Allenyl-β-Lactams: Versatile Scaffolds for the Synthesis of Heterocycles

Benito Alcaide*[a] and Pedro Almendros*[b]

ABSTRACT: The hybrid allenic β-lactam moiety represents an excellent building block for carbo- and heterocyclization reactions, affording a large number of cyclic structures containing different sized skeletons in a single step. This strategy has been studied under thermal and radical induced conditions. More recently, the use of transition metal catalysis has been introduced as an alternative relying on the activation of the allenic component. On the other hand, the intramolecular version has attracted much attention as a strategy for the synthesis of bi- and tricyclic compounds in a regio- and stereoselective manner. This overview focuses on the most recently developed cyclizations on 2-azetidinone-tethered allenes along with remarkable early works accounting for the mechanism, as well as for the regio- and diastereoselectivities of the cyclizations.

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Key words: allenes · alkynes · cyclization · lactams · radicals

Introduction

β-Lactams are not only the most commonly prescribed antibacterial agents,[1] but also exhibit some other biological activities, for which they are considered as enzyme inhibitors,[2] potential anticancer chemotherapeutics drugs,[3] and gene activation agents.[4] 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,[5] provide the motivation to explore new methodologies for the synthesis of substances based on the β-lactam core. In addition, 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.

On the other hand, allene chemistry has attracted considerable attention in recent years and several reviews on their preparation and reactivities have been published.[6] Allenes have shown an interesting reactivity and selectivity affording complex structures in a limited number of steps.[7] Upon appropriate activation, the C–C double bonds can be attacked by various *O*-, *N*-, or *C*-nucleophiles. In fact, the chemistry of allenes has been applied for the preparation of natural and non-natural products of interest. 2-Azetidinone-tethered allenes can be regarded as hybrids of the pharmacologically and chemically relevant subunits of β-lactam and 1,2-diene. This paper embraces the gamut of carbo- and heterocyclizations on allene-β-lactams which make possible the preparation of a variety of different-sized carbocycles and heterocycles, and will focus on the most recent findings

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Carbocyclizations

Radical cyclizations

Instead of an alkene or an alkyne, an allene component is a fascinating substrate in a free radical cyclization because of its unique reactivity and the synthetic use of the final products.[8] However, regioselectivity problems are significant. The regiochemical possibilities of a radical cyclization using allenes are shown in Figure 1.

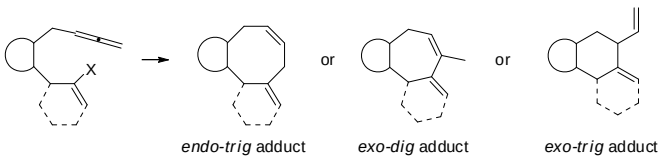
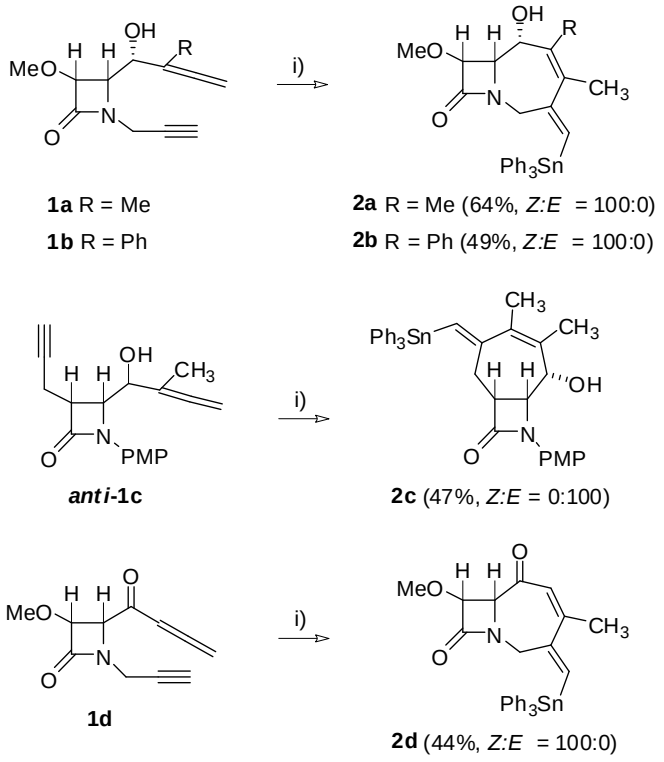


Figure 1. Possible regioisomers observed in the cyclization of allenes using free radicals.

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.[9] Starting allenes **1** were prepared via indium-mediated Barbier-type allenylation reactions of the corresponding β-lactam aldehydes in aqueous media.[9] In an initial study, it was found that allenynol **1a** when heated in the presence of triphenyltin hydride and

AIBN in benzene solution, gave the bicyclic β-lactam **2a** in 64% yield as a single regio- and *Z*-isomer. Tin-promoted cyclization of allenynol **1b** afforded the expected 2-azetidinone **2b** containing a medium-sized ring. Allenynol *anti*-**1c** having the alkynyl side chain at C3 instead of N1 underwent cyclization to afford the C3–C4 fused β-lactam **2c**. Similar behavior was observed for the free radical cyclization of allenynone **1d**, which afforded the heterobicyclic ketone **2d**. Interestingly, only bicycles **2** were found as a consequence of a totally regioselective radical cyclization onto the central carbon (Scheme 1). Neither the *endo-trig*-cyclized product nor the *exo-trig*-cyclized product was detected.



1a R = Me
1b R = Ph

2a R = Me (64%, *Z*:*E* = 100:0)
2b R = Ph (49%, *Z*:*E* = 100:0)

***anti*-1c**

2c (47%, *Z*:*E* = 0:100)

1d

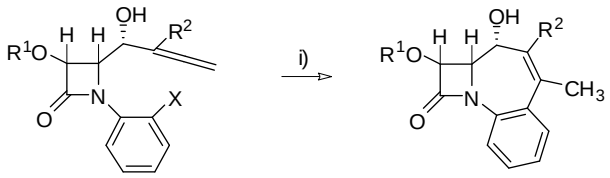
2d (44%, *Z*:*E* = 100:0)

Scheme 1. Preparation of bicyclic β-lactams through radical cyclization of allenynes. Reagents and conditions: i) Ph_3SnH (1.2 eq), AIBN (0.1 eq), benzene, reflux.

Benito Alcaide (right) was born in Aldea del Rey, Ciudad Real, Spain, in 1950. He received his B.S. degree (1972) and Ph.D. degree (1978) from the Universidad Complutense de Madrid (UCM) under the supervision of Professor Franco Fernández. After a 4-year period working on the chemistry of α-iminoketones and related compounds, he began working on β-lactam chemistry. In 1984 he assumed a position of Associate Professor of Organic Chemistry and in 1990 was promoted to Full Professor at the UCM. His current recent interests include β-lactam chemistry, asymmetric synthesis of compounds of biological interest, free radicals, cycloaddition reactions, allenes, metal-promoted cyclizations, C–C coupling reactions, and organocatalysis.

Pedro Almendros (left) was born in Albacete (Spain) in 1966. He received his B. S. degree (1989) and his Ph. D. degree (1994) from the Universidad de Murcia under the supervision of Profs. Molina and Fresneda. After three years (1995-1998) postdoctoral work with Prof. Eric J. Thomas (University of Manchester), supported by two postdoctoral grants (Spanish MEC and European Marie Curie), he joined the research group of Prof. Benito Alcaide (UCM, Madrid) in 1998 as Associate Researcher (Contrato de Reincorporación de Doctores y Tecnólogos). Subsequent appointments have included Assistant Professor at the UCM (2000-2002), and Científico Titular (Tenured Scientist) at the Instituto de Química Orgánica General, CSIC, Madrid. In 2007 he was promoted to Investigador Científico (Research Scientist) at the IQOG, CSIC, Madrid. He has co-authored over 130 research publications and 15 book chapters. Pedro has a Hirsch's index h = 32. His research interest includes β-lactam chemistry, allene chemistry, asymmetric synthesis, metal-promoted heterocyclizations, and C–C coupling reactions.

The extension of the above radical cyclization of 2-azetidinone-tethered allenynes to haloaryl allenes bearing the proradical center at N1 was explored. The tin-promoted radical reaction was also useful in the conversion of β-lactam allenes **3** having a bromo- or iodophenyl group at the nitrogen atom, into the corresponding bicyclic systems **4** with similar efficiency and selectivity (Scheme 2). Benzofused β-lactams **4** can be considered as superior cyclohomologous of benzocarbapenems and benzocarbacephems, which have been designed as suicide inactivators of β-lactamases.



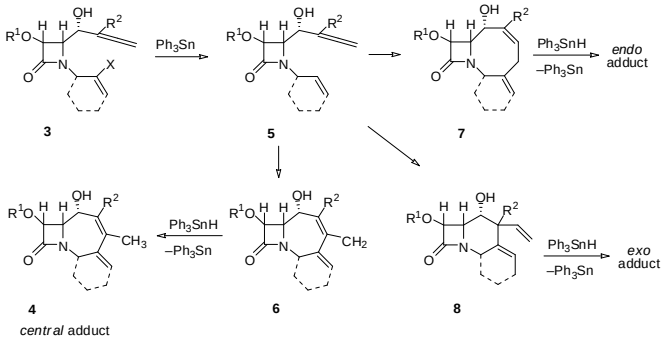
3

4 (41–52%)

R^1 = Me, Ph; R^2 = Me, Ph; X = Br, I

Scheme 2. Preparation of benzofused β-lactams through radical cyclization of haloaryl allenes. Reagents and conditions: i) Ph_3SnH (1.2 eq), AIBN (0.1 eq), benzene, reflux.

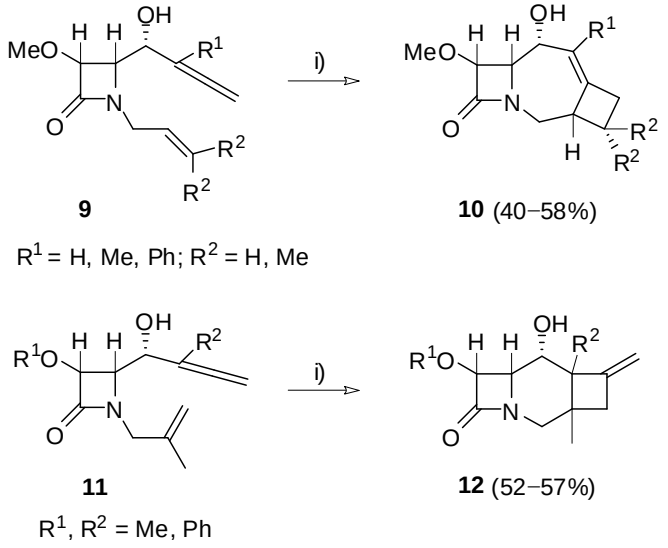
It is presumed that the stannyl radical, by addition to the terminal position of the triple bond in allenynes **1**, or through bromine abstraction in haloaryl allenes **3** gives the corresponding vinylic radical intermediates in the propagation step, followed by cyclization toward the central carbon atom of the allene moiety to give in a total regio- and stereoselective fashion fused cycles **2** and **4** via allylic radical intermediates. For haloaryl allenes (Scheme 3), while both *endo*- and *exo*-cyclizations of radical intermediates **5** would give vinylic radicals **7** and **8**, respectively, *central*-cyclization would lead to the energetically more favored allylic radicals **6**.



Scheme 3. Plausible pathway for the formation of benzofused β-lactams through radical cyclization of haloaryl allenes.

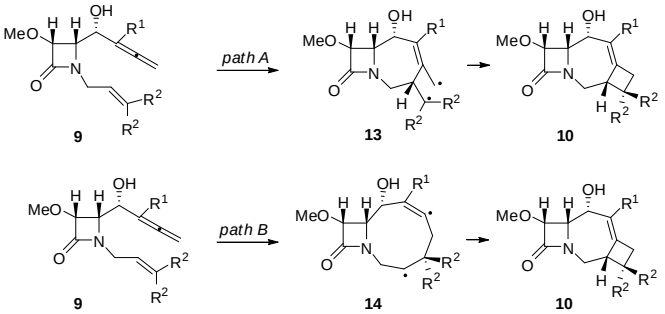
Cycloaddition reactions

The [2+2] cycloaddition of allenes represents an important strategy for the preparation of cyclobutane and cyclobutene derivatives with high atom economy.[10] Although the thermal process is forbidden, it has been studied photochemically, under thermal conditions involving diradical intermediates, and by the use of transition metal catalysts. The thermal [2+2] cycloaddition of 2-azetidinone-tethered enallenes has been used for the synthesis of strained tricyclic β-lactams containing a cyclobutane ring.[11] It was observed that the regioselectivity of this cycloaddition reaction is determined by the presence or absence of an alkyl substituent at the internal alkene carbon atom. Starting substrates **9** and **11** were prepared in a similar manner to allenols **1**. Treatment of enallenes **9** in toluene at 220 °C in a sealed tube afforded, in reasonable yields and complete regio- and diastereoselectivity, tricyclic β-lactams **10** (Scheme 4). The tricyclic ring structures **10** arise from the formal [2+2] cycloaddition of the alkene with the distal bond of the allene moiety. Interestingly, the regioselectivity of the process is not affected by the substitution at the allene group. On the other hand, it was observed that the presence of an internal substituent at the alkene moiety switched the regioselectivity. Thus, exposure of enallenes **11** to the above thermal conditions afforded methylenecyclobutane 2-azetidinones **12** as the sole products in reasonable yields (Scheme 4).



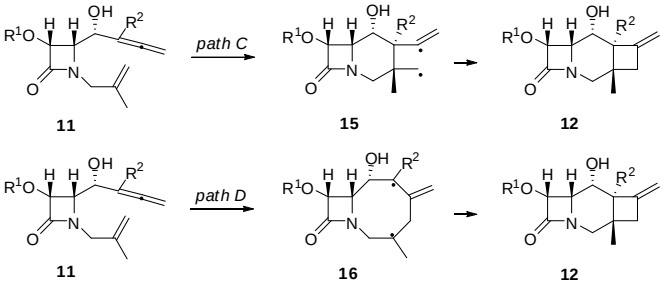
Scheme 4. Preparation of tricyclic β-lactams **10** and **12** by formal [2+2] cycloaddition reaction of 2-azetidinone-tethered enallenes **9** and **11**. Reagents and conditions: i) Toluene, 220 °C, sealed tube.

Formation of fused strained tricycles **10** has been rationalized by a radical mechanism involving an exocyclic diradical intermediate **13** through initial carbon–carbon bond formation between the central allene and proximal alkene carbon atoms (*path A*, Scheme 5). An alternative mechanism may also be proposed (*path B*, Scheme 5). This pathway would involve and endocyclic diradical intermediate **14**, arising from the initial attack of the terminal olefinic carbon onto the distal allene carbon. Both pathways would include a rapid ring closure of the diradical intermediates before bond rotation.



Scheme 5. Radical mechanistic proposals for the formation of strained tricycles **10**.

Analogously, formation of tricycles **12** has been rationalized by a mechanism which includes an exocyclic diradical intermediate **15** through initial carbon–carbon bond formation involving the proximal allene and internal alkene carbon atoms (*path C*, Scheme 6). An alternative pathway leading to compounds **12** has also been proposed in *path D*. This proposal would involve an endocyclic diradical intermediate **16**, arising from the initial attack of the terminal olefinic carbon onto the central allene carbon. The final ring-closing step of the diradical intermediates would account for the cyclobutane formation.

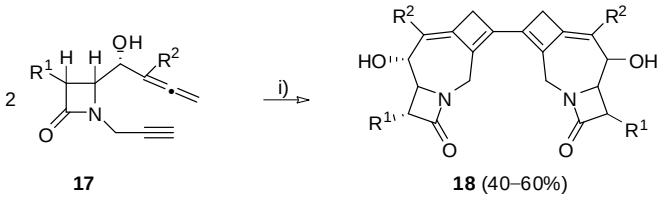


Scheme 6. Radical mechanistic proposals for the formation of strained tricycles **12**.

It seems that the regioselectivity in this type of [2+2] cycloaddition reaction is determined by the presence or absence of an alkyl substituent at the internal alkene carbon atom, as the enallenes **9** that are lacking a methyl group exclusively produced addition at the β,γ-double bond, while the allenenes **11**, which bear a methyl group at the internal olefinic carbon underwent a formal [2+2] cycloaddition reaction at the α,β-double bond. *Path A* (Scheme 5) looks valid for the formation of products **10**. For this case, the Me group stabilizes the exocyclic diradical, and the presence of the double bond promotes the allylic radical **13** over the alternative endocyclic vinylic radical **14** in *path B*. However, it could be presumed that for the formation of compounds **12**, *path D* (Scheme 6) is more reasonable. The simultaneous stabilization of the endocyclic diradical **16** by the presence of a methyl substituent and allylic stabilization makes this radical favoured over the exocyclic diradical **15**.

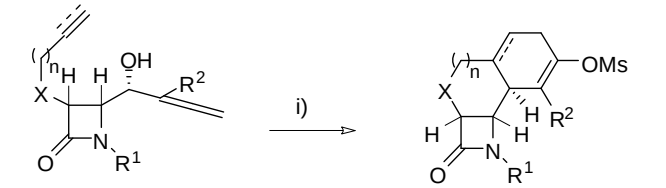
Copper-promoted domino alkyne homocoupling/double [2+2] bis(allenyne) cycloaddition of allenynes 17 afforded attached-ring

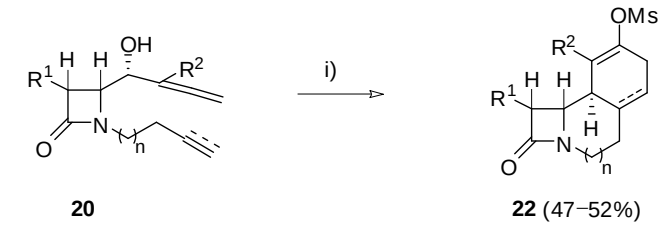
bis(tricyclic) β-lactams **18** in a straightforward fashion (Scheme 7).[12]



Scheme 7. Preparation of attached-ring bis(tricyclic) β-lactams **18**. Reagents and conditions: i) $Cu(OAc)_2$, K_2CO_3, MeCN, RT ⟶ 110°C.

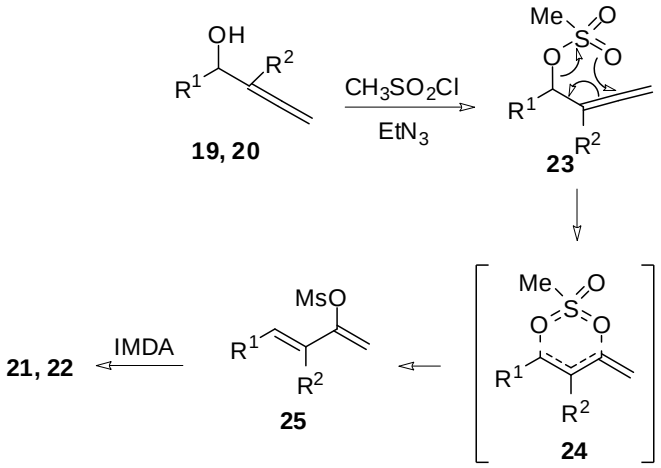
Cyclization precursors, allenes **17**, **19**, and **20** were readily obtained beginning from the appropriate 4-oxoazetidine-2-carbaldehyde via regio- and stereocontrolled indium-mediated Barbier-type carbonyl–allenylation reaction in aqueous media.[11] In Reaction of enallenes or allenynes **19** and **20** in the presence of methanesulfonyl chloride at 190 °C provided tricyclic azetidinones **21** and **22**. These tricycles have been obtained from monocyclic allenols, masked functionalized dienes, via a domino allenol transposition/intramolecular Diels–Alder (IMDA) reaction process (Scheme 8).[13]





Scheme 8. Preparation of tricyclic β-lactams **21** and **22** by tandem allenol transposition/IMDA reaction. Reagents and conditions: i) CH_3SO_2Cl, Et_3N, toluene, sealed tube, 190 °C.

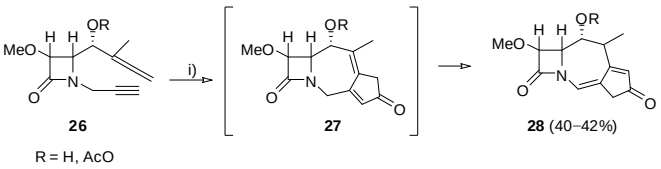
The mechanism of the one-pot allenol-diene transformation is depicted in Scheme 9.[14] The extremely high selectivity observed in the formation of dienes may point to a pericyclic reaction pathway. Accordingly, the allenol component reacts with methanesulfonyl chloride resulting in a methanesulfonate intermediate. Next, the in situ generated α-allenic methanesulfonate **23** suffers a [3,3]-sigmatropic rearrangement, involving the six-membered cyclic transition structure **24**, to give the corresponding mesyloxy-diene counterpart **25**.



Scheme 9. Plausible pathway for the formation of tricyclic β-lactams through tandem allenol transposition/IMDA reaction.

Metal-catalyzed reactions

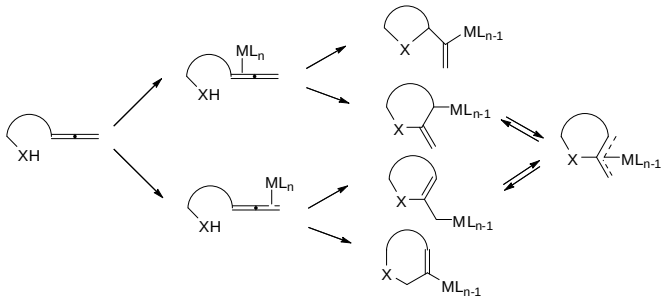
The Pauson–Khand reaction is a formal [2+2+1] cycloaddition involving an alkene, an alkyne and carbon monoxide. Several studies have greatly enhaced the synthetic utility of this process through the use of allenes in place of alkenes.[15] The less exploited allenic variant of the Pauson–Khand type cycloaddition has been explored in 2-azetidinone-tethered allenynes **26**.[16] Substitution patterns on allenynes **26** 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 **28** bearing a central seven-membered ring as the only isomer. Cycloadducts **28** presumably arises from the isomerization of the initially formed adducts **27** (Scheme 10). Conjugation of the dienone moiety with the lone pair of the nitrogen atom is believed to promote the formation of compounds **28**.



Scheme 10. Mechanistic proposal to explain the cobalt-promoted formation of tricyclic β-lactams from allenynes. Reagents and conditions: i) $Co_2(CO)_8$, Me_3NO, CH_2Cl_2, RT.

Heterocyclizations

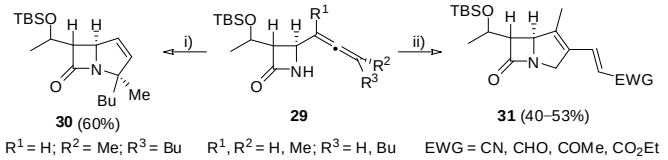
Allene heterocyclization chemistry has led to many synthetically useful transformations.[6–7] In particular, the transition-metal catalyzed cyclization of allene derivatives bearing nucleophilic substituents such as hydroxy, carbonyl, carboxy, thio, and amino groups, has attracted considerable attention in recent years. However, regioselectivity problems are significant (*endo-trig* versus *exo-dig* versus *endo-dig* versus *exo-trig* cyclization) (Scheme 11). Intramolecularization of the reactions, usually by placing the group at such distance that five- or six-membered rings are formed, should solve the positional selectivity problems because normally larger rings are unfavored.



Scheme 11. Possible regioisomers observed in the heterocyclization of allenes using metal catalysis.

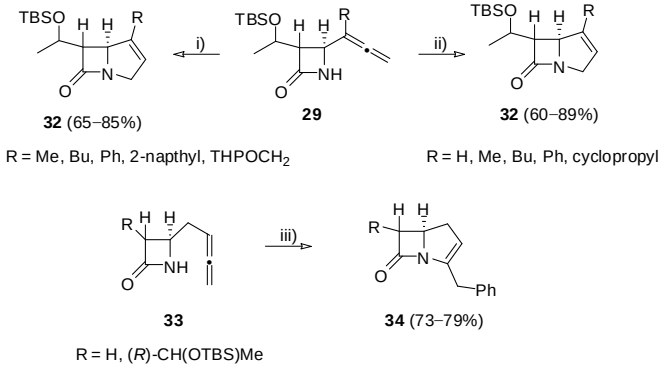
Aminocyclizations

Nitrogen heterocycles comprise one of the largest families or organic compounds, and many pharmacologically active molecules contain one or more nitrogen heterocycles.[17] The construction of the bicyclic β-lactam carbapenem nucleus using aminoallene chemistry is a formidable challenge. The seminal work from Liebeskind's group in 1988 on the silver- and palladium-promoted cyclizations of 4-allenyl-2-azetidinones **29** to Δ^1-carbapenems **30** and **31** may be considered the first report (Scheme 12).[18]



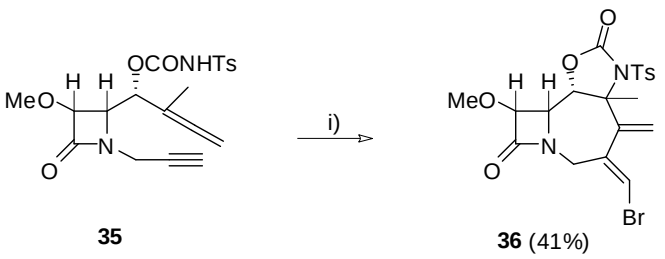
Scheme 12. Preparation of Δ^1-carbapenems by silver- and palladium-promoted aminoallene cyclizations. Reagents and conditions: i) 50 mol% $AgBF_4$, CH_2Cl_2, RT; ii) 100 mol% $PdCl_2$, Et_3N, H_2C=CH-EWG, CH_2Cl_2, RT.

More recent contributions include the catalytic use of metal salts (gold-, platinum-, and palladium-base catalysts) for the aminocyclization of allene-substituted β-lactams **29** and **33** to Δ^1-carbapenems **32** and Δ^2-carbapenems **34** (Scheme 13).[19–21]



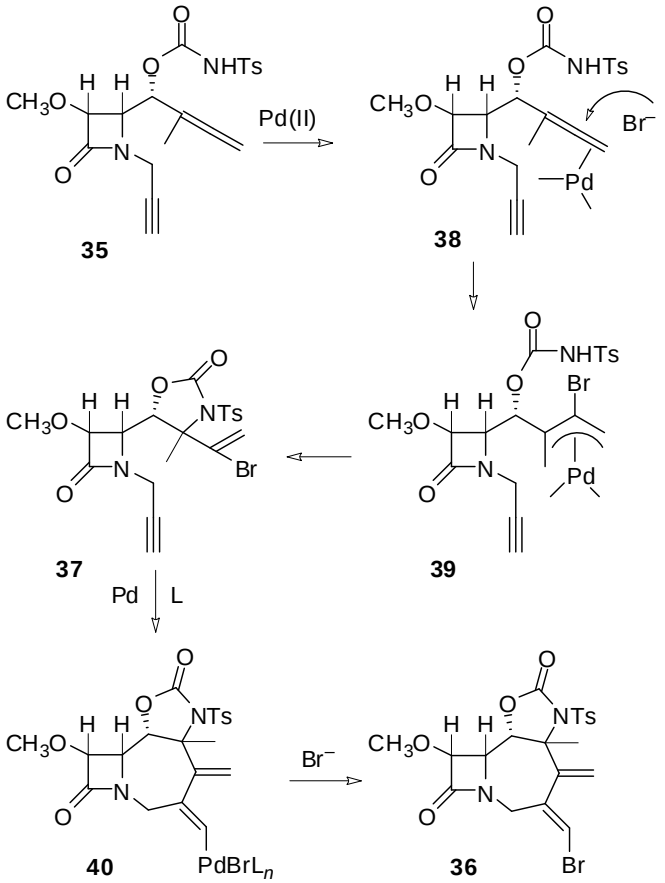
Scheme 13. Preparation of Δ^1- and Δ^2-carbapenems through metal-catalyzed aminoallene cyclizations. Reagents and conditions: i) 5 mol % $AuCl_3$, CH_2Cl_2, RT; ii) 5 mol % $PtCl_2$, toluene, 40 ºC; iii) 10 mol % $Pd(PPh_3)_4$, PhI, MeCN, reflux.

The 1,2-functionalization of the allene moiety in 2-azetidinone-tethered carbamate derivatives has been explored.[16] Reaction of carbamate **35** 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_2CO_3 under an atmospheric pressure of oxygen, resulted in the formation of the tricyclic β-lactam **36** (Scheme 14). Compound **36** was isolated in moderate yield as the only isomer, indicating that both the regio- and stereoselectivity are extremely high.



Scheme 14. Preparation of tricyclic β-lactam **36** by palladium-catalyzed aminoallene cyclization. Reagents and conditions: i) $Pd(OAc)_2$ 10 mol%, LiBr, $Cu(OAc)_2$, K_2CO_3, O_2, acetonitrile, RT.

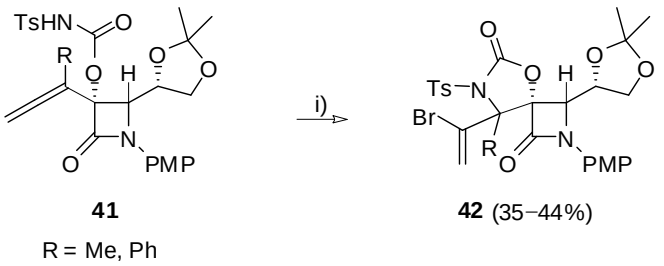
The formation of compound **36** could be rationalized in terms of an unprecedented domino allene amidation/intramolecular Heck–type reaction. Compound **37** must be the not isolable intermediate. A likely mechanism for **37** should involve a (π-allyl)palladium intermediate. The allene-palladium complex **38** 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 **39**. Then, an intramolecular amidation reaction on the (π-allyl)palladium complex must account for intermediate **37** formation. Compound **37** evolves to tricycle **36** via a Heck–type-coupling reaction. The alkenylpalladium intermediate **40**, generated in the *7-exo-dig* cyclization of bromoenyne **37**, was trapped by the bromide anion to yield the fused tricycle **36** (Scheme 15). Thus, the same catalytic system is able to promote two different, but sequential catalytic cycles.



Scheme 15. Plausible pathway for the formation of tricyclic β-lactam **36** by palladium-catalyzed cyclization.

Starting substrates, 2-azetidinone-tethered allenols **41**, were prepared according to literature protocols via indium-mediated

carbonyl-allenylation reactions of the corresponding α-oxo lactams under Barbier-type conditions.[22] Similarly, the palladium(II)-catalyzed 1,2-bromoamidation of allenes **41** take place smoothly, obtaining the spiranic oxazolidinone-β-lactams **42** as single isomers (Scheme 16).[22–23]



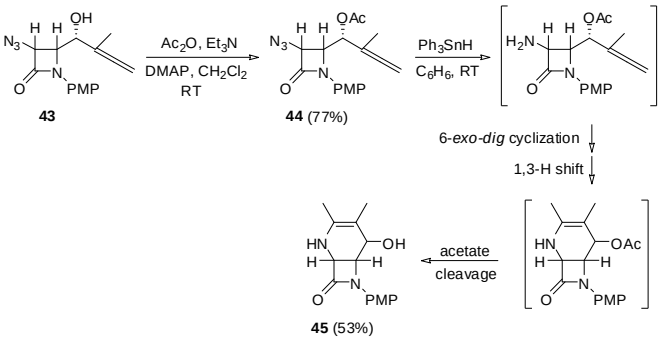
41

R = Me, Ph

42 (35–44%)

Scheme 16. Preparation of spirocyclic β-lactams by palladium-catalyzed aminoallene cyclization. Reagents and conditions: i) $Pd(OAc)_2$ 10 mol%, LiBr, $Cu(OAc)_2$, K_2CO_3, O_2, acetonitrile, RT.

A stereocontrolled access to a 4-hydroxypipecolic acid analogue with a bicyclic β-lactam structure has been developed by using allenic hydroamination reaction in a 2-azetidinone-tethered azide.[24] When it was tried to reduce azide **43** using the triphenylphosphine method, a complex reaction mixture was observed. Fortunately, it was found that 2-azetidinone-tethered azidoallenic acetate **44** when treated at room temperature with triphenyltin hydride in benzene solution, gave in a totally regioselective fashion the bicyclic 4-hydroxypipecolic acid analogue **45** through a 6-*exo-dig* aminocyclization with concomitant acetate cleavage (Scheme 17).



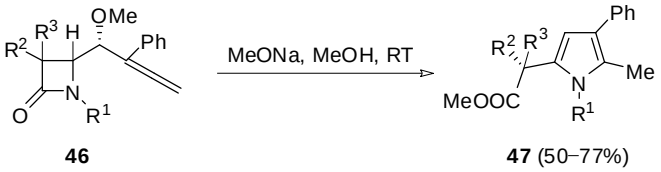
43

44 (77%)

45 (53%)

Scheme 17. Preparation of a β-lactam-based 4-hydroxypipecolic acid analogue through aminoallene cyclization.

An interesting formation of highly functionalized pyrrole derivatives from allene-β-lactams has been accomplished.[25] The reaction of phenyl allenes **46** with sodium methoxide at room temperature did not give the expected β-allenamines, affording instead the corresponding 1,2,3,5-tetrasubstituted pyrroles **47** (Scheme 18). From a mechanistic point of view, the preparation of heteroaromatic compounds **47** could be explained through a bond breakage process on the four-membered lactam followed by allene cyclization, with concomitant aromatization. The N1–C2 bond cleavage of the β-lactam nucleus in 2-azetidinone-tethered allenes **46** gave the non-isolable allenic-β-amino esters **48**, which after a totally regioselective cyclization onto the central carbon atom of the neighbouring allene under the reaction conditions followed by aromatization of the pyrrolines **49** yielded pyrroles **47** (Scheme 19). The pyrrole formation must be driven by relief of the strain associated with the four-membered ring, on forming a more stable five-membered ring.

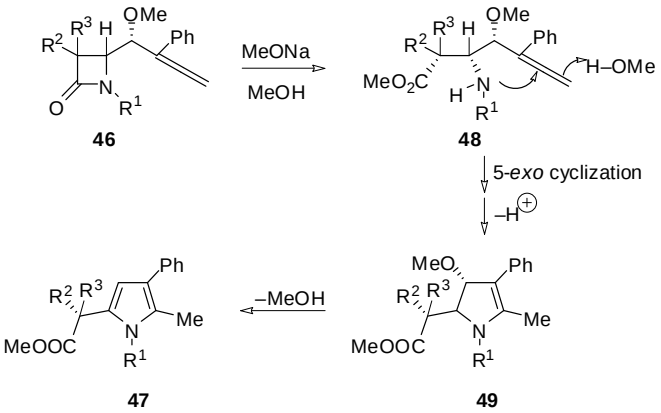


46

47 (50–77%)

R^1 = allyl, PMP; R^2 = Me, MeO, PhO; R^3 = H, allyl

Scheme 18. Direct preparation of tetrafunctionalized pyrroles from β-lactams by aminoallene cyclization.



46

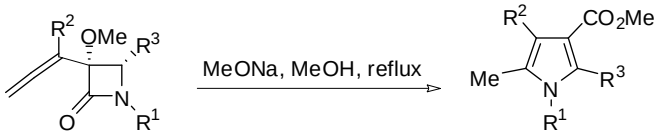
48

47

49

Scheme 19. Plausible pathway for the direct formation of tetrafunctionalized pyrroles from β-lactams by aminoallene cyclization.

The influence of the position of the allene moiety at the β-lactam ring for the one-pot synthesis of the pyrrole nucleus, was investigated by stirring quaternary α-allenyl derivatives **50** in a mixture of MeONa in MeOH at room temperature. After workup, the starting materials were recovered. Only after heating at reflux temperature did the β-lactam α-allenic ethers **50** react to form the corresponding heterocycles. New pentasubstituted pyrroles **51** were obtained in fair yields by means of the one-pot procedure, without the concomitant formation of any regioisomer (Scheme 20).



50

51 (49–68%)

R^1 = allyl, PMP; R^2 = Me, Ph; R^3 = Ar, furyl, dioxolanyl

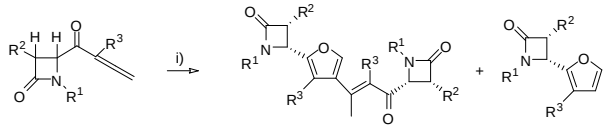
Scheme 20. Direct preparation of pentafunctionalized pyrroles from β-lactams by aminoallene cyclization.

Oxycyclizations

Furan, tetrahydrofuran, dihydropyran, and oxepane ether rings are ubiquitous structural units that are extensively encountered in a number of biologically active natural products and functional molecules, and therefore, their stereocontrolled synthesis remains an intensive research area. Among allene derivatives, allenones are of particular interest since they undergo selective cycloisomerization or dimerization reactions to afford furans. Marshall and co-workers discovered the Rh^I- or Ag^I-catalyzed selective cycloisomerization of α-allenones to substituted furans,[26] while Hashmi and co-workers reported the Pd^{II}-catalyzed dimerization of terminal α-allenones to afford 2,4-disubstituted furans.[27] More recently, the cycloisomerization of α-allenones catalyzed by Au^{III},[28] or by a palladatricyclo[4.1.0.0(2,4)]heptane catalyst have also been reported.[29] Thus, it appears that the only known efficient method for controlling the mode of reaction (cycloisomerization versus

dimerization) of α-allenones is the case of choice of catalyst. However, it has been reported that by adopting Pd^{II}-catalyzed conditions, the cycloisomerization/dimerization ratio of α-allenones is controlled by the substitution of the allene compound: unsubstituted allenones mainly afford dimerization, whereas allenones bearing an internal substituent favor the formation of cycloisomerization products.[30]

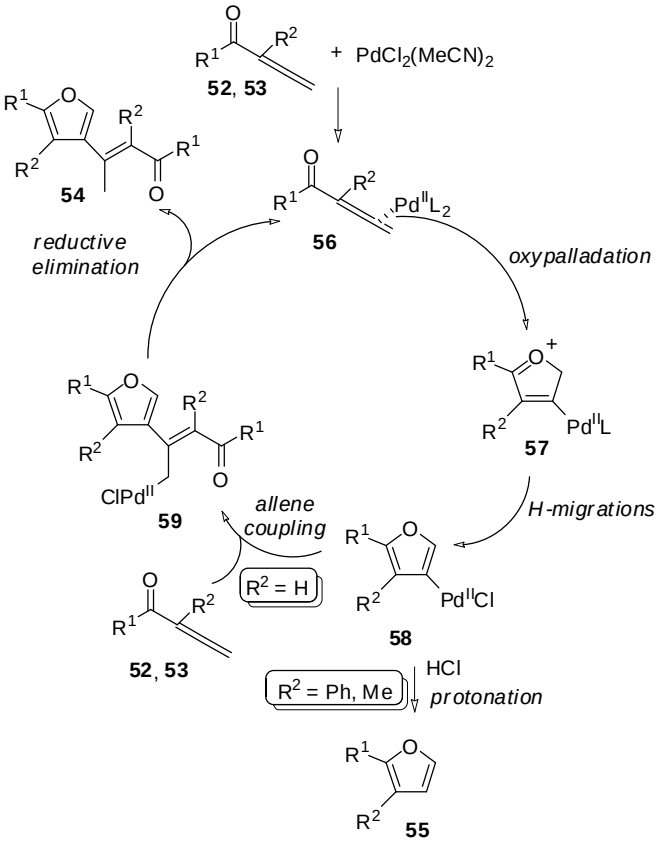
Because total control is observed for the dimerization and cycloisomerization reactions of aromatic α-allenones in the presence of catalytic amounts of $[PdCl_2(MeCN)_2]$, it was decided to test the effect of the nature of the α-allenone on the Pd^{II}-catalyzed process. To study whether or not the switching of dimerization to cycloisomerization could be applied to aliphatic derivatives, β-lactams **52a–d** bearing an unsubstituted α-allenone and β-lactams **53a–h** bearing a substituted α-allenone were treated under similar conditions. In the event, useful control was observed, because internally substituted α-allenones gave good or total selectivities in favor of cycloisomerization products **55** (Scheme 21). The role of the bulky β-lactam ring is noticeable for the unsubstituted α-allenones **52**, because in addition of major dimerization adducts **54** considerable amounts of the unexpected cycloisomerization products are normally obtained.



52a R^1 = PMP, R^2 = MeO, R^3 = H	**54a** R^3 = H (60%)	**55a** R^3 = H (16%)
53a R^1 = PMP, R^2 = MeO, R^3 = Me	**54b** R^3 = Me (7%)	**55b** R^3 = Me (45%)
53b R^1 = PMP, R^2 = MeO, R^3 = Ph		**55c** R^3 = Ph (81%)
52b R^1 = Bn, R^2 = MeO, R^3 = H	**54c** R^3 = H (70%)	**55d** R^3 = H (9%)
53c R^1 = Bn, R^2 = MeO, R^3 = Me		**55e** R^3 = Me (65%)
53d R^1 = Bn, R^2 = MeO, R^3 = Ph		**55f** R^3 = Ph (81%)
52c R^1 = PMP, R^2 = PMPCOO, R^3 = H	**54d** R^3 = H (64%)	
53e R^1 = PMP, R^2 = PMPCOO, R^3 = Me	**54e** R^3 = Me (32%)	**55g** R^3 = Me (50%)
53f R^1 = PMP, R^2 = PMPCOO, R^3 = Ph		**55h** R^3 = Ph (72%)
52d R^1 = Bn, R^2 = PMPCOO, R^3 = H	**54f** R^3 = H (72%)	**55i** R^3 = H (10%)
53g R^1 = Bn, R^2 = PMPCOO, R^3 = Me		**55j** R^3 = Me (87%)
53h R^1 = Bn, R^2 = PMPCOO, R^3 = Ph		**55k** R^3 = Ph (58%)

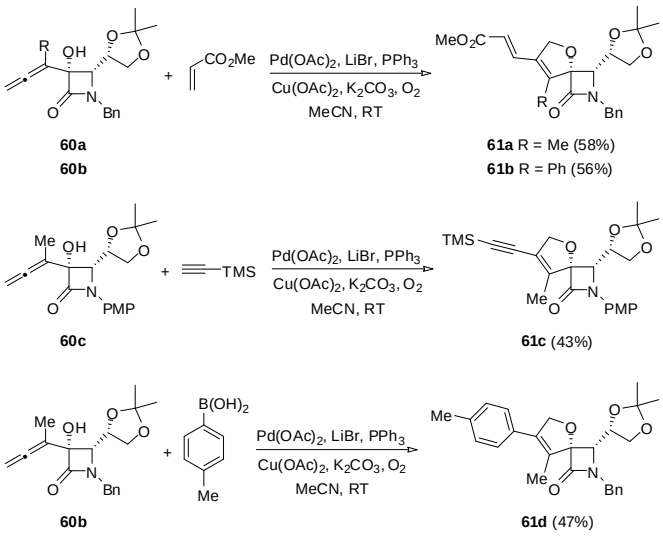
Scheme 21. Substrate controlled switching of dimerization to cycloisomerization in 2-azetidinone-tethered α-allenic ketones. Reagents and conditions: i) 5 mol % $[PdCl_2(MeCN)_2]$, MeCN, RT.

The pathway proposed in Scheme 22 looks valid for the formation of products **54** and **55**. It could be presumed that the initially formed allenepalladium complex **56** undergoes an intramolecular attack by the ketone group (oxypalladation), giving rise to the furan intermediate **57**, which after H-migrations affords the aromatic palladium species **58**. Palladafuran **58** may suffer a protonation with the in situ generated HCl to yield furans **55**. Alternatively, intermediate **58** is trapped by other allenone molecule in a subsequent coupling process leading to dimers **54** via **59**. The formation of the *E* isomer in alkene derivatives **54** is the consequence of an addition of the organometallic species to the allene side remote from the acyl group. It may be inferred that different steric effects in the organometallic species **58** may be responsible for the different reactivity preference, stabilizing one of the intermediates rather than the other. Dimerization falters in the presence of sterically encumbering allenones. Probably, dimerization via **59** is restricted by the steric hindrance of the R^2 substituent (R^2 = Me or Ph) when a second molecule of allenone **53** is trying to approach to the palladafuran **58**.



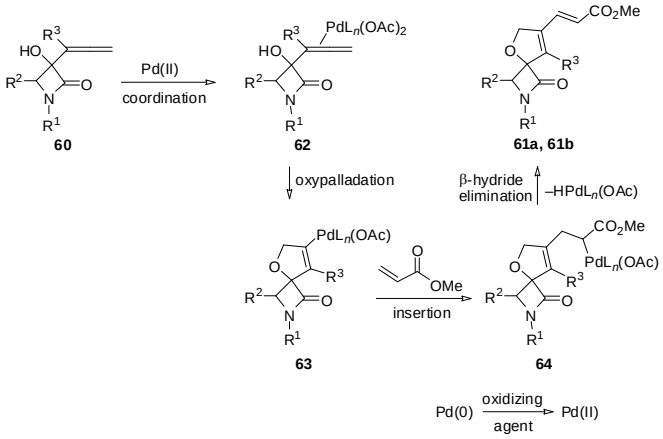
Scheme 22. Mechanistic explanation for the substrate controlled switching of dimerization to cycloisomerization in α-allenic ketones.

Despite allenes offer expeditious routes to a wide range of heterocycles, metal-catalyzed domino heterocyclization–functionalization reaction of allenes are relatively unknown.[31] A regioselective metal-catalyzed spirocyclization of α-allenols–cross coupling (Heck, Sonogashira, and Suzuki) reaction sequence, leading to potentially bioactive spirocyclic β-lactam derivatives has been developed.[32] It was found that reaction of α-allenols **60** with methyl acrylate in the presence of $Pd(OAc)_2$ afforded the allene cyclization-Heck trapping products **61a** and **61b** in a reasonable isolated yield. When (trimethylsilyl)acetylene or tolylboronic acid were used as the cross-coupling agent under the optimized conditions, the corresponding domino Sonogashira or Suzuki–Miyaura adducts **61c** and **61d** were obtained (Scheme 23). Thus, the same catalytic system is able to promote two different, but sequential catalytic cycles, allowing different transformations in a single reaction flask.



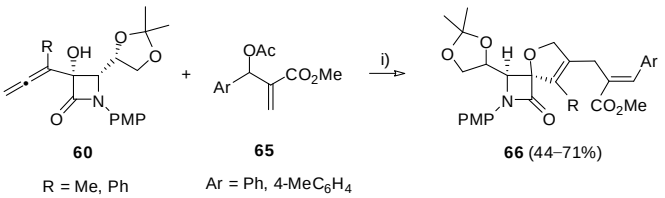
Scheme 23. One-pot synthesis of enantiopure spirocyclic 2-azetidinones **61** through metal-catalyzed domino cyclization of α-allenols–cross coupling (Heck, Sonogashira, and Suzuki) reactions.

The formation of spirolactams **61** could be rationalized in terms of a novel sequence domino cyclization of α-allenols–cross coupling reactions. A palladium(II)-catalyzed mechanism for the domino sequence leading to spiranic adducts **61** is proposed in Scheme 24. It could be presumed that the initially formed allenepalladium complex **62** undergoes an intramolecular attack by the hydroxyl group (oxypalladation), giving rise to the spirocyclic vinylic palladium species **63**. Next, dihydrofuranylpalladium intermediate **63** is trapped by the cross-coupling reagents leading to compounds **61**. For example, the palladium species **63** can then form the intermediate **64** in a subsequent Heck reaction with acrylate, which leads to the final spirocycles **61** and Pd^0 in a β-hydride elimination. 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.



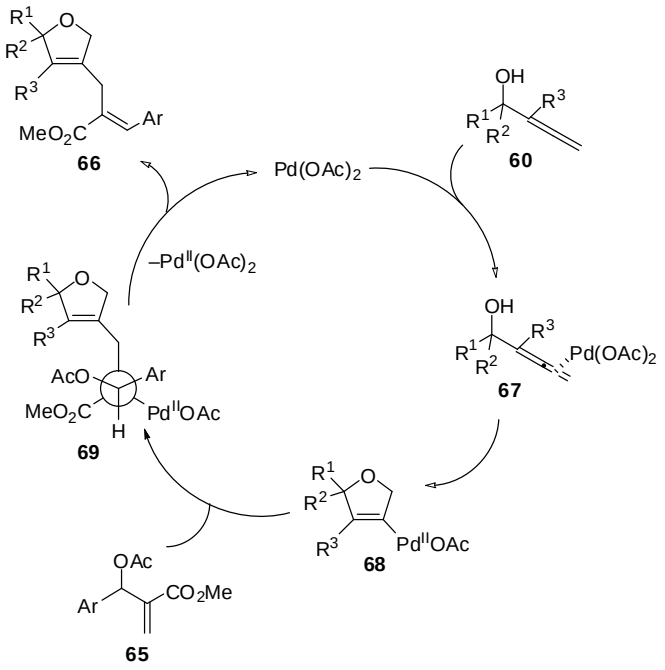
Scheme 24. Rationalization for the metal-catalyzed domino allene cyclization-coupling sequence.

The first examples on the reaction of an allene and a Baylis–Hillman (BH) adduct, namely the palladium-catalyzed cyclizative coupling reaction of α-allenols **60** with BH acetates **65** has been recently disclosed.[33] The transformation of allenols **60** into spirocyclic disubstituted dihydrofuran β-lactams **66** was readily achieved in moderate yields, by treatment with BH acetates in the presence of palladium(II) acetate (5 mol%) (Scheme 25).



Scheme 25. Palladium-catalyzed preparation of enantiopure spiroazetidinones **66**. Reagents and conditions: i) 5 mol % $Pd(OAc)_2$, K_2CO_3, TDMPP, DMSO, RT. PMP = 4-$MeOC_6H_4$. TDMPP = tris(2,6-dimethoxyphenyl)phosphine.

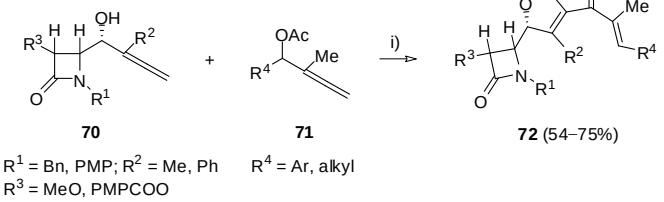
The catalytic cycle proposed in Scheme 26 looks valid for the formation of products **66** through the heterocyclization cross-coupling reaction of α-allenols and BH acetates. Initial palladium(II)-coordination to the 1,2-diene moiety of the α-allenol component **60** gives an allenepalladium complex **67**, which suffers regiocontrolled intramolecular oxypalladation generating a dihydrofuranylpalladium intermediate **68**. Species **68** then undergoes a cross-coupling reaction with the BH acetate **65**. The coupling of vinyl palladium(II) intermediates **68** with protected BH adducts **65** leading to species **69** takes place regioselectively at the methylenic carbon atom of **65** remote from the acetate group. Finally, *trans*-β-deacetoxypalladation generates in a highly steoselective manner [(2,5-dihydrofuran-3-yl)methyl]acrylates **66** as single *E*-isomers with concomitant regeneration of the Pd^{II} species. The formation of the *E* isomer in alkene derivatives **69** is the consequence of an addition of the organopalladium species to the alkene side remote from the acyl group.



Scheme 26. Mechanistic explanation for the palladium-catalyzed oxycyclization/cross coupling reaction between α-allenols and BH acetates.

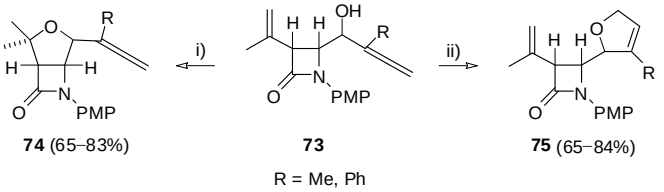
Although many efforts have been made for transition metal-catalyzed cyclization of functionalized allenes, cross-coupling reactions of two different allenes are almost unexplored.[34] A mild, palladium(II)-catalyzed reaction of α-allenols and α-allenic esters in a heterocyclization/cross-coupling sequence, that is applicable to a wide range of substitution patterns has been developed for the preparation of 2,3,4-trifunctionalized 2,5-dihydrofurans, including β-lactam derivatives. The heterocyclizative cross-coupling between 2-azetidinone-tethered allenols **70** and α-allenic acetates **71** resulted

in the achievement of β-lactam–dihydrofuran hybrids **72** in good yields (Scheme 27).[35]



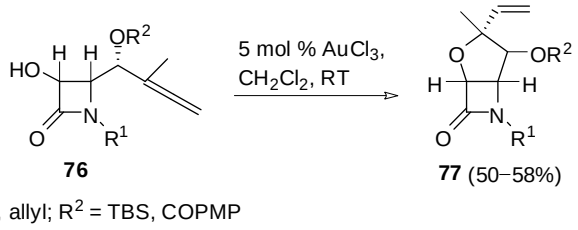
Scheme 27. Palladium-promoted preparation of 2-azetidinone-tethered buta-1,3-dienyl 2,5-dihydrofurans **72**. Reagents and conditions: i) 5 mol % $PdCl_2$, DMF, RT.

A resplendent age of noble metal catalysis has bloomed in the last years. Particularly, gold and platinum complexes are excellent catalysts for the formation of C–C and C–heteroatom bonds.[36] Recently, iron salts have emerged as powerful alternatives in view of their inexpensiveness and environmental friendliness.[37] The chemodivergent metal-catalyzed heterocyclization of alcohols bearing both an allene and an alkene center has been reported. Starting from 2-azetidinone-tethered enallenols **73**, $FeCl_3$ was able to chemospecifically catalyze the cyclization in favour of the alkene component to exclusively afford β-lactam-tetrahydrofuran hybrids **74** in good isolated yields (Scheme 28).[38] Besides total chemocontrol, the reaction was regiospecific and only the five-membered ring ether was formed, without the presence of the isomeric six-membered ring. By contrast, when the cyclization of olefinic α-allenols **73** was catalyzed by precious metal salts ($AgNO_3$, $[PtCl_2(CH_2{=}CH_2)]_2$, and $AuCl_3$), allene cycloisomerization adducts **75** were afforded as sole isomers (Scheme 28).



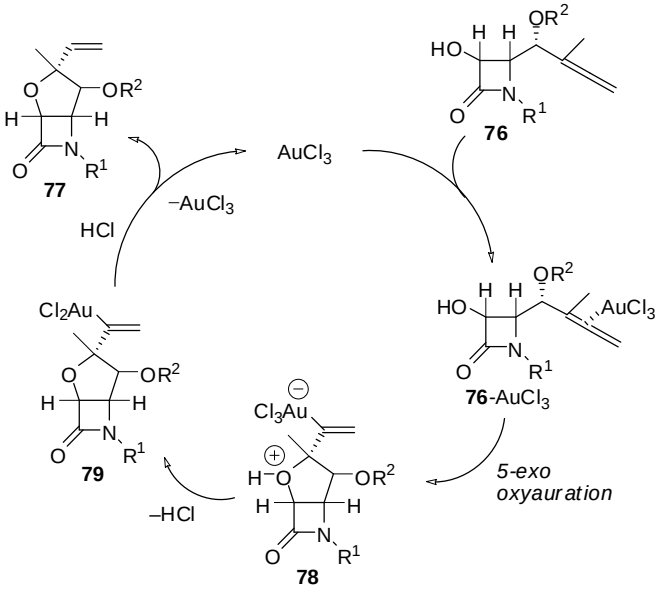
Scheme 28. Chemodivergent metal-catalyzed preparation of β-lactam- dihydrofuran- and tetrahydrofuran-hybrids **74** and **75**. Reagents and conditions: i) 10 mol % $FeCl_3$, DCE, sealed tube, 80 °C. ii) 5 mol % $AuCl_3$, CH_2Cl_2, RT. DCE = 1,2-Dichloroethane.

Despite that transition metal-catalyzed reactions of α-allenols leading to heterocyclization products have attracted a great deal of interest, relatively little work has been performed on intramolecular cyclizations of γ-allenols.[39] Combined experimental and computational studies on the regioselectivity control in the metal-catalyzed O–C funtionalization of 2-azetidinone-tethered γ-allenols have been performed.[40] The general reactivity of 2-azetidinone-tethered γ-allenols toward the regioselective hydroalkoxylation reaction was tested with substrate **76a** (R^1 = Bn, R^2 = TBS) by the use of $[PtCl_2(CH_2{=}CH_2)]_2$, $AgNO_3$, AuCl and $AuCl_3$ as catalysts. $[PtCl_2(CH_2{=}CH_2)]_2$ and $AgNO_3$ afforded rather low yield or disappointing diastereomeric mixture of bicycle **77a**. Although $AgNO_3$ was less diastereoselective than $[PtCl_2(CH_2{=}CH_2)]_2$ (60:40 vs 100:0), it was a more efficient catalyst affording adduct **77a** in reasonable yield. Gratifyingly, it was found that Au salts were effective as 5-*exo* selective hydroalkoxylation catalysts. $AuCl_3$ was selected as catalyst of choice because of its superior performance, affording tetrahydrofuran-2-azetidinones **77** in moderate yields (Scheme 29). No regioisomeric products were detected, giving exclusively the fused five-membered oxacycle.



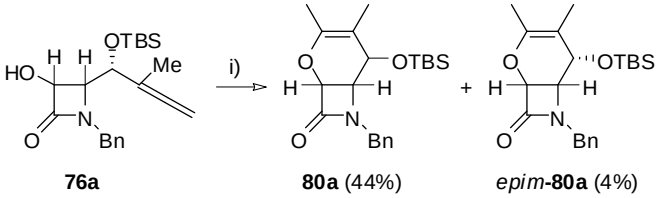
Scheme 29. Gold-catalyzed preparation of five-membered oxacycles **77**.

A possible pathway for the achievement of bicyclic tetrahydrofurans **77** from γ-allenols **76** may initially involve the formation of a complex **76**-$AuCl_3$ through coordination of the gold trichloride to the proximal allenic double bond. Next, regioselective 5-*exo* oxyauration forms zwitterionic species **78**. Loss of HCl followed by protonolysis of the carbon–gold bond of **79** affords products **77** and regenerates the gold catalyst (Scheme 30).

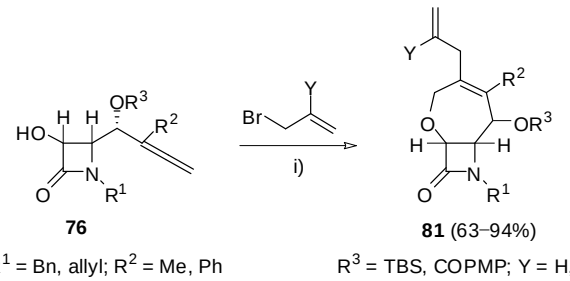


Scheme 30. Possible pathways for the gold-catalyzed preparation of bicycles **77**.

Having found a solution for the 5-*exo* selective hydroalkoxylation, it was next examined the more intricate heterocyclizative problem associated with tuning of the regioselectivities of γ-allenols. It should be mentioned that one of the challenges for modern synthesis is to create distinct types of complex molecules from identical starting materials based solely on catalyst selection. Specifically, subjection of the γ-allenol **76a** to the lanthanide amide-catalyzed protocol did afford dihydropyran **80a** (Scheme 31); the nucleophilic attack taking place at the central allene carbon via a 6-*endo* cyclization.[41] In addition, partial epimerization was observed through the isolation of *epim*-**80a**. Worthy of note, the Pd^{II}-catalyzed cyclizative coupling reaction of γ-allenols **76** with allyl halides gave impressive yields (up to 94%) of the desired seven-membered adducts **81** (Scheme 32) as the sole products, resulting from a 7-*endo* oxycyclization.[42] Notably, the judicious choice of catalyst (Au, La, or Pd) allows to modulate the ring size (five, six, or seven) of the fused oxacycle.

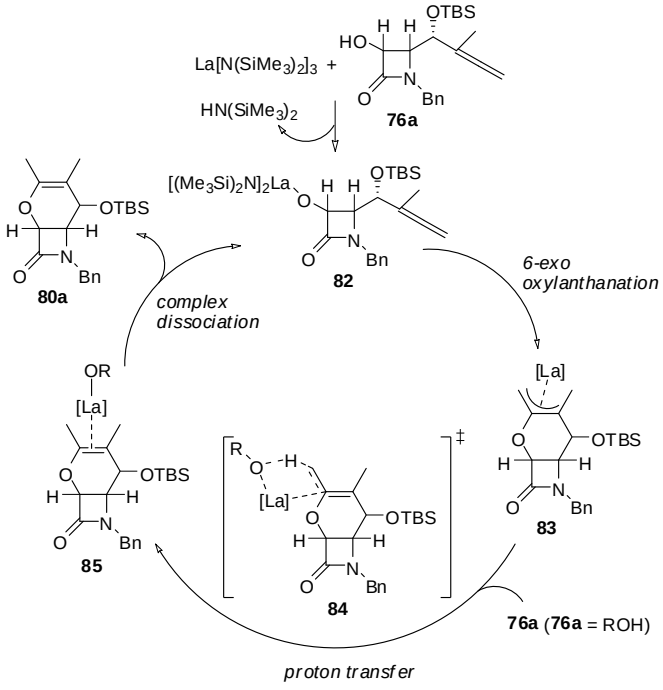


Scheme 31. Lanthanum-promoted preparation of six-membered oxacycles **80a** and *epim*-**80a**. Reagents and conditions: i) 5 mol % $La[N(SiMe_3)_2]_3$, toluene, reflux. TBS = *t*-Butyldimethylsilyl.



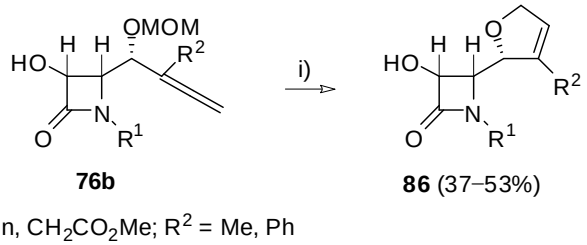
Scheme 32. Palladium-promoted preparation of seven-membered oxacycles **81**. Reagents and conditions: i) 5 mol % $PdCl_2$, DMF, RT. PMP = 4-$MeOC_6H_4$. TBS = *t*-Butyldimethylsilyl.

Scheme 33 comprises a mechanistic rationale for the $La[N(SiMe_3)_2]_3$-promoted conversion of methyl γ-allenol **76a** into fused tetrahydropyran **80a**. Firstly, lanthanum precatalyst formed the alkoxide–La compound **82** through protonolysis at the La–$[N(SiMe_3)_2]_3$ bond by allenol **76a**. Subsequently, one π-bond of the oxallene–La complex regiospecifically adds across the La–O functionality of **82** to afford oxacyclic intermediate **83** by 6-*exo* cyclization to the central allene carbon. The intervention of a second molecule of allenol **76a** facilitates the proton transfer step to afford species **85** via transition state **84**, which after dissociation delivers oxacycle **80a** and regenerates **82**, thus re-initiating the catalytic cycle.

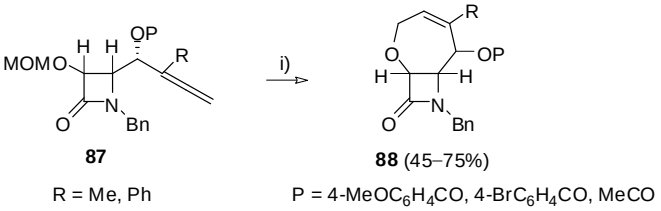


Scheme 33. Mechanistic explanation for the La(III)-catalyzed heterocyclization reaction of γ-allenol **76a**.

Having demonstrated the stability of the benzoate and TBS-protective groups to the metal-catalyzed conditions, it was decided to see if (methoxymethyl)oxy substitution has a beneficial impact on the cyclization reactions. In the event, when γ-allenols **76** were treated with $AuCl_3$ the 2,5-dihydrofurans **86** were the sole products (Scheme 34). These transformations may involve a chemoselective (5-*endo-trig* versus 7-*endo-trig*) allenol oxycyclization with concomitant MOM ether deprotection. Taking into account the above results, it was decided to test if the metal-catalyzed preparation of bicycles **77** can be directly accomplished from MOM protected γ-allenol derivatives **87**. Thus, when allenic MOM ethers **87** were treated with $AuCl_3$, the 5-*exo* mode was completely reverted to a 7-*endo* cyclization to afford bicycles **88** in fair yields (Scheme 35). 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 **76a** gave 5-*exo* hydroalkoxylation, while MOM protected γ-allenol derivatives **87** exclusively underwent a 7-*endo* oxycyclization. Thus, it has been demonstrated that regioselectivity control in the metal-catalyzed O–C functionalization of γ-allenols can be achieved both through the choice of catalyst (Au versus La versus Pd) as well as through the nature of the γ-allenol (free versus protected). It appears to be the first time that such an effect has been discovered.

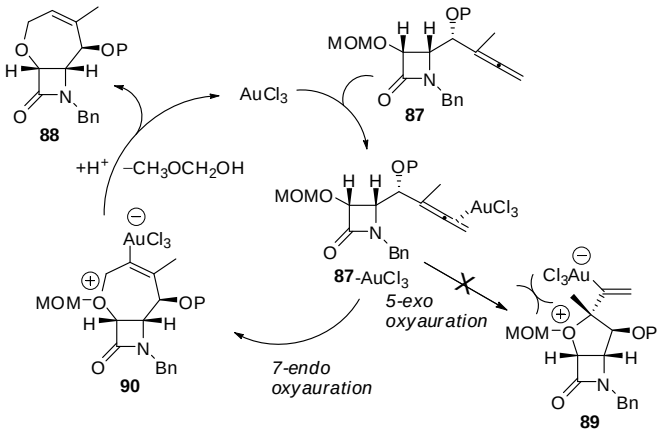


Scheme 34. Au(III)-catalyzed heterocyclization reaction of γ-allenol derivatives **76**. Reagents and conditions: i) 5 mol % $AuCl_3$, CH_2Cl_2, RT. MOM = $MeOCH_2$.



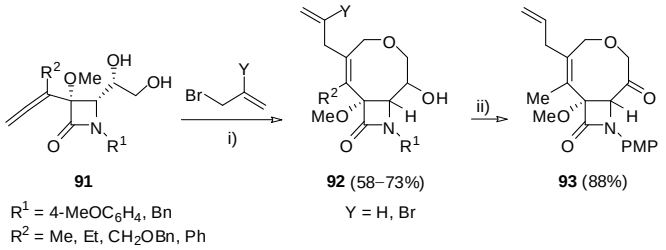
Scheme 35. Au(III)-catalyzed heterocyclization reaction of MOM protected γ-allenol derivatives **87**. Reagents and conditions: i) 5 mol % $AuCl_3$, CH_2Cl_2, RT. MOM = $MeOCH_2$.

The pathway proposed in Scheme 36 looks valid for the formation of products **89** from MOM protected γ-allenol derivatives **87**. It could be presumed that the initially formed allenegold complex **87**-$AuCl_3$ undergoes an intramolecular attack (7-*endo* versus 5-*exo* oxyauration) by the (methoxymethyl)oxy group, giving rise no to species **89** but to the tetrahydrooxepine intermediate **90**. Protonolysis of the carbon–gold bond linked to an elimination of methoxymethanol would then liberate the bicycle type **88** with concomitant regeneration of the Au^{III} species. Probably, the proton in the last step of the catalytic cycle comes from the trace amount of water present in the solvent or the catalyst. In the presence of MOM group, 5-*exo* cyclization falters. As calculations reveals, 5-*exo* oxyauration via **89** is restricted by the steric hindrance between the (methoxymethyl)oxy group and the substituents at the quaternary stereocenter.



Scheme 36. Mechanistic explanation for the Au^{III}-catalyzed heterocyclization reaction of MOM protected γ-allenol derivatives **87**.

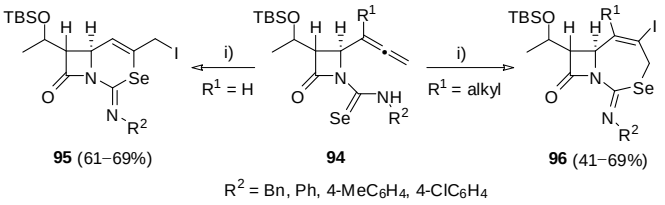
The metal-catalyzed cyclization of 1,2-dienes with two contiguous nucleophiles presents a severe limitation, especially in the context of chemoselectivity. To probe the feasibility of heterocyclization reactions in β-lactam allenic diols by way of palladium catalysis, 2-azetidinone-tethered γ,δ-allendiols **91** were tested as substrates. Interestingly, *trans*-fused β-lactam oxocines **92** were obtained in good yields in a totally chemo- and regioselective fashion using the $PdCl_2$-catalyzed cyclizative coupling reaction with allyl halides (Scheme 37), through an 8-*endo*-*trig* cyclization by attack of the primary hydroxy group to the terminal allene carbon.[43] Apparently, this is the first example of an 8-*endo* cyclization at the terminal allene carbon of a δ-allenol. Chemical evidence of the presence of a new eight-membered oxacycle fused to the β-lactam ring was obtained by oxidation of adduct **92a** (R^1 = 4-$MeOC_6H_4$, R^2 = Me) with Dess–Martin periodinane to afford ketone **93** (Scheme 37).



Scheme 37. Preparation of oxocines **92** and oxocinone **93**. Reagents and conditions: i) 5 mol % $PdCl_2$, DMF, RT. ii) Dess–Martin periodinane, CH_2Cl_2, RT, 2 h. PMP = 4-$MeOC_6H_4$.

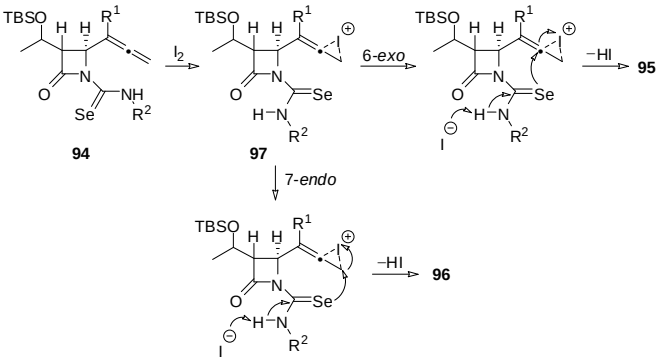
Selenacyclizations

The heterocyclization reaction of alleneselenoureas **94** using iodine has been examined.[44] When unsubstituted allenes were used, the iodine reaction resulted in the formation of 3-selena-1-dethiacephems **95** as the major product with traces of the five-membered product (Scheme 38). Good yields were obtained in all cases, irrespective of the nature of the substituent present on the selenourea group. Seven-membered ring products were not detected under these reaction conditions. Thus, these reaction conditions show high regioselectivity toward six-membered rings. By contrast, when alleneselenoureas **94** bearing alkyl groups at the allenyl position were examined with iodine, it was found that regiochemistry in the iodocyclization reaction was affected by the nature of the R^1 group at the allenyl position. The reaction of substituted alleneselenoureas **94** with 1.25 equiv of iodine afforded inseparable mixtures of selenazepines **96** along with their corresponding five-membered isodethiaselenapenams as minor component (Scheme 38). Thus, this iodocyclization method provides a novel approach for the synthesis of six- and seven-membered selenium-containing heterocycles.



Scheme 38. Preparation of selenacycles **95** and **96**. Reagents and conditions: i) 1.25 equiv I_2, CH_2Cl_2, RT.

A plausible mechanism for the formation of **95** and **96** has been proposed (Scheme 39). The reaction of **94** with iodine gave iodonium **97** and released an iodine anion at the same time. With the assistance of the iodine anion, intramolecular nucleophilic attack of selenium in the selenourea group on the center carbon of allene (when R^1 = H) in the favored *exo* mode affords the corresponding cyclization product **95**, whereas attack of selenium in the selenourea group on the terminal carbon of allene (when R^1 = CH_3, C_2H_5, or *n*-C_5H_{11}) in the favored *endo* mode affords the corresponding cyclization product **96** accompanied by the simultaneous elimination of hydrogen iodide.

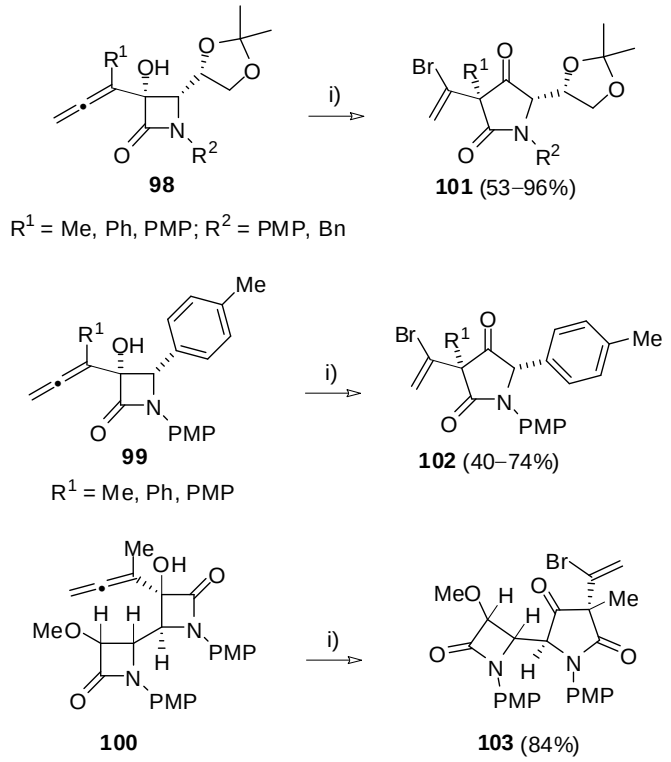


Scheme 39. Mechanistic explanation for the iodine-promoted heterocyclization reaction of alleneselenoureas **94**.

The above results shown that the presence of allenyl groups at the N1, C3 and C4 positions of the β-lactam ring is compatible with the more of the approaches. The difference from the cyclization modes arises from the inertia encountered sometimes with the cyclization towards the lactam nitrogen, rather than the placement of the allene moiety. It may be postulated that the amide resonance should both decrease the mobility of the intermediates and also force a planarity which is not compatible with the cyclization processes.

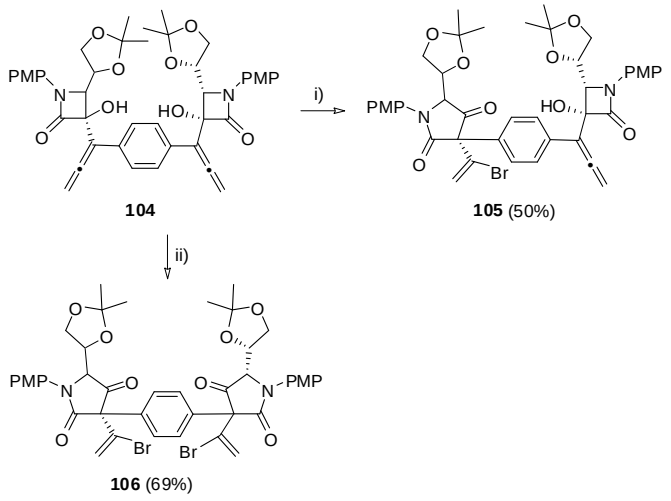
Rearrangements

N-Bromosuccinimide (NBS) is a very effective reagent for the ring expansion reaction of 2-azetidinone-tethered allenols, resulting in the regio-, chemo-, and stereocontrolled preparation of pyrrolidine-2,4-diones (tetramic acids), a structural feature found in many natural products, which display a wide spectrum of biological activities (antibacterial, antifungal, antitumoral, antiviral, insecticide, and receptor antagonist activity). Excellent yields and selectivities were achieved for the carbon–carbon bond cleavage in the electrophilic ring opening reaction of allenic β-lactams **98–100** to afford functionalized tetramic acids **101–103** (Scheme 40).



Scheme 40. Rearrangement reaction of 2-azetidinone-tethered allenols **98** to tetramic acid derivatives **91** by NBS treatment. Reagents and conditions: i) NBS (1.3 equiv), dichloromethane, RT. PMP = 4-MeOC$_6$H$_4$.

The controlled conversion of bis(allene-β-lactam) **104** into either the tetramic acid/β-lactam hybrid **105** or the bis(tetramic acid) **106** is also worthy of note. While substrate **104** was shown to undergo clean double expansion to bis(tetramic acid) **106**, mono-ring expansion yielding hybrid **105** was found to be the preferred pathway when employing one equivalent of NBS (Scheme 41).[45]



Scheme 41. Controlled rearrangement reaction of bis(allenol-β-lactam) **104** to tetramic acid derivatives **105** and **106** by NBS treatment. Reagents and conditions: i) NBS (1.0 equiv), dichloromethane, RT, 24 h; ii) NBS (3.0 equiv), dichloromethane, RT, 24 h. PMP = 4-MeOC$_6$H$_4$.

Conclusion

In this overview we have presented the most recent advances in carbo- and heterocyclization reactions of allenes bearing a β-lactam ring, showing this methodology to be an established process to access a large number of cyclic structures containing different sized skeletons. The reactions discussed herein demonstrate the high synthetic potential of 2-azetidinone-tethered allenes undergoing cyclization under several reaction conditions with almost complete regioselectivity, which is controlled by the stereo-electronic nature of the substituents attached to the allene moiety. In addition it has been demonstrated that metal-catalyzed carbo- and heterocyclizations proceed in most of the cases with better regio- and stereoselectivity control, which are not accesible under thermal or radical conditions. It is believed that the continued and renewed investigation on cyclization reactions of allenic β-lactams will discover new patterns of reactivity, enabling new sinthetic strategies.

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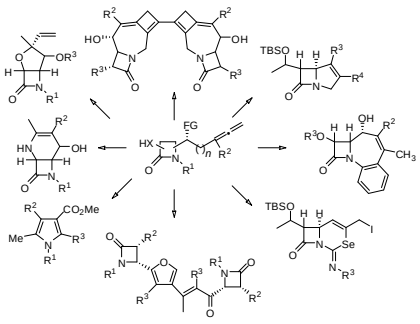
Allenyl-β-Lactams: Versatile Scaffolds for the Synthesis of Heterocycles



The hybrid allenic β-lactam moiety represents an excellent building block for carbo- and heterocyclization reactions, affording a large number of cyclic structures containing different sized skeletons in a single step. This strategy has been studied under thermal and radical induced conditions. More recently, the use of transition metal catalysis has been introduced as an alternative relying on the activation of the allenic component. On the other hand, the intramolecular version has attracted much attention as a strategy for the synthesis of bi- and tricyclic compounds in a regio- and stereoselective manner.

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