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Diversity-Oriented Preparation of Enantiopure Spirocyclic 2-Azetidinones from α-Oxo-β-lactams through Barbier-Type Reactions followed by Metal-Catalyzed Cyclizations

Benito Alcaide,[a,*] Pedro Almendros,[b,*] Teresa Martínez del Campo,[a] and Raquel Rodríguez-Acebes[a]

[a] Departamento de Química Orgánica I. Facultad de Química. Universidad Complutense de Madrid, 28040 Madrid, Spain
Fax: (+34)-91-394-4103; e-mail: alcaideb@quim.ucm.es
[b] Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain
Fax: (+34)-91-5644853; e-mail: iqoa392@iqog.csic.es

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Abstract: Novel, simple, and convenient strategies to diversely functionalized spirocyclic β-lactams have been developed by using different metal-mediated carbonyl addition/cyclization reaction sequences. Spirocyclization precursors, 2-azetidinone-tethered homoallylic alcohols, bromohomoallylic alcohols, homopropargylic alcohols, (buta-1,3-dien-2-yl)methanols, and α-allenols have been obtained by regioselective addition of stabilized organometallic reagents to azetidine-2,3-diones in an aqueous environment. Ruthenium-, silver-, and palladium-catalyzed reactions of the above monocyclic unsaturated alcohol derivatives provided oxaspiro-β-lactams.

Keywords: C–C coupling; cyclization; lactams; palladium; spiro compounds

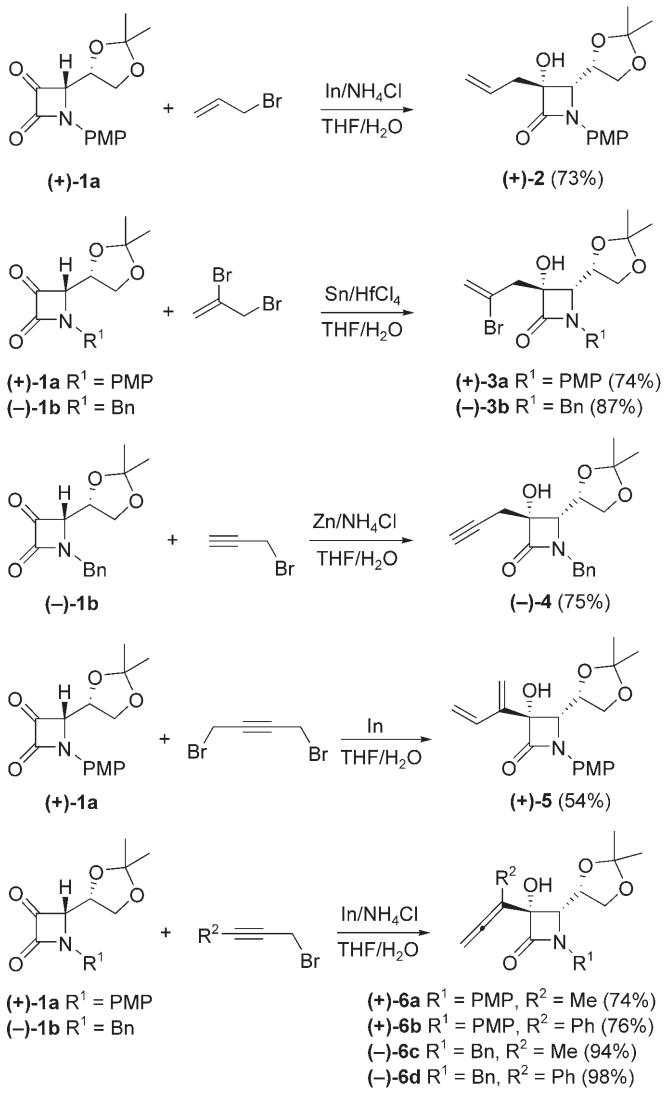
Introduction

Systems containing one carbon atom common to two rings, spirocyclic compounds, represent an important structural organization.[1] On the other hand, the importance of the stereoselective synthesis of β-lactams is ever increasing in connection with structure-activity relationship studies and the development of new derivatives of the β-lactam antibiotics and inhibitors of β-lactamases.[2] In addition, there are many important non-antibiotic uses of 2-azetidinones in fields ranging from enzyme inhibition,[3] to the use of these products as starting materials to develop new synthetic methodologies.[4] Spirocyclic β-lactams behave as β-turn mimetics,[5] as well as enzyme inhibitors,[6] they are precursors of α,α-disubstituted β-amino acids,[7] and the spiranic β-lactam moiety is present in chartellines,[8] a family of marine natural products. Due to the importance of this structural framework, the development of simple and convenient methodologies for the synthesis of the spiro-β-lactam assembly continues to be a challenging area in organic chemistry.[9] It occurred to us that the development of syntheses of aesthetically appealing molecular architectures containing both the β-lactam moiety and oxaheterocyclic frameworks linked with an interesting and appropriate spiro-bridge represents an attractive endeavour in organic and medicinal chemistry. Our combined interest in the area of β-lactams and the synthetic use of metals,[10] led us to explore novel, simple, and convenient metal-assisted methodologies for the preparation of diversely functionalized spiranic-2-azetidinones.[11]

Results and Discussion

Starting substrates, enantiopure azetidine-2,3-diones (+)-**1a** and (−)-**1b**, were prepared from the corresponding (*R*)-2,3-*O*-isopropylideneglyceraldehyde-derived imine, *via* Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification and Swern oxidation.[12] Homoallyl alcohol (+)-**2**, bromohomoallylic alcohols (+)-**3a** and (−)-**3b**, homopropargylic alcohol (−)-**4**, (buta-1,3-dien-2-yl) alcohol (+)-**5**, and α-allenyl alcohols **6a–d** were regiospecifically prepared using our recently developed metal-mediated Barbier-type carbonyl allylation, bromoallylation, 1,3-butadien-2-ylation, propargylation, or allenylation reactions of azetidine-2,3-diones **1** in aqueous media (Scheme 1).[12]

With the advent of well-defined, practically air-stable, and functional-group tolerant metathesis cata-

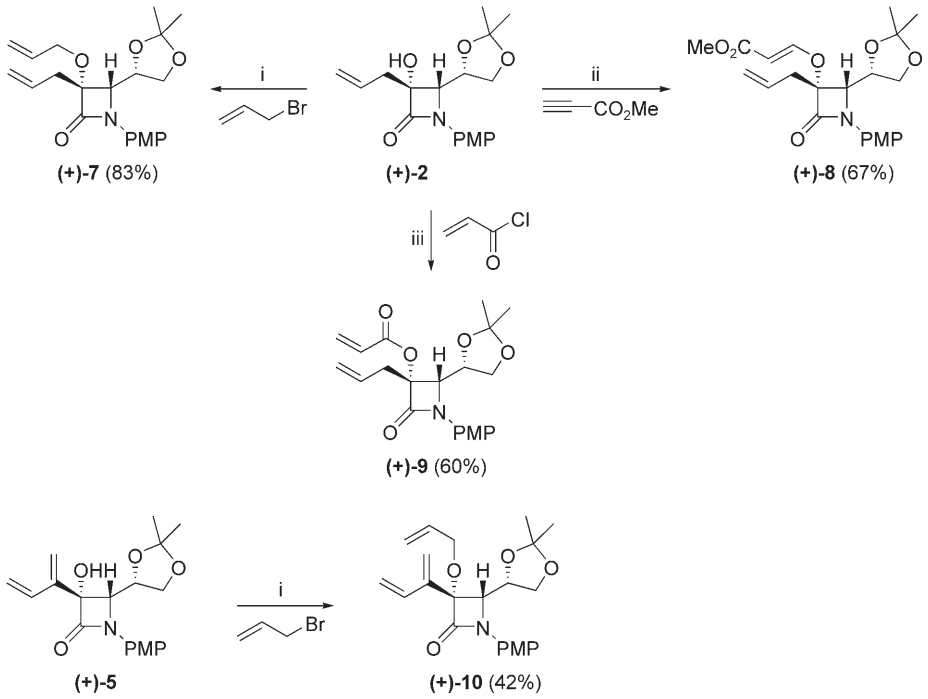


Scheme 1. Regio- and estereoselective preparation of unsaturated alcohols **2**–**6**.

lysts, e.g., the first, $[Cl_2(PCy_3)_2Ru{=}CHPh]$, and second, $[Cl_2(Im)(Cy_3P)Ru{=}CHPh]$, generations of Grubbs' ruthenium-based catalysts, ring-closing metathesis (RCM) has become one of the most powerful and reliable approaches to construct a ring system.[13] Our first task was to develop a method for the synthesis of appropriately substituted metathesis precursors. The treatment of homoallyl alcohol (+)-**2** either with allyl bromide or methyl propiolate, under different basic conditions, gave dienes (+)-**7** and (+)-**8**, respectively (Scheme 2). Sodium hydride-promoted *O*-acylation of alcohol (+)-**2** with acryloyl chloride provides dienic substrate (+)-**9** (Scheme 2). To further expand the scope of substrates to submit to RCM we thought of the buta-1,3-dien-2-yl moiety, bearing an extra alkene group. Following the same alkylation strategy used to obtain diene (+)-**7**, the required triene (+)-**10** was smoothly prepared from (buta-1,3-dien-2-yl) alcohol (+)-**5** (Scheme 2).

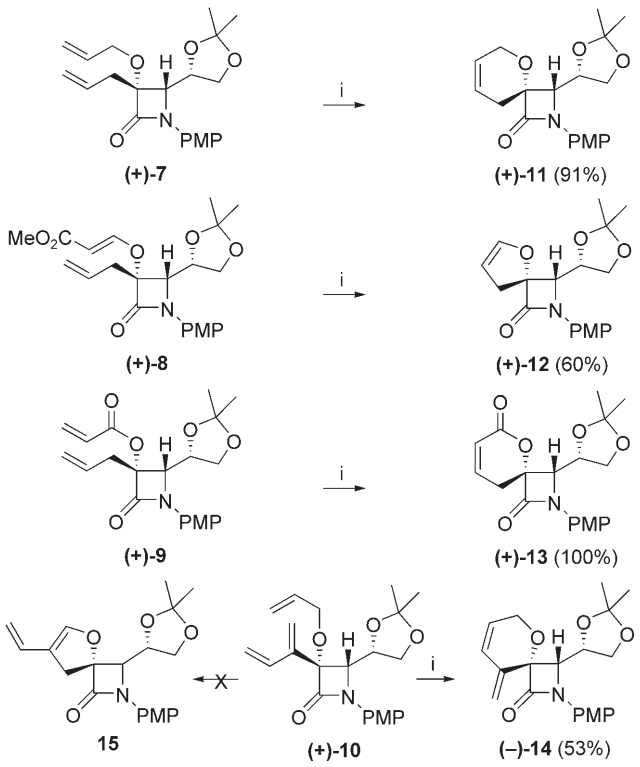
Our novel 2-azetidinone-tethered diene substrates **7**–**10** provided an opportunity to investigate the synthetic potential of the spiro-forming RCM reaction. The use of this approach in the synthesis of spirocyclic 2-azetidinones has not been hitherto applied. Our objective was the synthesis of oxaspiro-β-lactam structures containing five- and six-membered rings. Unfortunately, dienes **7**–**10** 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_2Cl_2, 25 °C). The major part of the reaction mixture was composed of unreacted dienes. While the reasons for this lack of cyclization were not definitively established, we attributed the low reactivity of the systems **7**–**10** to either the ring strain inherent to the spirocyclic product or kinetic problems associated with its formation. It was found that dienic substrates **7**–**10** 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 °C), good yields of unusual β-lactams **11**–**13** containing dihydrofuran, dihydropyran and dihydropyranone spiranic rings were obtained (Scheme 3). The six-membered spiro compound (−)-**14** which bears an exocyclic methylene was achieved when the spirocyclization took place on triene (+)-**10**. No traces of the five-membered regioisomer **15** could be detected, because only the least substituted double bond of the 1,3-diene system reacted (Scheme 3).

Enyne metathesis is the bond reorganization of an alkene and an alkyne which has emerged as an important new method for 1,3-diene synthesis.[14] We decide to investigate the intramolecular version of this bond reorganization in enyne-β-lactams. The allene moiety represents a versatile and useful building block in organic synthesis, specially in the area of transition metal-assisted reactions.[15] However, the information available on the use of allenes in metathesis-type reactions is very scarce,[16] with only two available examples on the exposure of the enallene moiety to metathesis catalysts giving isomerization products.[17] Enyne metathesis precursors (+)-**16** and (+)-**17** were synthesized under phase-transfer conditions by treatment of homoallyl alcohol (+)-**2** or homopropargyl alcohol (−)-**4** with propargyl bromide or allyl bromide, respectively. Enallene (+)-**18** was achieved through sodium hydride-promoted *O*-acylation of α-allenol (+)-**6a** with acryloyl chloride. Treatment of enynes (+)-**16** and (+)-**17** with first generation Grubbs' carbene under our diene ring-closing metathesis conditions, did not furnish the desired spirocycles. Our next attempts at cyclization were undertaken by using the imidazolidinylidene analogue, the



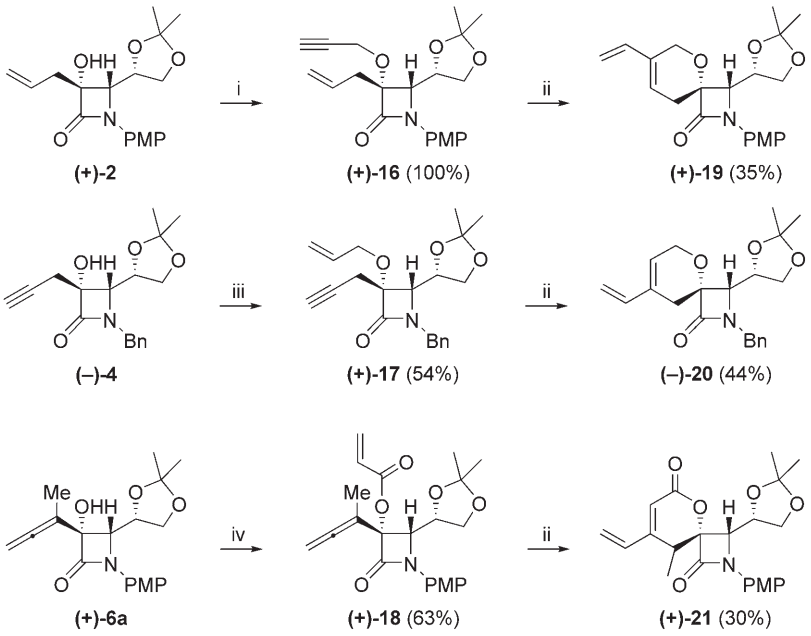
Scheme 2. Preparation of metathesis precursors **7**–**10**. *Reagents and conditions*: i) TBAI, CH_2Cl_2, NaOH (aq. 50%) (1:1), room temperature, 16 h. ii) CH_2Cl_2, Et_3N, 0 °C, 1 h. iii) NaH, THF, room temperature, 1 h.

more active second generation Grubbs' carbene. In this way, the spirocyclization was effective on enyne-β-lactams (+)-**16** and (+)-**17** to afford the inner-outer-ring dienes (cyclic dienes in which one of the double bonds is *endo*-cyclic) (+)-**19** and (+)-**20** (Scheme 4). Despite the lack of precedents for RCM on enallenes, we submitted enallene (+)-**18** to the second generation Grubbs' catalyst. Interestingly, the spirocyclic diene-2-azetidinone (+)-**21** was generated (Scheme 4). Despite the modest yield obtained in the synthesis of compound (+)-**21** (single isomer, 30% for RCM step), it deserves special mention because, to the best of our knowledge, successful exposure of the enallene moiety to RCM reaction conditions has not been previously reported. A plausible mechanism for the formation of (+)-**21** involves an initial allenyl-propargyl rearrangement promoted by Grubbs' carbene,[18] followed by RCM of the resulting enyne (Scheme 5).

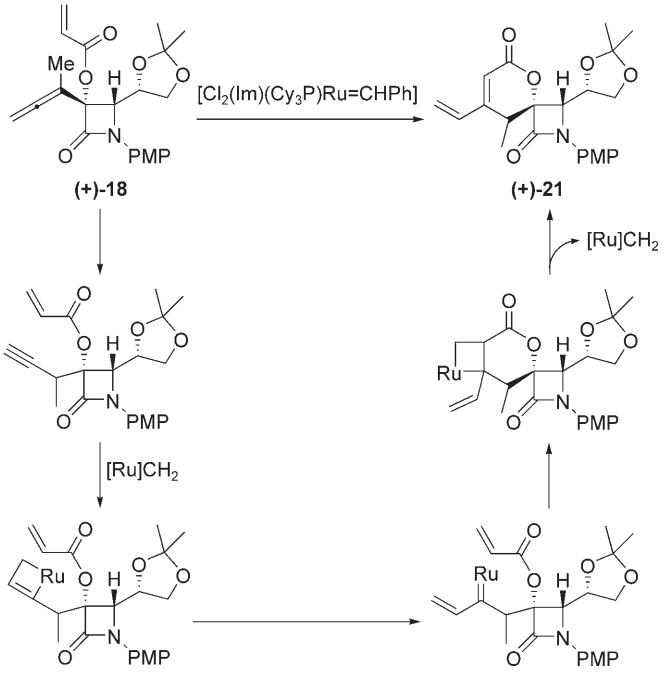


Scheme 3. Preparation of spirocyclic β-lactams **11**–**14** through RCM. *Reagents and conditions*: i) [$Cl_2(PCy_3)_2Ru$=CHPh], toluene, reflux; **11**: 7 h; **12**: 16 h; **13**: 33 h; **14**: 12 h.

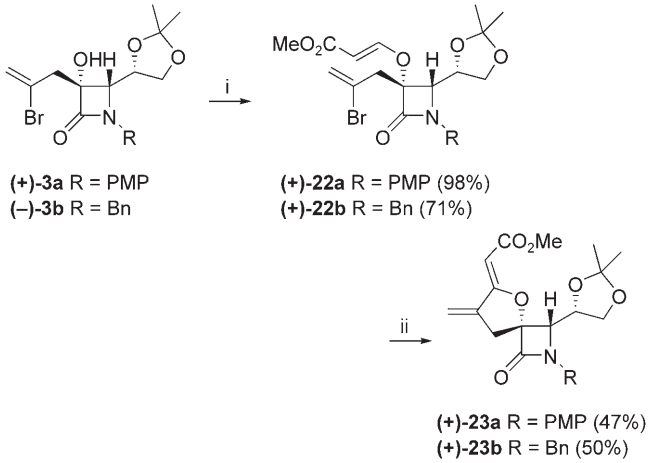
The palladium-catalyzed coupling of olefins with aryl or vinyl halides, known as the Heck reaction, is a standard method for carbon-carbon bond formation in organic synthesis.[19] We set out to evaluate a novel strategy for the construction of the oxacyclic core of spiranic β-lactams, which is based on a Heck spirocyclization. The cyclization precursors (+)-**22a** and (+)-**22b** were easily prepared through a Michael-type process by treatment of bromohomoallylic alcohols (+)-**3a** and (−)-**3b** with methyl propiolate in the presence of Et_3N. The palladium-catalyzed reaction of bromo dienes **22** was complete after a few hours, and afforded spirocycles (+)-**23a** and (+)-**23b** as single regio- and stereoisomers (Scheme 6). The Heck spirocycliza-



Scheme 4. Preparation of spirocyclic β-lactams **19**–**21** through enyne metathesis. *Reagents and conditions*: i) Propargyl bromide, TBAI, CH_2Cl_2, NaOH (aq. 50%) (1:1), room temperature, 16 h. ii) [Cl_2(Im)(Cy_3P)Ru=CHPh], toluene, reflux; **19**: 6 h; **20**: 4 h; **21**: 16 h. iii) Allyl bromide, TBAI, CH_2Cl_2, NaOH (aq. 50%) (1:1), room temperature, 16 h. (iv) Acryloyl chloride, NaH, THF, room temperature, 1 h.



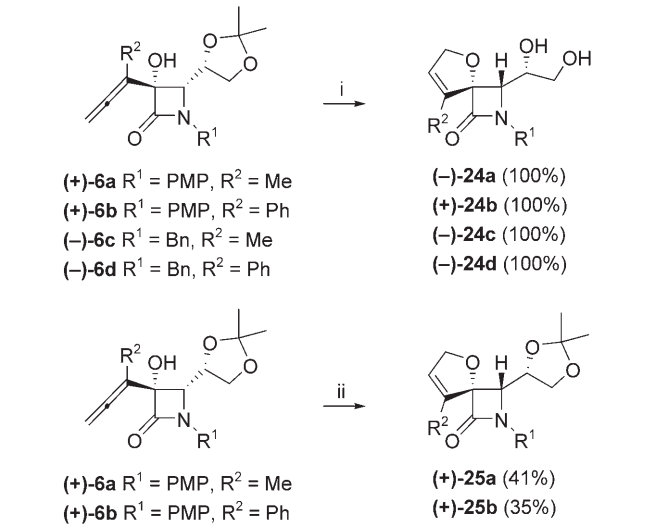
Scheme 5. Mechanistic explanation for the formation of spirocycle **21**.



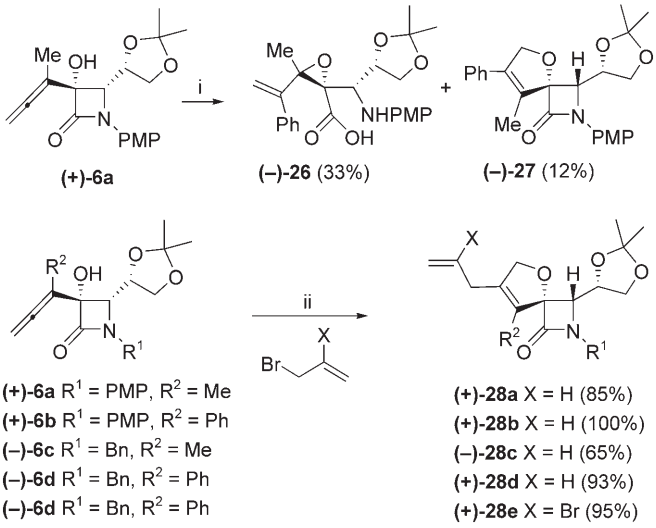
Scheme 6. Preparation of spirocyclic β-lactams **23** through Heck reaction. *Reagents and conditions*: i) Methyl propiolate, CH_2Cl_2, Et_3N, 0 °C, 1 h. ii) $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 105 °C; **23a**: 6 h; **23b**: 4 h.

tion reaction is regioselective, giving five-membered heterocycles. In addition, it is stereoselective because the Heck adducts were obtained as single geometric isomers.

Taking into account that allenes bearing a nucleophilic center can be cyclized on treatment with a wide variety of transition metal catalysts,[20] we turned our attention to metal-based cyclization reactions in our β-lactam-tethered α-allenic alcohols **6**. Our initial work began with the $AgNO_3$-induced reaction of α-allenols **6a–d**, to give, with concomitant acetonide cleavage, the spirocyclic dihydrofurans **24a–d** in quantitative yields (Scheme 7).[21] The use of the Pd-(PPh_3)$_4$/Ag_2CO_3 system afforded spiro compounds



Scheme 7. Silver-promoted preparation of spirocyclic β-lactams **24** and **25**. *Reagents and conditions*: i) $AgNO_3$ (1 equiv.), acetone-H_2O (1:1), reflux; **24a**: 3 h; **24b**: 6 h; **24c**: 6 h; **24d**: 6 h. ii) 5 mol% $Pd(PPh_3)_4$, Ag_2CO_3 (2 equivs.), toluene, sealed tube, 180 °C; **24a**: 0.5 h; **25b**: 4 h.



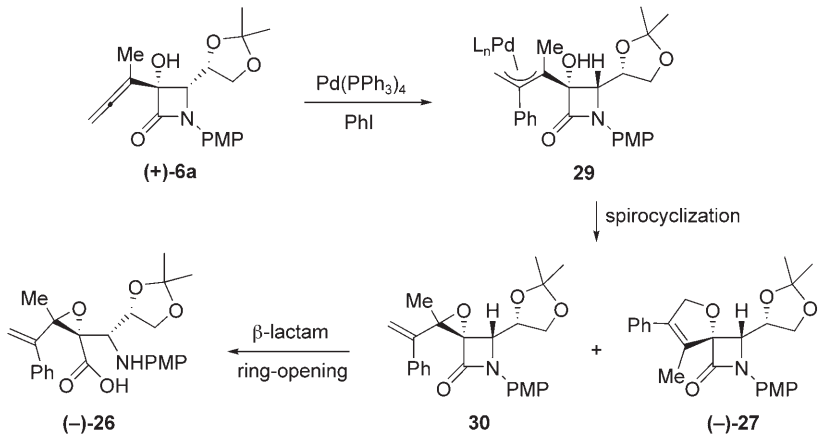
Scheme 8. Palladium-promoted preparation of spirocyclic β-lactams **27** and **28**. *Reagents and conditions*: i) PhI (1.1 equivs.), 5 mol% $Pd(PPh_3)_4$, K_2CO_3 (4 equivs.), DMF, 85 °C, 45 h. ii) 5 mol% $PdCl_2$, DMF, room temperature, **28a**: 3 h, **28b**: 2 h; **28c**: 4 h; **28d**: 1.5 h; **28e**: 23 h.

(+)-**25a** and (+)-**25b** albeit in modest yields (Scheme 7).

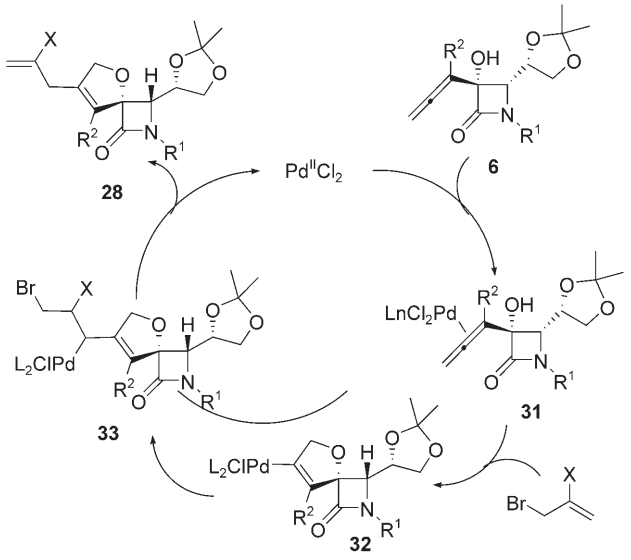
The palladium-catalyzed cyclizative coupling reaction of α-allenols **6** with aryl and alkenyl halides was explored next. It was observed that the $Pd(PPh_3)_4$-catalyzed reaction of α-allenol (+)-**6a** and iodobenzene afforded as main product the oxirane β-amino acid (−)-**26**, together with the regioisomeric spiranic dihydrofuran-β-lactam (−)-**27** (Scheme 8).[22] The formation of epoxide (−)-**26** involves concomitant ring opening of the β-lactam nucleus, probably because of the ring strain of the intermediate spirocyclic epoxy-2-azetidinone which cannot survive under the reaction conditions. The transformation of allenols **6** into spirocyclic disubstituted dihydrofuran β-lactams **28** 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 8).

Scheme 9 outlines a mechanistic hypothesis for the achievement of compounds (−)-**26** and (−)-**27**. The Pd(0)-catalyzed insertion of iodobenzene generated the corresponding (π-allyl)palladium intermediate **29**. Then, an intramolecular oxycyclization reaction on the (π-allyl)palladium complex must account for the formation of the spiranic oxirane intermediate **30** or its regioisomer (−)-**27**. Subsequent β-lactam ring opening of the spirocyclic epoxy-2-azetidinone **30** under the reaction conditions, afforded the oxirane β-amino acid (−)-**26**. The formation of spirocyclic azetidinones **28** could be explained following a Pd(II)-catalyzed mechanism.[23] Initial Pd(II)-coordination gave an allenepalladium complex **31**. Species **31** suffers an intramolecular cycloetherification reaction to give the palladadihydrofurans **32**. Intermediate **32** reacted with the appropriate allyl bromide to form intermediates **33** which, after dehalopalladation, generated spiro-β-lactams **28** with concomitant regeneration of the Pd(II) species (Scheme 10).

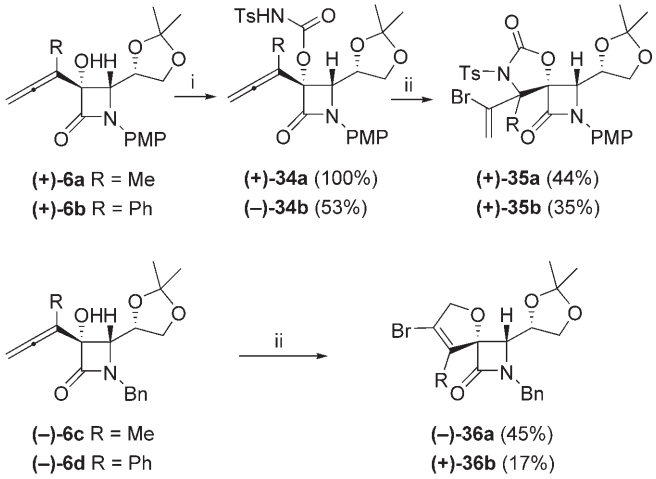
To expand the scope of these interesting intramolecular allene cyclizations, we decided to test the reactivity of the carbamate moiety as internal nucleophile in the intramolecular metal-catalyzed addition to allenes by using a Pd–Cu bimetallic system. α-Allenols (+)-**6a** and (+)-**6b** were derivatizated through reaction with tosyl isocyanate to give the α-allene carbamates (+)-**34a** and (−)-**34b**. Interestingly, the 1,2-bromoamidation of the allenes **34** took place smoothly, obtaining the spiranic oxazolidinone-β-lactams (+)-**35a** and (+)-**35b** as single isomers (Scheme 11). Next, we decided to test if this transformation could be accessible through the palladium(II)-catalyzed reaction of the allenol moiety itself. The bromodihydrofurans (−)-**36a** and (+)-**36b** were prepared as single isomers *via* the palladium-induced intramolecular 2,3-oxybromination of α-allenols (−)-**6c** and (−)-**6d** (Scheme 11). Of special interest is the reversal on the regioselectivity in the nucleophilic insertion of allenols **6**, by comparison with the cyclization of the carbamate derivatives **34** under the same reaction conditions. The palladium-catalyzed intramolecular cyclization of simple γ-allenic alcohols has been recently reported by Bäckvall and co-workers.[24] However, the dramatic change on the regioselectivity by the effect of the tether length should be noted . These authors obtained the 1,2-addition products, while we obtained the 2,3-addition products.



Scheme 9. Mechanistic explanation for the formation of spirocycles **26** and **27**.



Scheme 10. Mechanistic explanation for the formation of spirocyclic β-lactams **28**.



Scheme 11. Palladium/copper-promoted preparation of spirocyclic β-lactams **35** and **36**. *Reagents and conditions*: i) TsNCO, NaH, THF, room temperature, 3 h. ii) $Pd(OAc)_2$, LiBr, $Cu(OAc)_2$, K_2CO_3, MeCN, O_2, room temperature; **35a**: 24 h; **35b**: 4 d; **36a**: 23 h; **36b**: 6 d.

A likely mechanism for the generation of spirocycles **35** and **36** should involve the initial formation of a (π-allyl)palladium species. The allenepalladium complex **37** and **31** are formed initially and suffer a nucleophilic attack by the bromide to produce σ-allylpalladium species, which rapidly equilibrate to the corresponding (π-allyl)palladium intermediates **38** and **39**. Then, an intramolecular cycloetherification reaction on the (π-allyl)palladium complex must account for the formation of spiranic oxazolidinones and bromodihydrofuran intermediates **35** and **36** (Scheme 12 and Scheme 13).

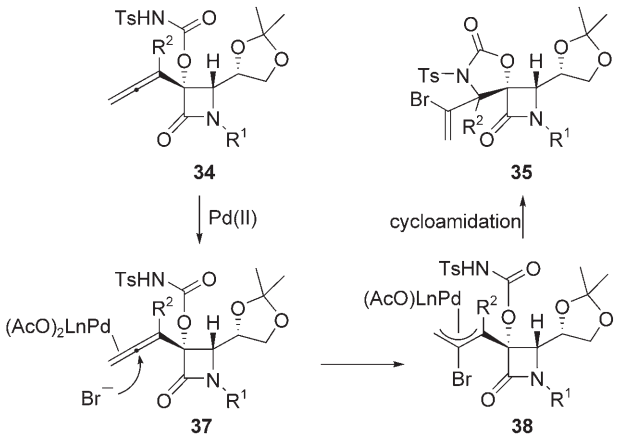
Conclusions

In conclusion, the present study provides the first diversity-oriented preparation of the spiro-β-lactam framework, which is an important structural motif in some biologically relevant compounds. We have shown that the use of Barbier-type carbonyl addition reactions on azetidine-2,3-diones followed by metal-promoted cyclizations on the resulting unsaturated alcohols is a useful methodology for the preparation of a variety of diversely functionalized oxaspirocyclic 2-azetidinones.

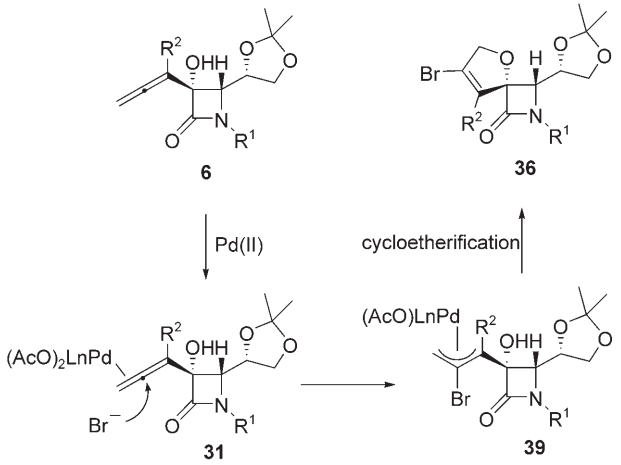
Experimental Section

General Methods

Melting points were taken using a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 781 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-



Scheme 12. Mechanistic explanation for the formation of spirocyclic β-lactams **35**.



Scheme 13. Mechanistic explanation for the formation of spirocyclic β-lactams **36**.

300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except where otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were taken on an HP5989A spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Optical rotations were measured using a Perkin–Elmer 241 polarimeter. Specific rotation $[\alpha]_D$ is given in deg $cm^2 g^{-1}$ at 25 °C, and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification. THF was distilled from Na-benzophenone. Benzene, dichloromethane and triethylamine were distilled from CaH_2. Flame-dried glassware and standard Schlenk techniques were used for moisture sensitive reactions. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh).

General Procedure for the Ring-Closing Metathesis (RCM) Reaction of Precursors 7–10 and 16–18; Preparation of Spirocyclic β-Lactams 11–14 and 19–21

To a solution of the appropriate precursor (0.20 mmol) in anhydrous toluene (6 mL), protected from the sunlight, was added in portions $[Cl_2(Cy_3P)_2Ru=CHPh]$ or $[Cl_2(Im)(Cy_3P)Ru=CHPh]$ (0.01 mmol) under argon. The resulting mixture was heated at reflux until complete disappearance of the starting material (TLC), and was concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes or ethyl acetate/dichloromethane mixtures gave analytically pure compounds **11**–**14** or **19**–**21**.[25]

General Procedure for the Heck Reaction of Bromodienes 22; Preparation of Spirocyclic β-Lactams 23

Palladium(II) acetate (0.03 mmol), triphenylphosphine (0.07 mmol), and potassium carbonate (7.0 mmol) were sequentially added to a solution of the corresponding bromodiene **22** (1.0 mmol) in dimethylformamide (15 mL), and the mixture was heated at 105 °C in a sealed tube. After disappearance of the starting material (TLC), the reaction mixture was cooled at room temperature and diluted with ethyl acetate (10 mL). The organic phase was washed with water (4×5 mL) and brine (3×5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate or dichloromethane/ethyl acetate mixtures gave analytically pure spiranic β-lactams **23**.[25]

General Procedure for the Silver-Induced Reaction of α-Allenols 6; Preparation of Spirocyclic β-Lactams 24

Silver nitrate (0.20 mmol) was added to a stirred solution of the corresponding α-allenol **6** (0.20 mmol) in acetone/water (1:1) (0.4 mL). The reaction was refluxed until disappearance of the starting material (TLC). The mixture was allowed to reach room temperature before brine (2 mL) was added, and then it was extracted with ethyl acetate (4×5 mL). The organic extract was washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded the corresponding spiranic dihydrofuran adducts **24** in analytically pure form.[25]

Pd(0)-Catalyzed Cyclization of α-Allenols 6; Preparation of Spirocyclic β-Lactams 25

$[Pd(PPh_3)_4]$ (15 mg, 0.013 mmol) was added to a mixture of the corresponding α-allenol **6** (0.25 mmol), and silver carbonate (138 mg, 0.5 mmol) in DMF (2 mL) under Ar, and the resulting mixture was heated at 180 °C until disappearance of the starting material (TLC). The reaction was then quenched with brine (2.5 mL), the mixture was extracted with ethyl acetate (4×5 mL), and the combined extracts were washed twice with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded the corresponding spiranic dihydrofuran adducts **25** in analytically pure form.[25]

Pd(0)-Catalyzed Coupling Cyclization of α-Allenol (+)-6a with PhI; Preparation of Oxirane γ-Amino Acid (−)-26 and Spirocyclic β-Lactam (−)-27

$[Pd(PPh_3)_4]$ (7.2 mg, 0.006 mmol) was added to a mixture of α-allenol (+)-**6a** (40 mg, 0.12 mmol), phenyl iodide (26 mg, 0.13 mmol), and potassium carbonate (66 mg, 0.48 mmol) in DMF (1 mL) under Ar, and the resulting mixture was heated at 85 °C for 45 h. The reaction was then quenched with brine (1.2 mL), the mixture was extracted with ethyl acetate (4×2 mL), and the combined extracts were washed twice with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded 17 mg (33 %) of the more polar compound (−)-**26** and 6 mg (12 %) of the less polar compound (−)-**27** after chromatography eluting with hexanes/ethyl acetate (1:1).[25]

General Procedure for the Pd(II)-Catalyzed Coupling Reaction of α-Allenols 6 with Allyl Bromide; Preparation of Spirocyclic β-Lactams 28

Palladium(II) chloride (0.005 mmol) was added to a stirred solution of the corresponding α-allenol **6** (0.10 mmol) in *N*,*N*-dimethylformamide (0.6 mL). The reaction mixture was stirred under an argon atmosphere until disappearance of the starting material (TLC). Water (0.5 mL) was added before being extracted with ethyl acetate (3×4 mL). The organic phase was washed with water (2×2 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure spiranic 2-azetidinones **28**.[25]

General Procedure for the Palladium(II)-Catalyzed Cyclization of α-Allenic Carbamates 34; Preparation of Spirocyclic β-Lactams 35

Palladium(II) acetate (0.012 mmol), lithium bromide (0.656 mmol), potassium carbonate (0.16 mmol) and copper(II) acetate (0.28 mmol) were sequentially added to a stirred solution of the corresponding α-allenic carbamate **34** (0.134 mmol) in acetonitrile (7 mL). The resulting suspension was stirred at room temperature under an oxygen atmosphere until disappearance of the starting material (TLC). The organic phase was diluted with brine (2 mL), extracted with ethyl acetate (3×5 mL), washed with brine (2 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure spiranic 2-azetidinones **35**.[25]

General Procedure for the Palladium(II)-Catalyzed Oxybromination of α-Allenic Alcohols 6; Preparation of Spirocyclic β-Lactams 36

Palladium(II) acetate (0.01 mmol), lithium bromide (0.74 mmol), potassium carbonate (0.18 mmol) and copper(II) acetate (0.32 mmol) were sequentially added to a stirred solution of the corresponding α-allenic alcohol **6** (0.15 mmol) in acetonitrile (5 mL). The resulting suspension was stirred at room temperature under an oxygen atmosphere until disappearance of the starting material (TLC). The organic phase was diluted with brine (2 mL), extracted with ethyl acetate (3×5 mL), washed with brine (2 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure spiranic 2-azetidinones **36**.[25]

Supporting Information

Compound characterization data for all compounds as well as experimental procedures not included in the Experimental Section.

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