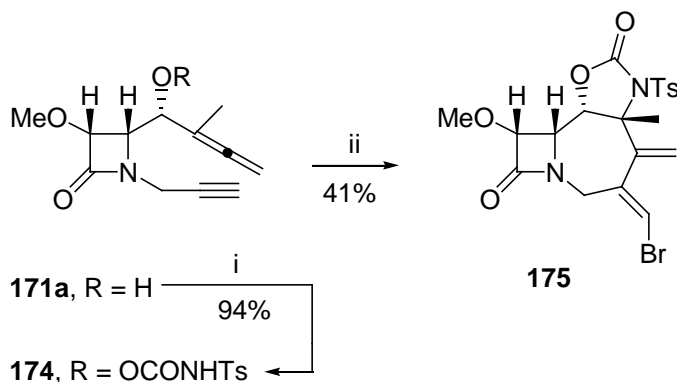
Scheme 61 i) TsNCO, THF, RT; ii Pd(OAc)$_2$ 10 mol%, LiBr, Cu(OAc)$_2$, K$_2$CO$_3$, O$_2$, acetonitrile, RT.

The formation of compound **175** could be rationalized in terms of an unprecedented domino allene amidation/intramolecular Heck–type reaction. Compound **176** must be the not isolable intermediate. A likely mechanism for **176** should involve a (π-allyl)palladium intermediate. The allene-palladium complex **177** is formed initially and suffers a nucleophilic attack by the bromide to produce a σ-allylpalladium intermediate, which rapidly equilibrates to the corresponding (π-allyl)palladium intermediate **178**. Then, an intramolecular amidation reaction on the (π-allyl)palladium complex must account for intermediate **176** formation. Compound **176** evolves to tricycle **175** via a Heck–type-coupling reaction. The alkenylpalladium intermediate **179**, generated in the *7-exo-dig* cyclization of bromoenyne **176**, was trapped by the bromide anion to yield the fused tricycle **175** (Scheme 62). Thus, the same catalytic system is able to promote two different, but sequential catalytic cycles.
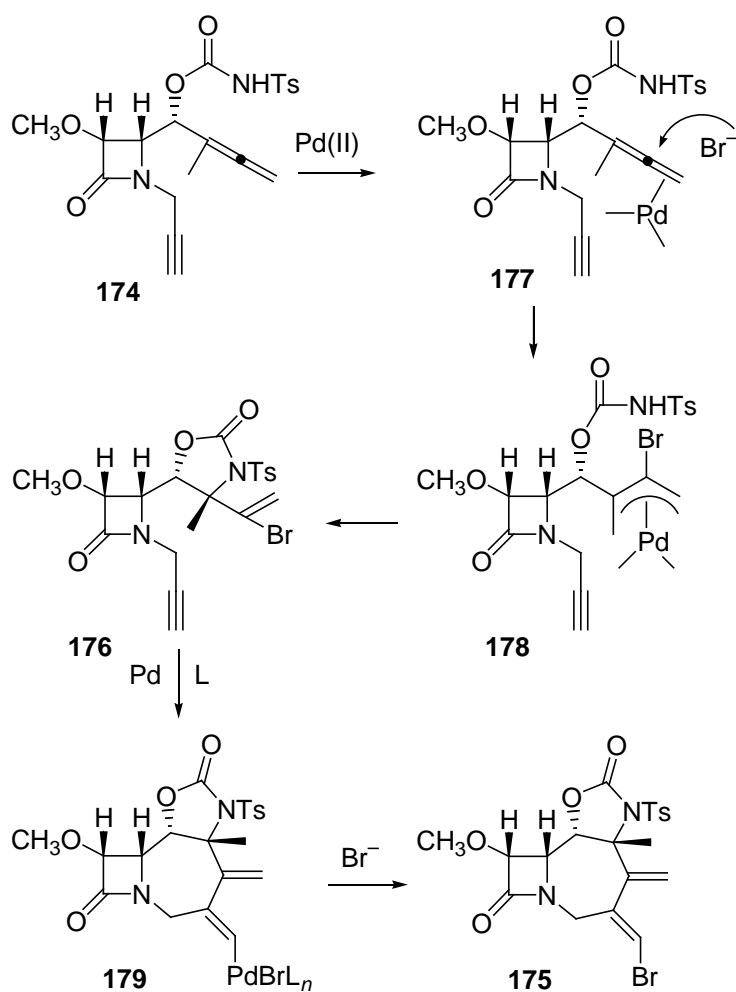
Scheme 62

The reactivity of the allenynol moiety itself under these cascade conditions was also explored [49]. Interestingly, treatment of allenynols **171a**, **180** and **181** under the above palladium-catalyzed domino reaction conditions afforded the bridged medium-sized ring tricycles **182** as single isomers albeit in moderate yields (Scheme 63). Although complete conversion was observed by TLC and ^{1}H NMR analysis of the crude reaction mixtures, the high polarity of adducts **182** may be responsible for the modest isolated yields. Compounds **182** are remarkable since they possess an unusual pyramidalized bridgehead structure. An analogous cascade process to compound **175** formation seems to be taking part in this transformation. However, a dramatic change in the regioselectivity of the nucleophilic insertion into the (π-allyl)palladium intermediate **183** was observed when the bridged dihydrofurans were formed as the exclusive products. The thermochemically more stable five–membered intermediate **184** must be involved in the reaction rather than the corresponding regioisomeric oxirane. Taking into account the precedent explanation for fused compound **175** formation, Scheme 64 outlines a mechanistic hypothesis for the achievement of bridged compounds **182**.

171a n = 1   **182a** (48%)
180   n = 2   **182b** (26%)

181   **182c** (52%)
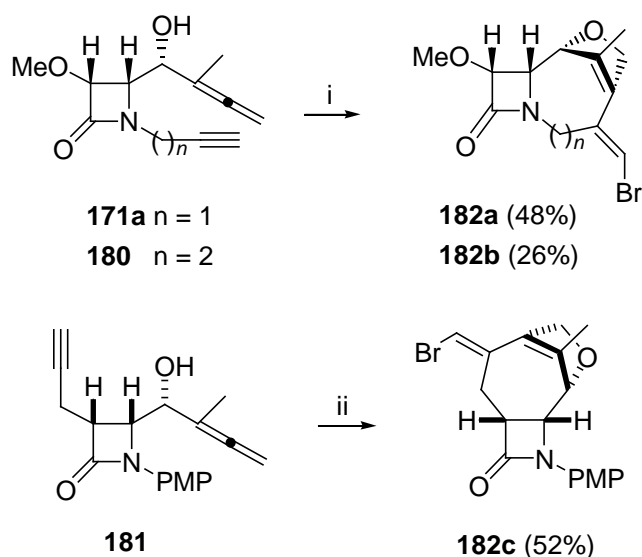
Scheme 63 i) Pd(OAc)$_2$ 10 mol%, LiBr, Cu(OAc)$_2$, K$_2$CO$_3$, O$_2$, acetonitrile, RT; ii Pd(OAc)$_2$ 10 mol%, LiBr, Cu(OAc)$_2$, K$_2$CO$_3$, O$_2$, acetonitrile, reflux.
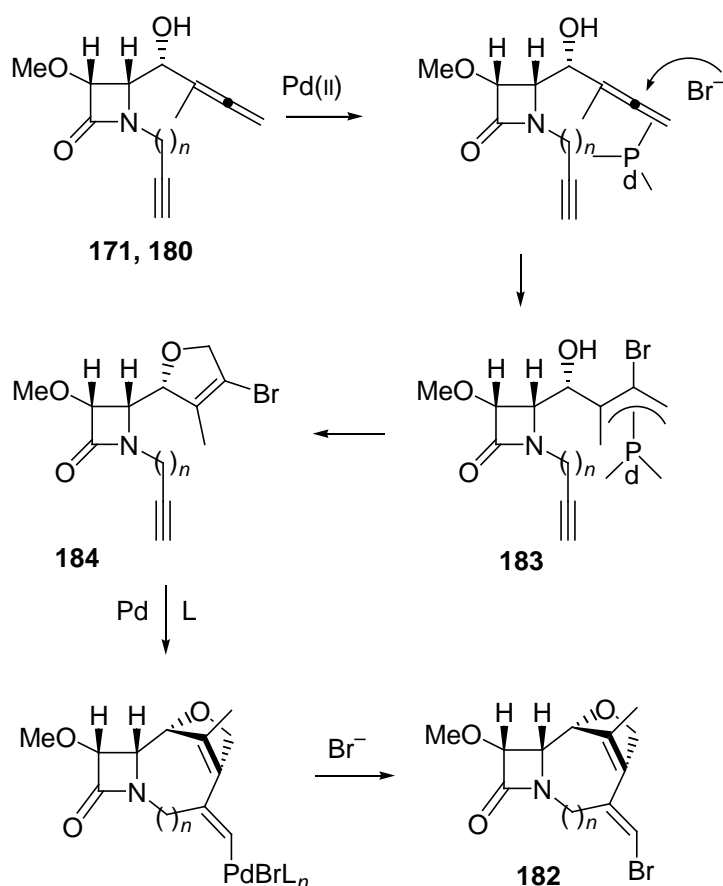
Scheme 64

γ-Allenol **185a** was used as initial substrate in a screen to identify regioselective hydroalkoxylation catalysts for the preparation of bicyclic β-lactams [50]. Thus, [PtCl$_2$(CH$_2$=CH$_2$)]$_2$ and AgNO$_3$ afforded rather low yield or disappointing diastereomeric mixture of bicycle **186a**. Although AgNO$_3$ was less diastereoselective than [PtCl$_2$(CH$_2$=CH$_2$)]$_2$ (60:40 vs 100:0), it was a more

44

efficient catalyst affording adduct **186a** in reasonable yield (54% vs 12%). Gratifyingly, it was found that Au[I] or Au[III] salts were effective as 5-*exo* selective hydroalkoxylation catalysts. AuCl₃ was selected as catalyst of choice because of its superior performance. No diastereo- or regioisomeric products were detected, giving exclusively the fused five-membered oxacycles **186** (Scheme 65). Tetrahydrofuran-fused 2-azetidinones **186** are remarkable since they bear a quaternary stereocenter.

185a R¹ = Bn
185b R¹ = allyl

5 mol % AuCl₃,
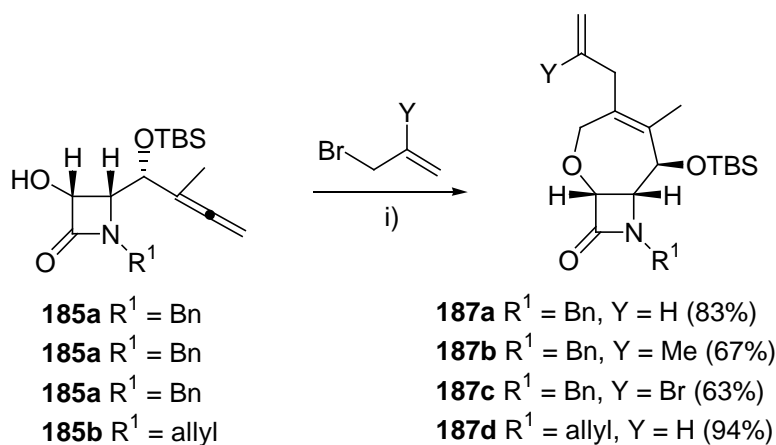CH₂Cl₂, RT

186a R¹ = Bn (57%)
**186b** R¹ = allyl (58%)
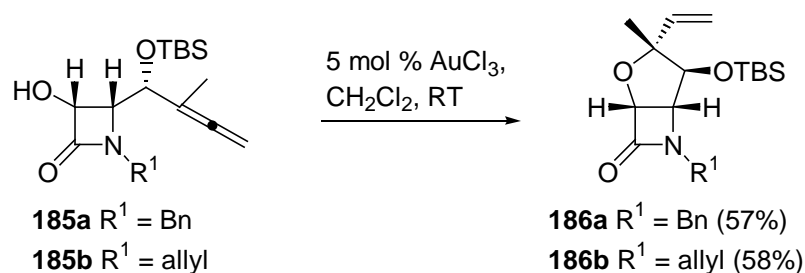
Scheme 65

Having found a solution for the 5-*exo* selective hydroalkoxylation, it was next examined the more intricate heterocyclizative problem associated with tuning the regioselectivity of γ-allenols. Worthy of note, the Pd[II]-catalyzed cyclizative coupling reaction of γ-allenols **185a** and **185b** with allyl halides gave impressive yields (up to 94%) of the desired seven-membered adducts **187a–d** (Scheme 66), resulting from a 7-*endo* oxycyclization [51].

185a R¹ = Bn
185a R¹ = Bn
185a R¹ = Bn
185b R¹ = allyl

187a R¹ = Bn, Y = H (83%)
187b R¹ = Bn, Y = Me (67%)
187c R¹ = Bn, Y = Br (63%)
187d R¹ = allyl, Y = H (94%)

Scheme 66 i) 5 mol % PdCl₂, DMF, RT.

When MOM protected γ-allenol derivatives **188a** and **188b** were used as starting materials for the Au[III]-catalyzed cycloisomerization, the 5-*exo* mode was completely reverted to a 7-*endo* cyclization to afford bicycles **189** in fair yields (Scheme 67). It seems that the reactivity in this type of Au[III]-catalyzed reactions is determined by the presence or absence of a methoxymethyl protecting group at the γ-allenol oxygen atom, as the free γ-allenols **185a** and **185b** gave 5-*exo* hydroalkoxylation, while MOM protected γ-allenol derivatives **188a** and **188b**

exclusively underwent a 7-*endo* oxycyclization [51]. No other isomers or side products were detected.

188a P = 4-BrC$_6$H$_4$CO
188b P = PMPCO

189a P = 4-BrC$_6$H$_4$CO (58%)
189b P = PMPCO (45%)
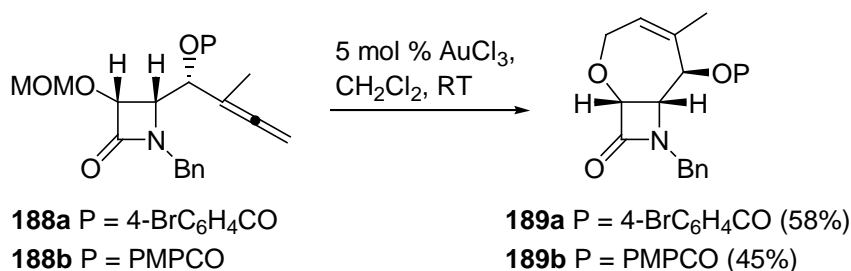
Scheme 67

The pathway proposed in Scheme 68 looks valid for the formation of products **189**. It could be presumed that the initially formed allenegold complex **190** undergoes an intramolecular attack (7-*endo* versus 5-*exo* oxyauration) by the (methoxymethyl)oxy group, giving rise no to species **191** but to the tetrahydrooxepine intermediate **192**. Protonolysis of the carbon–gold bond linked to an elimination of methoxymethanol would then liberate the bicycle **189** with concomitant regeneration of the Au^{III} species. Probably, the proton in the last step of the catalysis cycle comes from the trace amount of water present in the solvent or in the catalyst. In order to confirm the mechanistic proposal of Scheme 68, labeling studies with deuterium oxide were performed. Thus, the addition of two equivalents of D$_2$O to the solution of MOM protected γ-allenol **188b** and AuCl$_3$ in dichloromethane caused the disappearance of the peak at 6.35 ppm, which is the signal of the proton H4, on the 2-oxa-8-azabicyclo[5.2.0]non-4-en-9-one **189b**. The fact that the AuCl$_3$-catalyzed conversion of allenol **188b** into bicycle **189b** in the presence of 2 equiv of D$_2$O afforded 4-[D]-**189b** as judge by ^{1}H NMR spectroscopy, suggests that a deuterolysis of the carbon–gold in species **192** has occurred. It may be inferred that different steric effects in the organometallic species **191** and **192** may be responsible for the different reactivity preference, stabilizing one of the intermediates rather than the other. In the presence of MOM group, 5-*exo* cyclization falters. Probably, 5-*exo* oxyauration via **191** is restricted by the steric hindrance between the (methoxymethyl)oxy group and the substituents at the quaternary stereocenter [52].
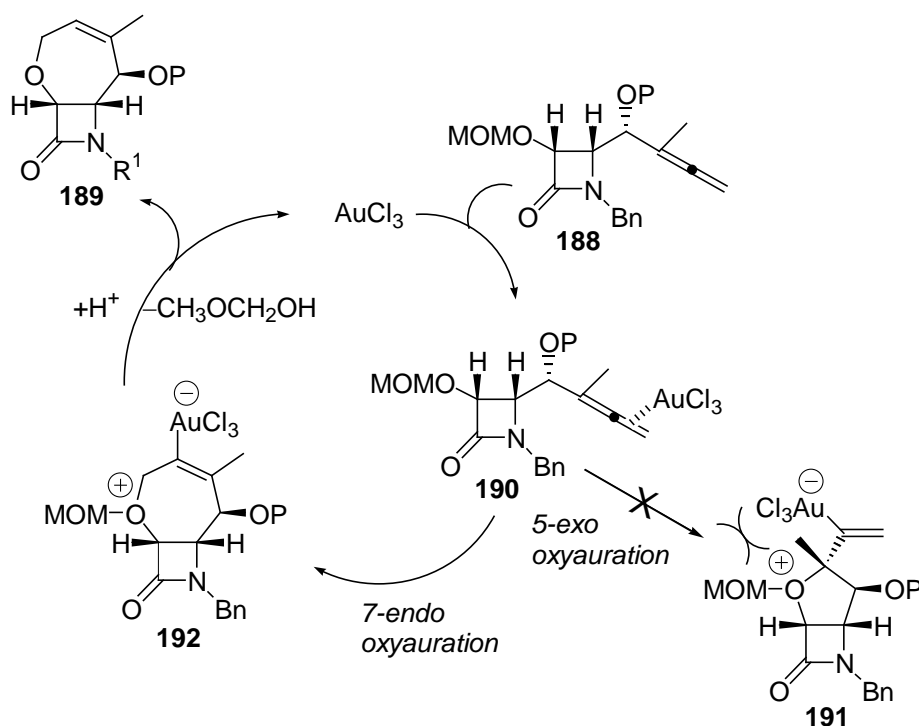
Scheme 68

A synthetic route to β-lactam-fused enediynes by intramolecular Kinugasa reaction has been successfully developed. The method has widened the scope of Kinugasa reaction in the synthesis of sensitive systems like tricycle **193** (Scheme 69) [53].
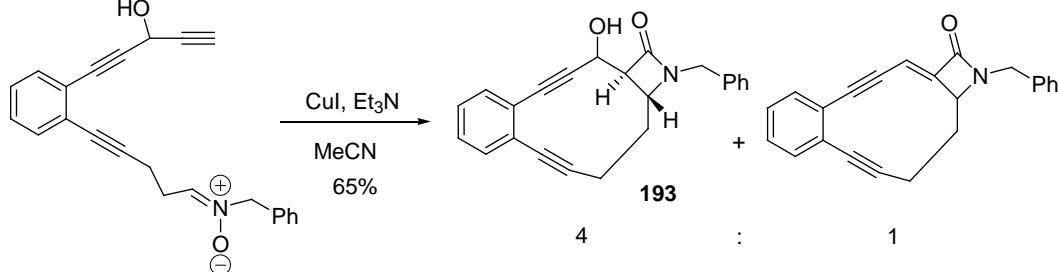
Scheme 69

3.4
Using Cyclization Reactions

A wide range of α,β-unsaturated aldehydes, including 3-alkyl derivatives, undergo *N*-heterocyclic carbene (NHC)-catalyzed annulations with *N*-sulfonyl ketimines under mild conditions to provide bicyclo[3.2.0]lactams **194** with outstanding diastereo- and enantioselectivity (Scheme 70) [54]. This concise route to β-lactams established four new chiral centers in a single operation. Although this process could occur via the intermediacy of a catalytically generated

homoenolate equivalent, the stereochemical outcome supports a tandem or concerted aza-benzoin/oxy-Cope reaction as the key bond-forming step.
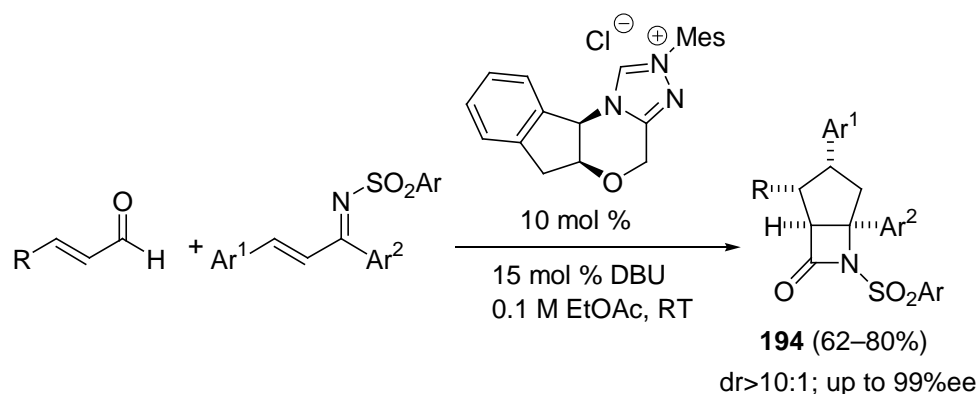
Scheme 70

Two different stereocontrolled accesses to new 4-hydroxypipecolic acid analogues with a bicyclic β-lactam structure have been developed by using intramolecular reductive amination or allenic hydroamination reactions in 2-azetidinone-tethered azides [55]. When it was tried to reduce azide **195** using the triphenylphosphine method, a complex reaction mixture was observed. Fortunately, it was found that 2-azetidinone-tethered azidoallenic acetate **196** when treated at room temperature with triphenyltin hydride in benzene solution, gave in a totally regioselective fashion the bicyclic 4-hydroxypipecolic acid analogue **197** through a 6-*exo-dig* aminocyclization with concomitant acetate cleavage (Scheme 71). Exposure of aldol adduct **198** to the Ph$_3$P–H$_2$O reductive system did afford a mixture of highly polar compounds, which could not be characterized. The hydrogenation reaction of azidoaldol **198** performed in the presence of Boc$_2$O revealed through ^{1}H NMR monitoring the formation of little cyclization product, while the major components in the mixture were side-products. Then, it was decided to carry out reduction of the azide and *in situ* cyclization and protection of the resultant secondary amine as the benzylcarbamate. Interestingly, exposure of compound **198** to H$_2$ (1 atm) in ethyl acetate at room temperature in the presence of a catalytic amount of Pd (10% on C) followed by the addition of benzyl chloroformate, provided the 4-hydroxypipecolic acid analogue **199** with a bicyclic β-lactam structure (Scheme 72).
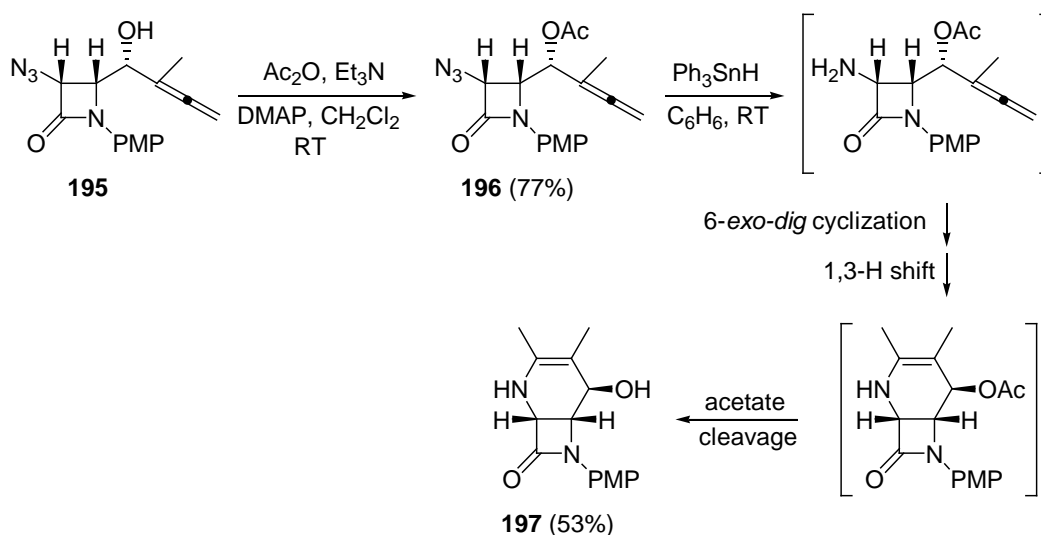
Scheme 71
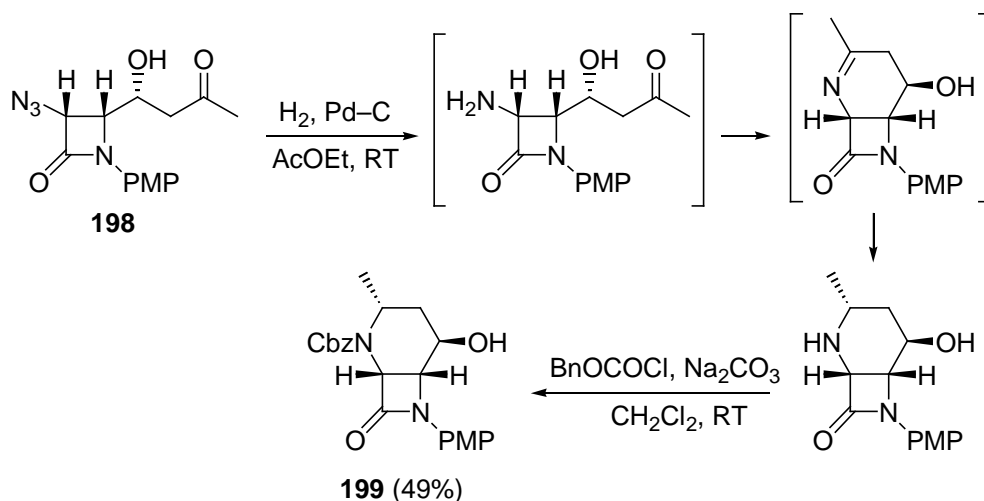
Scheme 72

A convenient approach to synthesize novel selenium-β-lactams, namely 3-selena-1-dethiacephems **200**, was accomplished via the regioselective iodocyclization reaction (Scheme 73) [56]. The key starting materials, alkyne-selenoureas **201**, for this approach were readily prepared by the *N*-alkylation reaction of the corresponding previously known propargyl-azetidinones with a wide variety of isoselenocyanates under basic conditions. First, it was examined the reaction of β-alkyne-selenourea **201a** (R^2 = 4-ClC$_6$H$_4$) with 1.05 equiv of iodine or NIS in THF at room temperature. It was found that the reaction was highly dependent on the type of electrophile used. With NIS, it was obtained the desired 3-selena-1-dethiacephem **200a** (R^1 = H, R^2 = 4-ClC$_6$H) along with 3-aza-4-selenoxo-1-dethiacephem and 3-aza-4-oxo-1-dethiacephem. The 3-aza-4-oxo-1-dethiacephem was probably formed by the decomposition of 3-aza-4-selenoxo-1-dethiacephem. However, when the reaction was carried out using 1.05 equiv of

iodine, the desired product **200a** was exclusively produced in good isolated yield (84%) with only a trace amount of byproducts (as indicated by TLC). To improve the yield of cyclization, different reaction conditions were then screened. CH_2Cl_2 was found to be the best solvent for the cyclization reaction. Furthermore, the reaction was heavily influenced by the amount of iodine added, and the best result was obtained when 1.25 equiv of iodine was used (92% yield). On the basis of the above results, the iodocyclization of other alkyne-selenoureas **201** with 1.25 equiv of iodine was conducted in CH_2Cl_2 at room temperature. A variety of 3-selena-1-dethiacephems **200** were obtained in good to excellent yields. The nature of the R^2 group on the selenourea had very little effect on the reaction rate or product yields. Aryl-substituted selenoureas gave slightly higher yield than alkyl-substituted selenoureas. The aryl substitution at alkynes was also well accommodated and afforded the cyclized products in excellent yields. The reaction shows high regioselectivity for six-membered ring selenacephems **200**. Seven-membered ring products were never detected under these reaction conditions.

201 (85–99%)   **200** (82–95%)
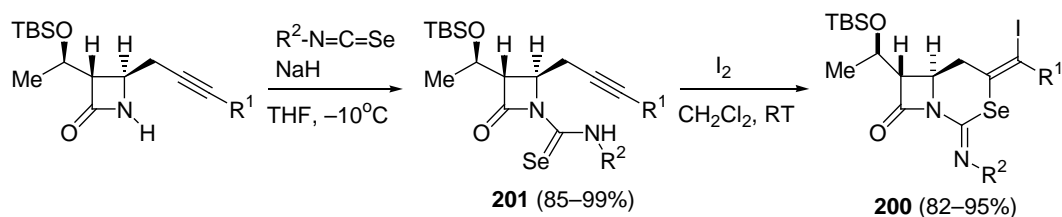
Scheme 73

4
Conclusion

The synthesis of spirocyclic and fused unusual β-lactam derivatives has been discussed. The 2-azetidinone skeleton has been extensively used as a template on which to build the carbo(hetero)cyclic structure joined to the four-membered ring, using the chirality and functionalization of the β-lactam ring as a stereocontrolling element. In many cases the compounds described in this chapter were included because of an interesting synthesis or structure, although limited biological data were found.

5
References

1.   (a) Singh GS (2004) Mini-Rev. Med. Chem. 4: 69; (b) Singh GS (2004) Mini-Rev. Med. Chem. 4: 93; (c) Niccolai D, Tarsi L., Thomas R. J. (1997) Chem Commun: 2333; (d) Southgate R. (1994) Contemp Org Synth 1:417; (e) Southgate R, Branch C, Coulton S, Hunt E (1993) Recent Progress

in the Chemical Synthesis of Antibiotics and Related Microbial Products, Lukacs G Ed., Springer: Berlin, 2:621; (f) Page I Ed. (1992) The Chemistry of β-Lactams, Chapman and Hall: London; (g) Morin RB, Gorman M Ed (1982) Chemistry and Biology of β-Lactam Antibiotics, Academic: New York.

2. (a) Cabri W, Di Fabio R (2000) Sanfetrinems From Bench to Market: The Evolution of Chemical Synthesis, Oxford University Press, Oxford, 72; (b) Kanno O, Kawamoto I (2000) Tetrahedron 56: 5639; (b) Hanessian S, Reddy B (1999) Tetrahedron 55: 3427; (c) Biondi S, Pecunioso A, Busi F, Contini SA, Donati D, Maffeis M, Pizzi DA, Rossi L, Rossi T, Sabbatine FM, (2000) Tetrahedron 56:5649; (d) Ghiron C, Rossi T The Chemistry of Trinems in Targets in Heterocyclic Systems-Chemistry and Properties, Attanasi OA, Spinelli D. Eds. (1997) Societa Chimica Italiana: Rome, 1:161. (e) Ngo J, Castañer J (1996) Drugs of the Future 21:1238.

3. Brown AG, Butterworth D, Cole M, Hanscomb G, Hood JD, Reading C (1976) J Antibiot 29:668.

4. Some of the more notable advances concern the development of mechanism-based serine protease inhibitors of elastase, cytomegalovirus protease, thrombin, prostate specific antigen, and cell metastasis and as inhibitors of acyl-CoA cholesterol acyl transferase. (a) Veinberg G, Vorona M, Shestakova I, Kanepe I, Lukevics E (2003) Curr Med Chem 10:1741; (b) Hogan PC, Corey EJ (2005) J Am Chem Soc 127:15386; (c) Clader JW (2004) J Med Chem 47:1; (d) Kvaerno L, Ritter T, Werder M, Hauser H, Carreira EM (2004) Ang Chem Int Ed 43:4653; (e) Burnett DA (2004) Curr Med Chem 11:1873; (f) Page MI, Laws AP (2000) Tetrahedron 56:5631; (g) Haley TM, Angier SJ, Borthwick AD, Singh R, Micetich RG (2000) Drugs 3:512.

5. It has been reported that β-lactams act to modulate the expression of glutamate neurotransmitter transporters via gene activation. Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, Jin L, Hoberg MD, Vidensky S, Chung DS, Toan SV, Bruijn LI, Su Zz, Gupta P, Fisher PB (2005) Nature 433:73.

6. (a) Macías A, Morán Ramallal A, Alonso E, del Pozo C, González J. (2006) J Org Chem 71:7721; (b) Bittermann H, Gmeiner P. (2006) J Org Chem 71: 97; (c) Bittermann H, Böckler F, Einsiedel J, Gmeiner P (2006) Chem Eur J 12:6315; (d) Alonso E, López-Ortiz F, del Pozo C, Peralta E, Macías A, González J. (2001) J Org Chem 66:6333.

7. For their evaluation as cholesterol absorption inhibitors, see: (a) Kambara T, Tomioka K (1999) J Org Chem 64:9282. For their evaluation as inhibitors of poliovirus and rhinovirus 3C-proteinases, see: (b) Skiles JW, McNeil D (1990) Tetrahedron Lett 31:7277.

8. (a) Macías A, Alonso E, del Pozo C, Venturini A, González J (2004) J Org Chem 69:7004; (b) Macías A, Alonso E, del Pozo C, González J (2004) Tetrahedron Lett 45:4657; (c) Alonso E, del Pozo C, González J (2002) Synlett 69; (d) Dolle RE, Li CS, Novelli R, Kruse LI, Eggleston D (1992) J Org Chem 57:128.

9. (a) Baran PS, Shenvi RA (2006) J Am Chem Soc 128:14028; (b) Sun C, Lin X, Weinreb SM (2006) J Org Chem 71:3159; (c) Baran PS, Shenvi RA, Mitsos CA (2005) Ang Chem Int Ed 44:3714; (d) Nishikawa T, Kajii S, Isobe M (2004) Synlett 2025; (e) Pinder JL, Weinreb SM (2003) Tetrahedron Lett 44:4141. Synthetic studies and biosynthetic speculation inspired by an unexpected reaction on the marine alkaloid chartelline C have been described: (f) Kajii S, Nishikawa T, Isobe M (2008) Chem Commun 3121.

10. (a) Alcaide B, Almendros P, Aragoncillo, C (2007) Chem Rev 107:4437; (b) Alcaide B, Almendros P (2004) Curr Med Chem 11:1921; (c) Deshmukh ARAS, Bhawal BM, Krishnaswamy D, Govande VV, Shinkre BA, Jayanthi A (2004) Curr Med Chem 11:1889; (d) Alcaide B, Almendros P (2002) Synlett 381; (e) Palomo C, Aizpurua JM, Ganboa I, Oiarbide M (2001) Synlett 1813; (f) Alcaide B, Almendros P (2001) Chem Soc Rev 30:226; (g) Palomo C, Aizpurua JM, Ganboa I, Oiarbide M

(1999) Amino-acids 16:321; (h) Ojima I, Delaloge F (1997) Chem So Rev 26:377; (i) Manhas MS. Wagle DR, Chiang J, Bose AK (1988) Heterocycles 27:1755.

11. Alonso E, del Pozo C, González J (2002) J Chem Soc Perkin Trans 1, 571.

12. del Pozo C, Macías A, López-Ortiz F, Maestro MA, Alonso E, González J (2004) Eur J Org Chem 535.

13. Arjona O, Murcia MC, Plumet J (2002) Tetrahedron Lett 34:6405.

14. Anklam S, Liebscher J (1998) Tetrahedron 54:6369.

15. (a) Nishikawa T, Kajii S, Isobe M (2004) Chemistry Lett 33:440; (b) Nishikawa T, Kajii S, Isobe M (2004) Synlett 2025.

16. Chowdari NS, Suri JT, Barbas III CF (2004) Org Lett 6:2507.

17. Clayden J, Hamilton SD, Mohammed RT (2005) Org Lett 7:3673.

18. Zanobini A, Gensini M, Magull J, Vidović D, Kozhushkov SI, Brandi A, de Meijere A (2004) Eur J Org Chem 4158.

19. Zanobini A, Brandi A, de Meijere A (2006) Eur J Org Chem 1251.

20. Alcaide B, Almendros P, Luna A, Torres MR (2008) Org Biomol Chem 6:1635.

21. Simone MI, Edwards AA, Tranter GE, Fleet GWJ (2008) Tetrahedron: Asymmetry 19:2887.

22. Alcaide B, Almendros P, Martínez del Campo T, Rodríguez-Acebes R (2004) Tetrahedron Lett 45:6429.

23. Alcaide B, Almendros P, Martínez del Campo T, Rodríguez-Acebes R (2007) Adv. Synth. Catal. 349:749.

24. Alcaide B, Almendros P, Rodríguez-Acebes R (2005) Chem Eur J 11:5708.

25. Alcaide B, Almendros P, Martínez del Campo T, Carrascosa R (2008) Chem Asian J 3:1140.

26. Alcaide B, Pardo C, Rodríguez-Ranera C, Rodríguez-Vicente A (2001) Org Lett 3:4205.

27. Alcaide B, de Murga RM, Pardo C, Rodríguez-Ranera C (2004) Tetrahedron Lett 45:7255.

28. (a) Desroy N, Robert-Peillard F, Toueg J, Duboc R, Hénaut C, Rager MN, Savignac M, Genêt JP (2004) Eur J Org Chem 4840; (b) Desroy N, Robert-Peillard F, Toueg J, Hénaut C, Duboc R, Rager MN, Savignac M, Genêt JP (2004) Synthesis 2665; (c) Duboc R, Hénaut C, Savignac M, Genêt JP, Bhatnagar N (2001) Tetrahedron Lett 42:2461.

29. (a) Alcaide B, Almendros P (1999) Tetrahedron Lett 40:1015; (b) Alcaide B, Almendros P, Salgado NR (2000) J Org Chem 65:3310.

30. Alcaide B, Almendros P, Pardo C, Rodríguez-Ranera C, Rodríguez-Vicente A (2003) J Org Chem 68:3106.

31. (a) Alcaide B, Almendros P, Aragoncillo C, Redondo MC (2005) Eur J Org Chem 98; (b) Alcaide B, Almendros P, Aragoncillo C, Redondo MC (2002) Chem Commun 1472.

32. Alcaide B, Almendros P, Aragoncillo C, Redondo MC, Torres MR (2006) Chem Eur J 12:1539.

33. (a) Alcaide B, Sáez E (2005) Eur J Org Chem 1680; (b) Alcaide B, Alonso JM, Aly MF, Sáez E, Martínez-Alcázar MP, Hernández-Cano F (1999) Tetrahedron Lett 40:5391. (c) Alcaide B, Sáez E (2000) Tetrahedron Lett 41:1647

34. Brown D, Brown GA, Andrews M, Large JM, Urban D, Butts CP, Hales NJ, Gallagher T (2002) J Chem Soc Perkin Trans 1, 2014.

35. Ruano G, Grande M, Anaya J (2002) J Org Chem 67:8243.

36. Alcaide B, Almendros P, Rodríguez-Vicente A, Ruiz MP (2005) Tetrahedron 61:2767.

37. (a) Alcaide B, Almendros P, Aragoncillo C (2001) J Org Chem 66:1612; (b) Alcaide B, Almendros P, Aragoncillo C (1999) Chem Commun 1913.

38. Penfold DJ, Pike K, Genge A, Anson M, Kitteringham J, Kilburn JD (2000) Tetrahedron Lett 41:10347.

39. Joshi SN, Puranik VG, Deshmukh ARAS, Bhawal BM (2001) Tetrahedron: Asymmetry 12:3073.

40. Alcaide B, Almendros P, Rodríguez-Acebes R (2005) Synthesis 2335.

41. (a) Alcaide B, Almendros P, Aragoncillo C (2003) Org Lett 5:3795; (b) Alcaide B, Almendros P, Aragoncillo C, Redondo MC (2007) J Org Chem 72:1604.

42. Alcaide B, Almendros P, Pardo C, Rodríguez-Vicente A, Ruiz MP (2005) Tetrahedron 61:7894.

43. (a) Barrett AGM, Baugh SPD, Braddock DC, Flack K, Gibson VC, Procopiou PA (1997) Chem Commun 1375; (b) Barrett AGM, Baugh SPD, Gibson VC, Giles MR, Marshall EL, Procopiou PA (1997) Chem Commun 155; (c) Barrett AGM, Baugh SPD, Braddock DC, Flack K, Gibson VC, Giles MR, Marshall EL, Procopiou PA, White AJP, Willians DJ (1998) J Org Chem 63:7893.

44. Barrett AGM, Ahmed M, Baker SP, Baugh SPD, Braddock DC, Procopiou PA, White AJP, Willians DJ (2000) J Org Chem 65:3716.

45. Tarling CA, Holmes AB, Markwell RE, Pearson ND (1999) J Chem Soc Perkin Trans 1, 1695.

46. (a) Alcaide B, Almendros P, Alonso JM, Redondo MC (2003) J Org Chem 68:1426; (b) Alcaide B, Almendros P, Alonso JM, Aly MF, Redondo MC (2001) Synlett 773.

47. Burwood M, Davies B, Díaz I, Grigg R, Molina P, Sridharan V, Hughes M (1995) Tetrahedron Lett 36:9053.

48. Alcaide B, Almendros P, Rodríguez-Acebes R (2005) J Org Chem 70:2713.

49. Alcaide B, Almendros P, Aragoncillo C (2002) Chem Eur J 8:1719.

50. Alcaide B, Almendros P, Martínez del Campo T (2007) Angew Chem Int Ed 46:6684.

51. Alcaide B, Almendros P, Martínez del Campo T, Soriano E, Marco-Contelles, JL (2009) Chem Eur J 15:1901.

52. Alcaide B, Almendros P, Martínez del Campo T, Soriano E, Marco-Contelles, JL (2009) Chem Eur J 15:1909.

53. Pal R, Basak A (2006) Chem. Commun 2992.

54. He M, Bode JW. (2008) J Am Chem Soc 130:418.

55. Alcaide B, Almendros P, Luna A, Martínez del Campo T (2008) J Org Chem 73:1635.

56. Garud DR, Koketsu M (2008) Org Lett 10:3319.

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