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Synthetic Methods

A Versatile Synthesis of β-Lactam-Fused Oxacycles through the Palladium-Catalyzed Chemo-, Regio-, and Diastereoselective Cyclization of Allenic Diols

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Abstract: Chemo-, regio- and stereocontrolled palladium-catalyzed preparations of enantiopure morpholines, oxocines, and dioxonines have been developed starting from 2-azetidinone-tethered γ,δ-, δ,ε-, and ε,ζ-allendiols. The palladium-catalyzed cyclizative coupling reaction of γ,δ-allendiols **2** with allyl bromide or lithium bromide was effective as 8-*endo* cyclization by attack of the primary hydroxy group to the terminal allene carbon to afford enantiopure functionalized oxocines; whereas the palladium-catalyzed cyclizative coupling reaction of 2-azetidinone-tethered ε,ζ-allendiols **4** furnished dioxonines **16** through a totally chemo- and regioselective 9-*endo* oxycyclization. By contrast, the palladium-catalyzed cyclizative coupling reaction of 2-azetidinone-tethered δ,ε-allendiols **3** with aryl and alkenyl halides exclusively generated six-membered-ring compounds **14a** and **15a**. These results could be explained through a 6-*exo* cyclization by chemo- and regiospecific attack of the secondary hydroxy group to the internal allene carbon. Chemo- and regiocontrol issues are mainly influenced by the length of the tether rather than by the nature of the metal catalysts and substituents. This reactivity can be rationalized by means of density functional theory calculations.

Introduction

The 2-azetidinone motif is used as a template on which to build cyclic structures fused to the four-membered ring and is also present in a large number of naturally occurring and medicinally relevant substances.[1] Moreover, the rigid structure and strain-driven reactivity make 2-azetidinone derivatives attractive as versatile intermediates in organic synthesis.[2] Over the past decades, vast efforts from chemists have been engaged by this area. Even so, complementary new approaches with high synthetic efficiency to build β-lactam-based structures remain highly desirable.

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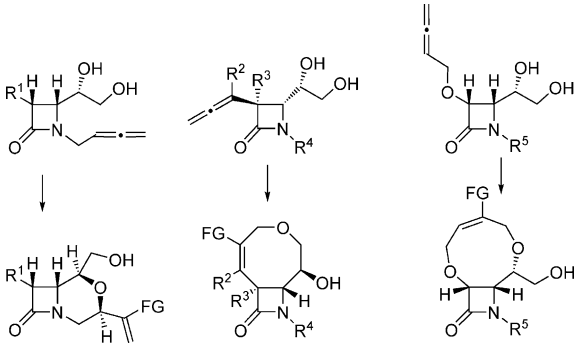
On the other hand, cyclic ethers are important structures frequently found in biologically active natural products such as acetogenins, prostaglandins, polyether antibiotics, and macrocyclic natural products, and great interest is focused on the development of new and efficient methods for the synthesis of oxygen heterocycles.[3] Catalytic regioselective O–H addition to the C=C bonds of pendant olefins is a highly desirable, atom-economical transformation for accessing oxygen-containing heterocycles. Thus, HO/cyclization across an allene moiety fulfills green chemical requirements more satisfactorily than conventional byproduct-producing substitution reactions. Though this mode of reactivity has previously been reported for allenols, similar reactions for the corresponding allenic diols have remained largely unexplored.[4]

The discovery of new reactivity and principles for controlling chemo-, regio- and stereoselectivity is a fundamental task for organic synthesis. Both the enormous potential of confrontation of two functional groups that are either reactive or inert (chemoselectivity) and the preferential reaction with one direction of bond-making (regioselectivity) joined to the possibility of stereocontrol can all be encountered in the heterocyclization reaction of allenic diols. Thus, although catalytic intramolecular allene hydroalkoxylation of 1,2-dienes bearing two contiguous nucleophilic centers offers many attractions, efficient transformations remain elusive due to additional selectivity problems. Depending on both the regioselectivity (*endo-trig* vs. *endo-dig* versus *exo-dig* vs. *exo-trig* cyclization) as well as the chemoselectivity (distal vs. proximal nucleophile cycliza-

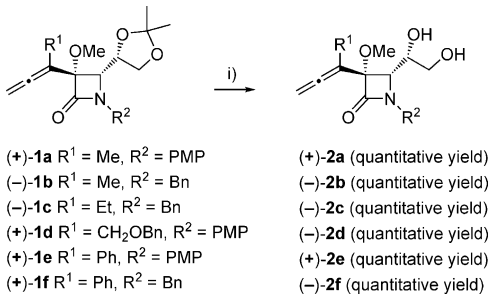
tion), any of the eight possible heterocycles could be the reaction products. Following our interest in heterocyclic and allene chemistry,[5] we now studied 2-azetidinone-tethered γ,δ-, δ,ε-, and ε,ζ-allendiols with the views to tracing their propensity to suffer selective palladium-catalyzed C–O bond-forming reactions (Scheme 1). A number of different oxabicyclic β-lactam products also emerged in the present study.



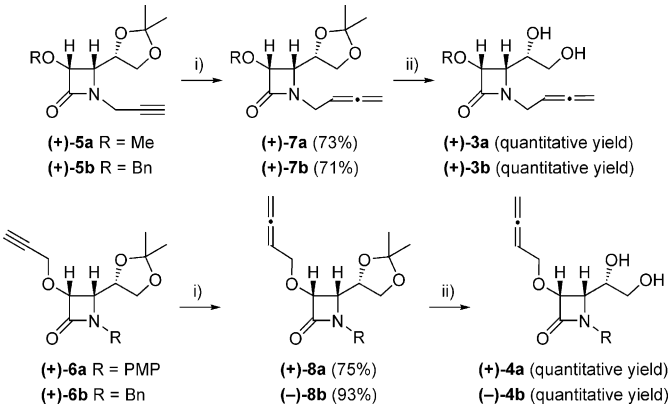
Scheme 1. General Scheme defining the processes that can take place.

Results and Discussion

To explore the effects of various substrates on palladium-catalyzed oxycyclization reactions, a number of new β-lactam allenic diols were synthesized. Starting materials, allenes **1a–f** were made from the corresponding azetidine-2,3-diones through an indium-mediated Barbier-type carbonyl–allenylation reaction in aqueous media using our previously described methodology.[6] Precursors for the oxacycle formation, enantiopure 2-azetidinone-tethered γ,δ-allendiols **2a–f** were smoothly obtained in quantitative yields by treatment of dioxolanes **1** with bismuth trichloride (Scheme 2). 2-Azetidinone-tethered δ,ε-allendiols **3a** and **3b** and 2-azetidinone-tethered ε,ζ-allendiols **4a** and **4b** were obtained in optically pure form from 2-azetidinone-tethered alkynyl dioxolanes **5** and **6**, respectively.[7] Terminal alkynes **5** and **6** were conveniently converted into allendiols **3** and **4** by treatment with paraformaldehyde in the presence of diisopropylamine and copper(I) bromide (Crabbé reaction),[8] followed by $BiCl_3$-catalyzed acetonide cleavage (Scheme 3).



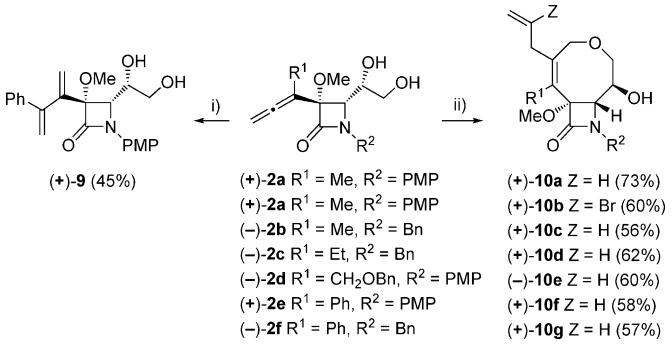
Scheme 2. Preparation of enantiopure γ,δ-allenic diols **2a–f**. Reagents and conditions: 50 mol% $BiCl_3$, $MeCN/H_2O$, RT, 72 h. PMP = 4-$MeOC_6H_4$.



Scheme 3. Preparation of enantiopure δ,ε-allenic diols **3a,b** and ε,ζ-allendiols **4a,b**. Reagents and conditions: i) $(CH_2O)_n$, iPr_2NH, CuBr, dioxane, reflux, 1 h; ii) 50 mol% $BiCl_3$, $MeCN/H_2O$, RT, 15 h. PMP = 4-$MeOC_6H_4$.

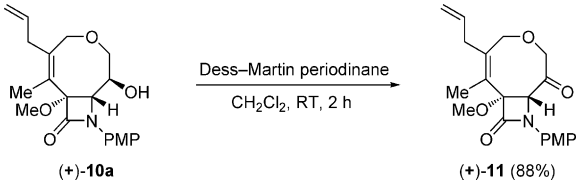
Our next efforts focused on the application of palladium catalysis to the selective construction of fused oxacycles starting from allenic diols having a β-lactam moiety. γ,δ-Allendiol **2a** was chosen as a model substrate for palladium-catalyzed oxycyclization reactions. Attempts to generate a bicyclic structure from **2a** by using Pd^0 catalysis in the presence of iodobenzene failed, because β-hydride elimination to afford diene **9** competes more effectively. Despite this failure, γ,δ-allendiols **2** were exposed to allyl bromide or 2,3-dibromoprop-1-ene under Pd^{II} catalysis in DMF. Much to our delight, adducts **10a–g** were obtained in good yields in a totally chemo- and regioselective fashion using the $[PdCl_2]$-catalyzed cyclizative coupling reaction with allyl halides (Scheme 4), through an 8-*endo* cyclization by attack of the primary hydroxy group to the terminal allene carbon. To the best of our knowledge, no example of an 8-*endo* cyclization at the terminal allene carbon of a δ-allenol has been reported. Thus, we present experimental evidence concerning the 8-*endo-trig* cyclization pathways in allene oxycyclization reactions that enriches Baldwin's rules for ring closure.

Traditional ring-closure strategies are effective for five- or six-membered rings, but problematic for medium-sized ring systems owing to entropic and transannular penalties incurred



Scheme 4. Preparation of diene **9** and oxocines **10**. Reagents and conditions: i) 5 mol% $[Pd(PPh_3)_4]$, PhI, K_2CO_3, toluene, 80 °C, 120 h; ii) 5 mol% $[PdCl_2]$, $CH_2{=}CH(Z)CH_2Br$, DMF, RT, **10a**: 14 h; **10b**: 16 h; **10c**: 16 h; **10d**: 15 h; **10e**: 15 h; **10f**: 16 h; **10g**: 19 h. PMP = 4-$MeOC_6H_4$.

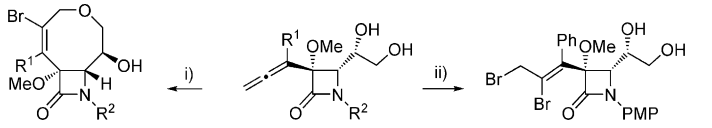
when bringing the two ends of a reactant together; eight- to ten-membered rings have shown to be the most challenging for cyclization strategies. Thus, fused bicycles **10** are remarkable, because they comprise an oxocine fused to a strained *trans*-β-lactam. HMBC experiments of 4-oxa-10-azabicyclo[6.2.0]decene derivatives **10** satisfactorily established information about the presence of a new eight-membered oxacycle fused to the β-lactam ring. Chemical evidence was obtained by oxidation of adduct **10a** with Dess–Martin periodinane to afford ketone **11** (Scheme 5).



(+)-**10a** (+)-**11** (88%)

Scheme 5. Preparation of oxocinone **11**. PMP = 4-$MeOC_6H_4$.

Our interest then turned to the cycloetherification reaction by way of palladium-induced oxybromination. Thus, γ,δ-allendiols **2** were treated with lithium bromide using a Pd–Cu bimetallic catalytic system. In the event, only the hydroxy group in δ-position participates in the $[Pd(OAc)_2]$-catalyzed regiocontrolled oxybromination reaction of methyl- and ethyl-γ,δ-allendiols **2a–c**, giving exclusively the eight-membered fused derivatives **12** (Scheme 6).[10] The use of the above oxybromination reaction conditions on phenyl γ,δ-allendiol **2e** changes the reactivity pattern, suppressing the oxycyclization while retaining the same regioselectivity of the bromination step. Thus, in the case of phenylallendiol **2e** we observed exclusive formation of the monocyclic dibromide **13**. The divergence between alkyl- and arylallendiols **2** may arise from the different stereoelectronic effect imparted by the phenyl group in the oxycyclization step, which directs the reaction toward a new bromide attack to the terminal allene carbon rather than toward a cycloetherification.



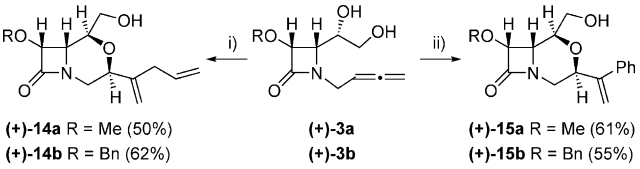
(+)-**12a** R^1 = Me, R^2 = PMP (50%)
(+)-**12b** R^1 = Me, R^2 = Bn (52%)
(+)-**12c** R^1 = Et, R^2 = Bn (44%)

(+)-**2a**
(–)-**2b**
(–)-**2c**
(+)-**2e**

(+)-**13** R^1 = Ph, R^2 = PMP (43%)

Scheme 6. Preparation of oxocines **12** and dibromide **13**. Reagents and conditions: i) 7 mol% $[Pd(OAc)_2]$, LiBr, $[Cu(OAc)_2]$, K_2CO_3, MeCN, O_2, RT, **12a**: 6 d; **12b**: 7 d; **12c**: 6 d; ii) 7 mol% $[Pd(OAc)_2]$, LiBr, $[Cu(OAc)_2]$, K_2CO_3, MeCN, O_2, RT, 8 d. PMP = 4-$MeOC_6H_4$.

To demonstrate the synthetic utility of this selective cycloetherification reaction in the synthesis of non-oxocine cyclic compounds, four additional allenic diols **3a,b** and **4a,b** were employed. The palladium-catalyzed cyclizative coupling reaction of 2-azetidinone-tethered δ,ε-allendiols **3a** and **3b** with aryl and alkenyl halides was explored next. It is worth mentioning that six-membered ring compounds **14a,b** and **15a,b** can also be exclusively generated under these conditions (Scheme 7). These results could be explained through a 6-*exo* cyclization by chemo- and regiospecific attack of the secondary hydroxy group to the internal allene carbon with concomitant incorporation of the unsaturated bromide into the central allene carbon. Besides, the reaction is totally diastereoselective so that just one diastereomer is formed (morpholines **14** and **15** bearing a quaternary stereocenter are formed as single isomers). Thus, by using a related allendiol homologue (δ,ε-allendiols **3** vs. γ,δ-allendiols **2**), both the chemo- and regioselectivity can be reversed, favoring the 6-*exo* cyclization of secondary hydroxy group towards the internal allene carbon (morpholine adduct) over the 8-*endo* cyclization by attack of the primary hydroxy group towards the terminal allene carbon (oxocine adduct).[9] The stereochemical assignments were based on a ^1H NMR evaluation, which involves the analysis of the coupling constants between the different protons of the cyclohexane ring, and in some cases were confirmed by NOE experiments.



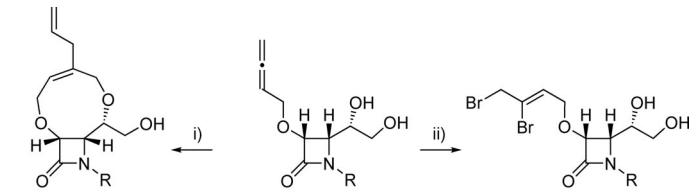
(+)-**14a** R = Me (50%)
(+)-**14b** R = Bn (62%)

(+)-**3a**
(+)-**3b**

(+)-**15a** R = Me (61%)
(+)-**15b** R = Bn (55%)

Scheme 7. Preparation of morpholines **14** and **15**. Reagents and conditions: i) 5 mol% $[PdCl_2]$, CH_2=CH(Z)CH_2Br, DMF, RT, 4 h; ii) 5 mol% $[Pd(PPh_3)_4]$, PhI, K_2CO_3, DMF, 80 °C, 15 h. DMF = *N*,*N*-dimethylformamide.

The one-atom longer allenic diols **4** were found to show a mixed behavior (regioselectivity similar to **2**, whereas chemoselectivity similar to **3**). Upon exposure to a catalytic amount of $[PdCl_2]$ in the presence of allyl bromide, ε,ζ-allendiols **4a,b** produced the 1,5-dioxonine derivatives **16a,b** in reasonable yields as single isomers (Scheme 8). The nine-membered oxacycles **16** may arise from a totally chemo- and regio-



(+)-**16a** R = PMP (61%)
(+)-**16b** R = Bn (58%)

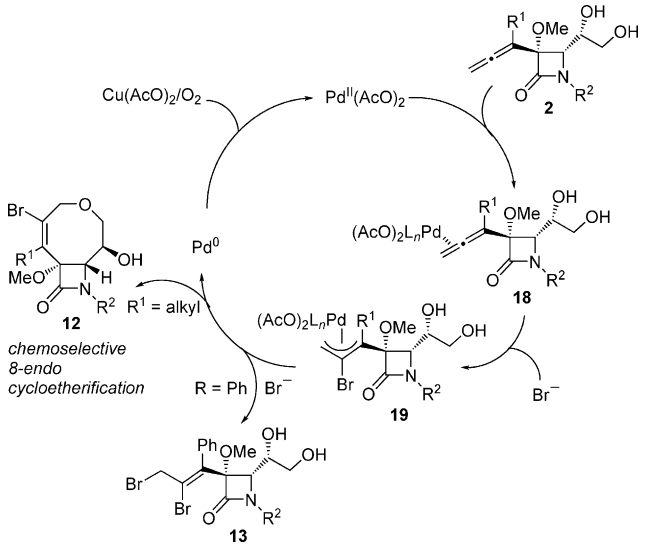
(+)-**4a**
(–)-**4b**

(+)-**17** R = Bn (48%)

Scheme 8. Preparation of dioxonines **16** and dibromide **17**. Reagents and conditions: i) 5 mol% $[PdCl_2]$, CH_2=CH(Z)CH_2Br, DMF, RT, 4 h; ii) 7 mol% $[Pd(OAc)_2]$, LiBr, $[Cu(OAc)_2]$, K_2CO_3, MeCN, O_2, RT, 2 d. PMP = 4-$MeOC_6H_4$.

selective 9-*endo* oxycyclization of the secondary hydroxy group to the terminal allene carbon with concurrent alkene functionalization. By contrast, the cyclization of ε,ζ-allenic diol **4b** was not as rewarding when it was treated with lithium bromide using a Pd–Cu bimetallic catalytic system. No ring-closing product could be detected in the reaction mixture, producing the dibromide **17** (Scheme 8).

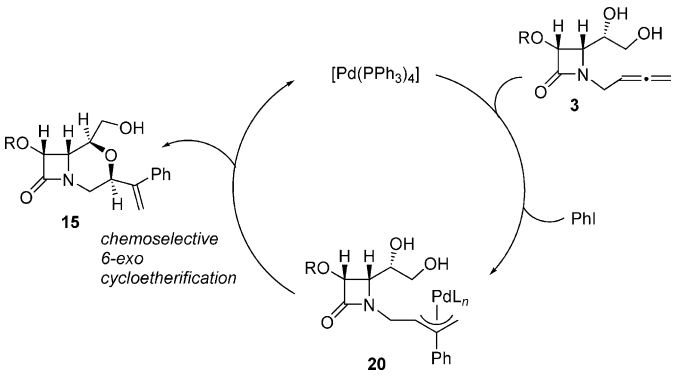
As shown in Scheme 9, the oxybromination reaction of alkyl γ,δ-allendiols **2a–c** proceeds through an external nucleophilic attack (Br^-) on the (π-allene)palladium complex **18** to afford the (π-allyl)palladium species **19**. Subsequent chemoselective



Scheme 9. Mechanistic explanation for the metal-catalyzed dibromination and bromoheterocyclization reaction of γ,δ-allendiols **2** under Pd–Cu bimetallic catalysis.

intramolecular attack by the primary hydroxyl group gives oxocines **12**. Formation of monocyclic dibromides **13** is the consequence of a second addition of the bromide ion to the allene side remote from the diol group. Finally, in situ-oxidation of Pd^0 to Pd^{II} by $[Cu(OAc)_2]$ completes the catalytic cycle. It may be inferred that different steric effects in the organometallic species **19** may be responsible for the different reactivity preference, stabilizing one of the intermediates rather than the other. Cicloetherification falters in the presence of sterically encumbering phenylallendiols. Probably, oxybromination through **19** is restricted by the steric hindrance of the R^1 substituent (R^1 = Ph) when the diol moiety is trying to approach to the palladacomplex **19**.

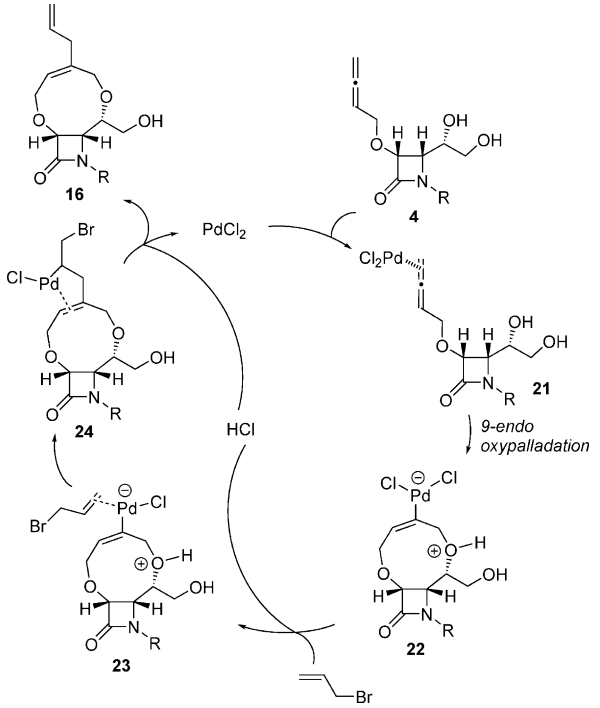
A mechanistic hypothesis for the achievement of morpholines **15** from δ,ε-allendiols **3** is outlined in Scheme 10. The Pd^0-catalyzed insertion of iodobenzene generated the corresponding (π-allyl)palladium intermediate **20**. Then, an intramolecular chemo-, regio-, and stereoselective 6-*exo* oxycyclization reaction on the (π-allyl)palladium complex must account for the formation of the fused bicycles **15** with concurrent regeneration of the Pd^0 catalytic species (Scheme 10). The reason for the total diastereoselectivity for 6-*exo* cyclization toward the



Scheme 10. Mechanistic explanation for the palladium-catalyzed oxycyclization of δ,ε-allendiols **3** in presence of iodobenzene.

internal allene carbon on species **20** to give adducts **15**, may be related to an easier attack of the incoming oxygen nucleophile to the allene-metal complex from the less-hindered face.

The palladium-catalyzed heterocyclization reaction of ε,ζ-allendiols **4** shows the same regioselectivity but different chemoselectivity as that observed under palladium catalysis for γ,δ-allendiols **2**, that is, the initial cyclization takes place preferentially by selective nucleophilic addition of the secondary hydroxylic oxygen to the activated terminal allene carbon. Scheme 11 outlines a mechanistic proposal[11] for the achievement of 1,5-dioxonines **16**. Initial Pd^{II}-coordination to the 1,2-diene moiety gave an allene palladium complex **21**, which suffers a chemo- and regioselective 9-*endo* oxycyclization reaction to give the intermediate palladatetrahydrodioxonine **22**. The presence of an allyl halide alternatively promotes a coupling reaction by trapping of the alkenyl–Pd intermedi-



Scheme 11. Mechanistic explanation for the palladium-catalyzed oxycyclization of ε,ζ-allendiols **4** in presence of allyl bromide.

ate. This process should be favored by the easy HCl release from the coordination to the metal center. The allyl coupling with the alkenyl–Pd^{II} intermediate occurs through a three-step mechanism: 1) Ligand displacement from the metal coordination sphere, 2) insertion into the allylic halide C=C bond to give a σ-C–Pd intermediate, and 3) *trans* β-elimination to afford the 1,5-dioxonine product. The palladium-coordinated HCl is easily displaced by the incoming allyl bromide in a fast ligand-interchange displacement mechanism to yield the η^2-complex **23** upon π-coordination of the C–C double bond to the metal. The coordinated alkene undergoes a 2,1-insertion into the Pd–alkyl bond in a stepwise process that proceeds through the formation of a η^2-Pd-complex **24**. A *cis/trans* isomerization of the chloride ligand takes place to reach the transition state, probably to reduce the back-bonding interaction and to favor the Pd–C bond formation. The η^2-Pd-complex then suffers a β-heteroatom elimination to give the coupling product **16** and the active catalyst [$PdCl_2$]. Probably, the liberated HCl plays a key role in promoting the dehalopalladation and inhibiting the usual β-H elimination.

Density functional theory (DFT) calculations have been carried out to gain more insight into the reaction mechanisms, chemo-, and regioselectivity of these processes.

To explore the reactivity of δ,ε-allendiols **3** to form morpholines **15**, we selected allenol **25** as a model substrate. The first step of the mechanism is an oxidative addition. Normally, theoretical calculations[12] have considered a concerted mechanism using bis(phosphine)palladium(0) ([PdL_2]), on the basis of the early experimental studies of oxidative addition of organohalides to [$Pd(PPh_3)_4$].[13] Kinetic studies also showed that in solution, PdL_4 easily dissociates one of the four phosphine ligands and the resulting [PdL_3] is in rapid equilibrium with [PdL_2].[14] However, in the last years it has been suggested that bulky phosphine ligands promote the oxidative addition through monophosphine palladium complexes [PdL], which are more active in the oxidative addition reactions.[15] Theoretical studies by Norrby and co-workers showed that the barriers calculated for oxidative addition of R_1X to [PdL] are significantly smaller than those to [PdL_2].[16] These results are in agreement with the observations by Hartwig et al. who found that a highly unsaturated monophosphine Pd^0 complex is the active species.[17] They also found that the intimate mechanism of oxidative addition is sensitive to the nature of the halide.[18]

For PhI, the calculations predicted that the monophosphine pathway is preferred.[18a] However, the bisphosphine pathway is very close to that for the monophosphine pathway, so both pathways might well be competitive and are not mutually exclusive.[19] The accessibility to the monophosphine Pd complex is thus key to obtain good catalytic activity. Very recently, Maseras and co-workers provided computational evidence for the formation of [Pd] solvent adducts. The results revealed that the bare [$Pd^0(PPh_3)$] shows a limited lifetime and suggested that the main pathway leading to formation of the reactant species [(PhX)Pd(PPh_3)] will proceed through the substitution of a PPh_3 ligand of [$Pd(PPh_3)_2$] by the incoming PhX substrate.[20]

On this basis, we have computed the oxidative addition from the complex [(PhI)$Pd^0(PMe_3)$] (**26**). This step goes to Pd^{II}-complex **27**, in which phosphine is *trans* to the aryl group (kinetically favored over the *cis*)[19] through transition state $\mathbf{TS_{26-27}}$. This exergonic process ($\Delta G = -4.9$ kcal mol^{-1}) proceeds by surmounting a low barrier of 1.6 kcal mol^{-1}.

The next step does not have to take place necessarily in the same ligand arrangement resulting from the oxidative addition, and an additional isomerization step is possible. In brief, the plausible processes involves low activation barriers (see Figures S1 and S2, the Supporting Information); thus, the isomerization of **27** to the *trans* arrangement of iodide and aryl (**27′**) takes place through two consecutive isomerizations[19] (**27**→**27″** and **27″**→**27′**, Figure 1) involving low-energy barriers (6.6 and 3.5 kcal mol^{-1}, respectively), with **27′** being more stable (by 12.3 kcal mol^{-1}) than **27** and that **27″** (*trans* arrangement of I and PMe_3, by 1.0 kcal mol^{-1}).

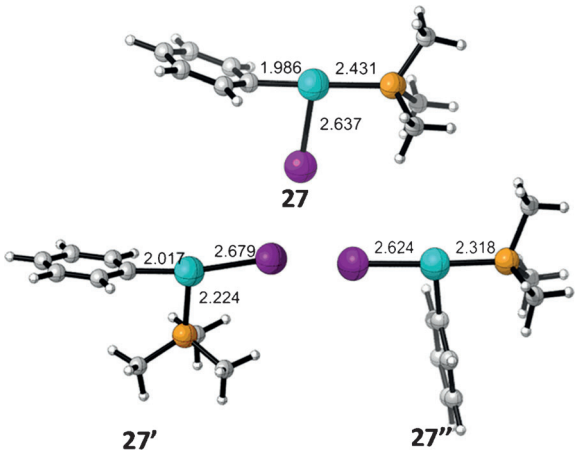
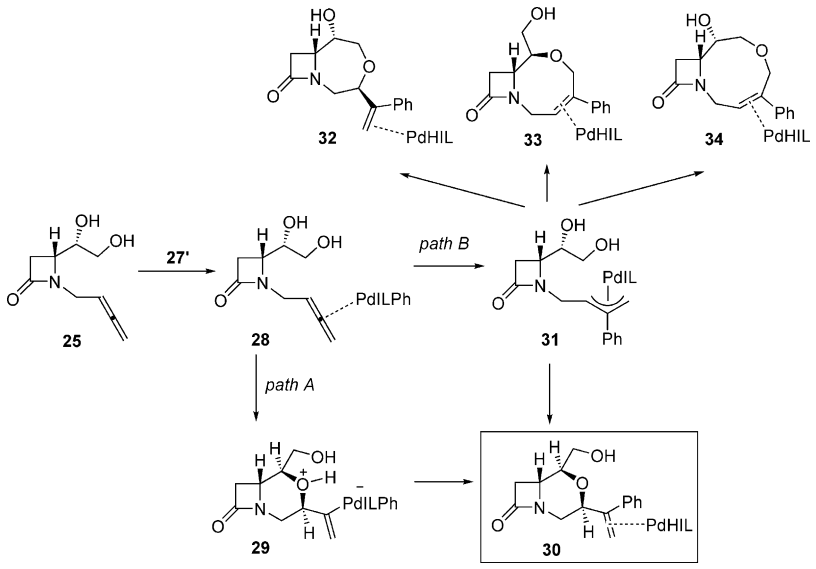


Figure 1. Optimized geometries of tricoordinate palladium complexes potentially involved in the catalytic cycle.

Two different coordination modes of the Pd^{II}-complex to the allenic double bond, that is, distal versus proximal, are possible. Thus, three potential geometries for the catalyst with respect to the coordinated allene have been taken into account, namely, with the phosphine group (**A,A′**), iodide (**B,B′**) and phenyl (**C,C′**, although unproductive for coupling) in a *trans* disposition regarding the distal and proximal double bonds of the coordinated allene. The π-coordination of one of the double bond of the allene moiety can give rise to six square-planar η^2-allene complexes **28A–28C′** (see Figure S3, the Supporting Information). They are 0.3–11.7 kcal mol^{-1} more stable than the isolated Pd^{II}-complex and allene (see Table S1, the Supporting Information), because of the interaction between the vacant site in the Pd center and the filled π orbital of the double bond. Due to a stronger back-donation by the phosphine ligand, the most stable complexes (by 4.0–10.3 kcal mol^{-1}) bear the phosphine ligand *trans* to the unsaturated group.

At this point, two different mechanisms can be postulated in the Pd-catalyzed cyclization of allenes with a nucleophilic functionality (Scheme 12): 1) Intramolecular nucleophilic attack on



Scheme 12. Possible reaction pathways for the formation of morpholines of type **15**.

the activated allene, followed by the coupling process (path A); 2) Carbopalladation of the allene leading to a π-allyl intermediate, which undergoes a subsequent intramolecular nucleophilic attack (path B).[21] Since both paths share a common initial reactant complex, the most stable complex (**28 A**), will be taken as reference for the following discussion.

For the first pathway (path A), we have considered the possible heterocyclization routes by nucleophilic attack of the δ- and ε-allenol functionalities on the three carbon atoms of the Pd^{II}-activated allene, starting from the six possible reactant complexes **28 A**–**28 C**′ (see the Supporting Information).

From a kinetic point of view, our calculations indicated that the preferred heterocyclization event involves the nucleophilic attack of the primary ε-OH group on the central allene carbon (through ε-$\mathbf{TS}_{8-exo-dig}$, with a barrier of 33.0 kcal mol^{-1}), which drives to the oxocine scaffold ε-$\mathbf{29}_{8-exo-dig}$. This result disagrees with the observed formation of morpholines **15**, which should proceed through a 6-*exo*-*trig* cyclization according to this mechanism (barrier of 34.8 kcal mol^{-1}). Moreover, these values for the heterocyclization are too high to take place under the experimental conditions. Additionally, the calculations on the following steps revealed that the coupling step also involves a high activation barrier.[22] Hence, this path can be ruled out since it is cannot account for the observed reactivity, and quimio- and regioselectivity.

As an alternative mechanism, we have also analyzed the path B (Scheme 12) involving carbopalladation of the allene leading to a η^3-allyl intermediate (**31**), followed by an intramolecular nucleophilic attack of the alcohol moiety.[23] Allenes insert into the Pd–C_{aryl} bonds to give η^3-allyl complexes in which a new bond forms between the previously metalated carbon and the central carbon of the allene moiety.[24,25] These insertion reactions have been widely investigated because they have been proposed as the key step in the palladium-catalyzed coupling reactions of 1,2-dienes and aryl halides to afford carbo- and heterocycles.[26]

Thus, path B (Scheme 12) involves coordination of the allene moiety to the metal center and subsequent insertion of the coordinated allene into the Pd–C bond to afford an η^3-allyl complex (**31**). The allene could coordinate to the palladium center in an η^2-mode through the distal or the proximal double bond, as was shown above, to form complexes **28**. As for path A, we have evaluated the effect of the ligands arrangement on the structure and energy outcomes. Coordination of the allene *trans* to the aryl group was not considered, as it is unproductive; only *cis* coordination is relevant for the insertion process.

Since a coordinated allene can switch the coordinated C=C double bond rapidly, it is reasonable to assume that the four precursor complexes **28 A**, **28 B**, **28 A**′, and **28 B**′, or at least **28 A** and **28 A**′, could participate in the insertion reaction, following possible reaction pathways.

Figure 2 summarizes the transition structures found for the plausible coupling routes between the aromatic group and the central allene carbon. The computed barriers for the structures bearing the iodide *trans* to the allene (transition structures $\mathbf{TS}_{28B'-31}$ and $\mathbf{TS}_{28B-31'}$) are higher than for the phosphine *trans*

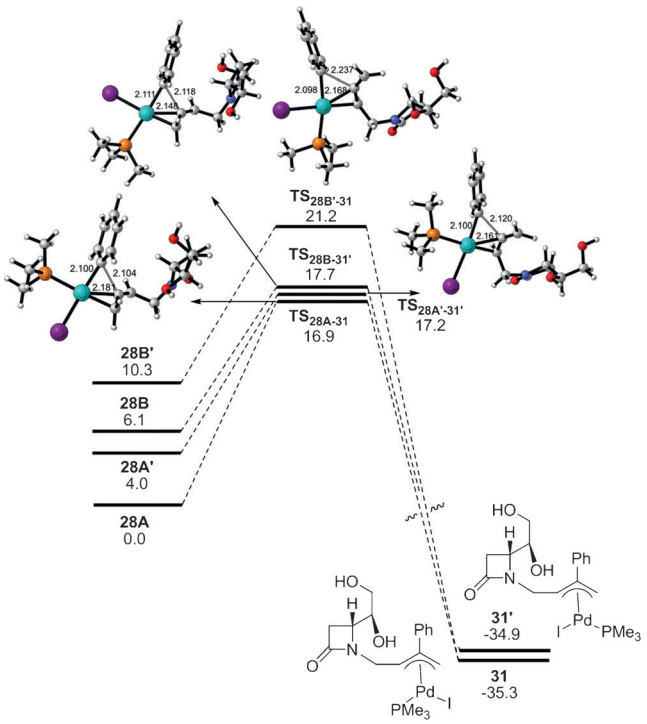


Figure 2. Free-energy profiles for the possible insertion steps.

complexes (TS_{28A-31} and $TS_{28A'-31'}$). These data are consistent with the fact that the more π-acceptor the ligand trans to the Pd–C_{allene} (PMe_3 vs. I^- (indeed, π-donor)), the lower should be the coupling barrier because it draws electron density away from the σ-Pd orbital, and this orbital is antibonding in the transition state.[22a] Additionally, these results are consistent with the common notion that stronger donor ligands, such as I^-, make the metal center more electron-rich (natural population analysis (NPA) charges of −0.062 and −0.053 *e* for **28B** and **28B′**, respectively, vs. −0.051 and −0.047 *e* for **28A** and **28A′**, respectively) and inhibit the C–C coupling.[27] The *trans* arrangement of the iodide ligand with respect to the allene constitutes a push–pull scenario that enhances the metal (d)-to-allene (π*) back-bonding interactions.[28] The second-order perturbation energy analysis (natural bond order (NBO) computations) reflects this effect, since this interaction is 27.91 kcal mol^{-1} for **28B** versus 16.59 kcal mol^{-1} for **28A**. It increases the π-electron density of the two carbons in the coordinated C=C bond, and, hence, increases the phenyl migration energy barriers.

On the other hand, the coordination of the distal bond implies lower barriers to reach the transition structures, probably also due to steric effects. In this process, the phenyl ring migrates to the central carbon of the coordinated allene, forming a new bond and, simultaneously, the palladium atom approached the non-coordinated double bond.

The transition structures evolve into two types of η^3-allyl intermediates, **31** and **31′**, in which the phosphine ligand is *trans* and *cis*, respectively, to C1. These processes are highly exergonic and therefore, probably irreversible. Complex **31′** is 0.4 kcal mol^{-1} less stable than the η^3-allyl complex **31**. This slight difference could be explained by the slightly greater steric hindrance due to the bulky iodide ligand. Notably, the possible insertion products of vinyl complexes were not observed in this study. It has been reported that solutions of related complexes[29] contain only the isomer in which the PR_3 is *trans* to the more substituted allylic carbon. In other studies, both *trans* and *cis* isomers were observed,[30] such as for complexes $PdI[CH_2C(Ph)CHR](PPh_3)$.[28b]

In most of the catalytic reactions mediated by these phosphine complexes, the aryl group is transferred to the central carbon of allenes. In contrast to the two terminal carbons of the isolated allene (NPA charges of −0.465 and −0.282 *e* for C1 and C3, respectively), the central carbon of the allene (C2) is electron-deficient (+0.088 *e*). Therefore, the migrating group (benzenide, NPA charge of −0.220 *e*) can preferentially attack the central carbon of allene in **28A**.[28] Occasionally, attachment of aryl to the terminal carbons of allenes has been also observed.[26m,31] To check this point, we have computed the insertion processes on the terminal and proximal allene carbon atoms. The computed activation barriers are 2.1 and 4.6 kcal mol^{-1} (Figure 3), respectively, higher than the insertion with the central allene carbon (TS_{28A-31}), in good agreement with the regioselectivity found experimentally.

The following heterocyclization step takes places by a chemo- and regioselective nucleophilic attack of the secondary OH moiety on the substituted carbon of the (η^3-allyl)Pd

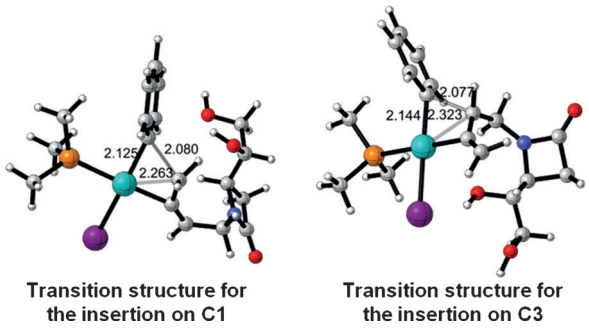


Figure 3. Optimized transition structures for the insertion on C1 and C3.

complex. In monosubstituted (η^3-allyl)Pd complexes, the regioselectivity of the nucleophilic attack is known to be sensitive to many factors, such as steric and electronic influences from the substrate substituents,[32] regiochemical memory,[33] preferred configuration[34] and dynamic exchange in the (η^3-allyl)Pd intermediate,[35] nucleophile,[36] and the nature of the ligands.[37–39]

In contrast to reactions of (η^3-allyl)Pd complexes with other nucleophiles,[40] and surpassing the regioselectivity for reactions of amines and phenols[41] or allylic fluorination,[42] a regioselective oxycyclization involving the substituted allylic carbon was obtained (Scheme 7).

The inherent electronic difference between phosphorus and halide results in a difference in Pd–C bond lengths,[43] as illustrated with the PdC1 bond length in **31** (2.225 Å), and in **31′** (2.186 Å) *trans* to phosphorous and iodide, respectively, and the PdC3 bond length (2.152 and 2.202 Å, respectively in **31** and **31′**). Norrby et al. found (for the nucleophilic addition to the intermediate [Pd(η^3-allyl)] complex) a preference for the terminus *trans* to phosphine of 11–13 kJ mol^{-1} rather than to an halide ligand.[44] Analogously, in nucleophilic additions to monosubstituted (η^3-allyl)Pd complexes, it has been assumed that (due to the relative *trans* influences of the ligands)[45] the nucleophile would preferentially attack the allylpalladium terminus *trans* to the phosphine ligand.[46]

The plausible transition structures involving both the allylic carbons and both the δ- and ε-OH functionalities have been calculated starting from the [Pd(η^3-allyl)] complexes **31** and **31′** (Figure 4). The optimized transition structures show an H-bonding interaction between the attacking nucleophile and the iodide. Any attempt to locate a transition structure lacking this interaction, was met with failure. This interaction is not feasible for the nucleophilic attack on C1 from the intermediate **31′** or on C3 from **31** without a severe steric distortion or from a *syn* conformation.[47] Hence, herein we only show the reasonable transition structures.

The results reveal a kinetic preference for the internal attack, through $TS_{31'-30''}$ (11.3 kcal mol^{-1} below the reactant complex) and $TS_{31'-32}$ (−9.1 kcal mol^{-1}), rather than for the terminal attack of the nucleophile, through TS_{31-33} (−5.9 kcal mol^{-1}) and TS_{31-34} (−4.2 kcal mol^{-1}) since the barriers are 5.8–7.1 kcal mol^{-1} higher for the later than for the former. Amazingly, the attack of the secondary alcohol moiety ($TS_{31'-30''}$) is the pre-

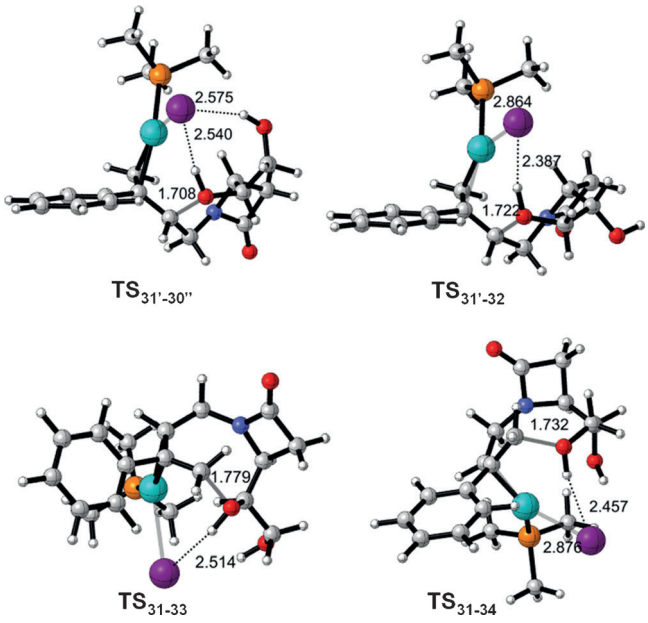


Figure 4. Optimized transition structures for the plausible heterocyclization step (path B).

ferred heterocyclization pathway, leading to the morpholine scaffold.

Previous theoretical studies on the nucleophilic addition to (η^3-allyl) palladium complexes have suggested that the reaction is controlled by the frontier orbitals rather than by the charges.[48] The presence of an electron-donating group on the allylic complex induces a polarization of the allyl orbitals. Thus, the n and π orbitals are polarized toward the nonsubstituted carbon (C1) and the π^* orbital toward the substituted carbon (C3). Due to this polarization of the n orbital toward the nonsubstituted carbon C1, the Pd–C1 interaction is stronger, whereas the Pd–C3 bond is weaker.[38] It has been found that a longer Pd–C bond corresponds to a more reactive allyl terminus, with each 0.01 Å elongation giving approximately a doubling in reactivity.[49] The lengthening of Pd–C3 allows the destabilizing four-electron interaction between the π-orbital and the metal to be diminished. The in-phase mixing with the π^*-orbital that is polarized toward the substituted carbon yields a larger contribution of this carbon in the LUMO orbital of the complex. The larger the coefficient in the LUMO on a carbon in the direction of the attack, which itself depends on the electron-donating character of the substituent, the more regioselective the reaction toward this carbon. Thus, the computed LUMO coefficients in **31′** for C1 and C3 are 0.432 and 0.987, respectively. Similar observations have been reported by Grady, Vicente, and co-workers in the synthesis of N-heterocycles, which suggested that the reaction takes place with the carbon bonded to the most electron-releasing substituents of the allyl group.[50]

These electronic effects due to the *trans* effect of the phosphine ligand, conformation and allylic substitution on the (η^3-allyl) palladium complex strongly point out a preferred nucleophilic attack on the substituted allylic carbon C3, in agreement with the experimental results. Hence, this mechanism (Figure 5) is energetically more favorable than path A and can account for the chemo- and regioselectivity.

The synthesis of medium-sized oxacycles,[3a,51] in particular eight and nine-membered rings,[52] has been and continues to be a challenging and fascinating endeavor in synthetic organic chemistry; this is due to unfavorable entropy and enthalpy factors that prevent the adaptation of traditional methods of ring formations, and accordingly there are few examples of synthesis of oxocines from allene derivatives. Mukai et al. reported a reliable and efficient procedure for constructing nine-membered oxacycles through an *endo*-mode ring-closing reaction of allenyl derivatives in a base-catalyzed process.[53] Gagné et al. developed a method to generate polyether skeletons

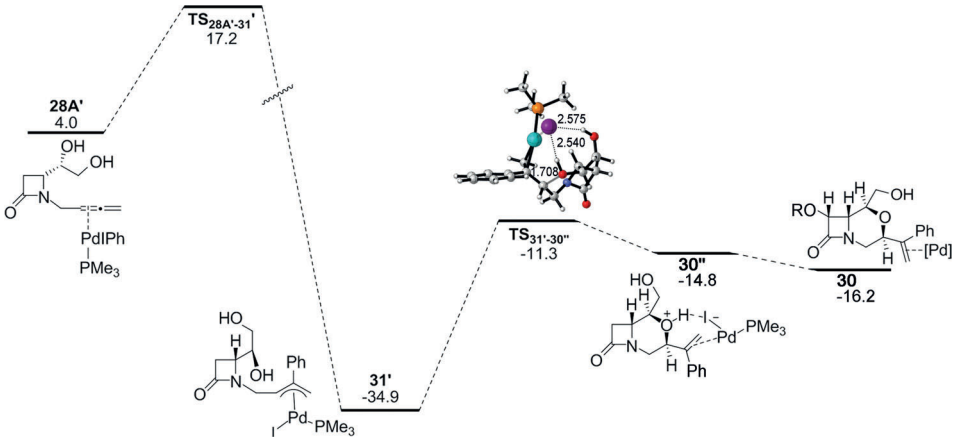
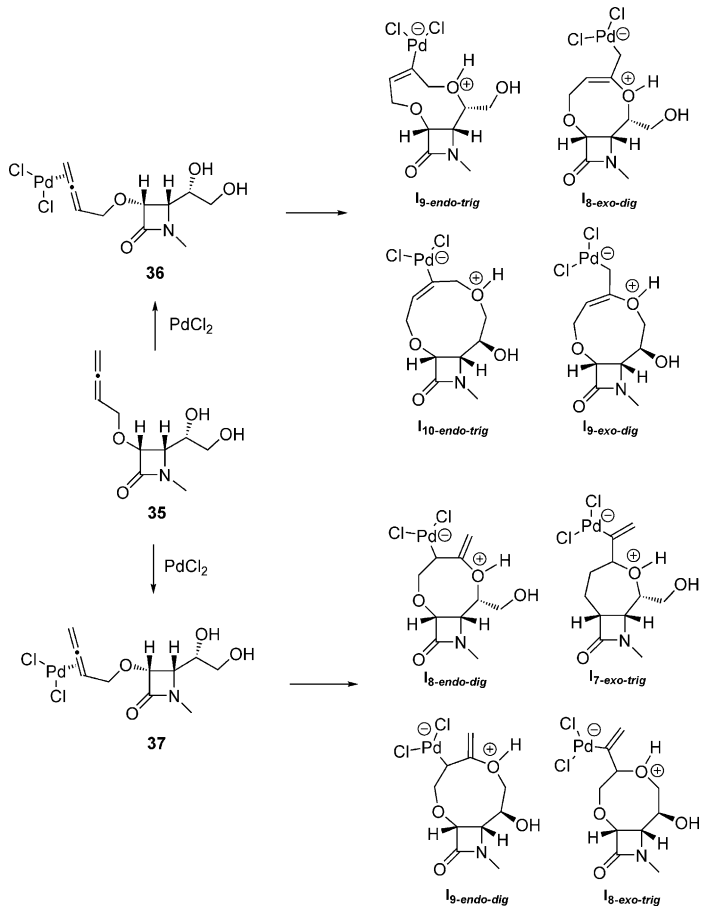


Figure 5. Free-energy profile (in kcal mol^{-1}) for the palladium-catalyzed oxycyclization of δ,ε-allendiols in presence of iodobenzene.

from allene-epoxide cascade reactions promoted by Au^{I}.[54] Majumdar et al. have synthesized several types of heterocycles by the utilization of various palladium complexes[55] in phosphine-free intramolecular Heck reactions.[56] In this context, the chemo- and regioselective 9-*endo* oxycyclization of the secondary hydroxy group to the terminal allene carbon merits a mechanistic rationalization.

As a model substrate for DFT calculations, we have selected compound **35** (Scheme 13). We have located two expected types of reactant complexes: 1) By π-coordination of the distal and 2) by π-coordination of the proximal alkene bonds of the allene to the catalyst, to form the η^2-allene structures **36** (Pd–C1 = 2.111 and Pd–C2 = 2.104 Å) and **37** (Pd–C2 = 2.090, and Pd–C3 = 2.121 Å), respectively. Unsurprisingly, the coordination



Scheme 13. Plausible [$PdCl_2$]-catalyzed heterocyclization routes.

of the allenic distal C=C bond to the catalyst gives rise to a more stable Pd-η^2-allene reactant complex (by 2.3 kcal mol^{-1}) due to lower steric hindrance effects. Scheme 13 shows the plausible intermediate structures that can be formed by intramolecular heterocyclization through attack of both ε- and ζ-OH groups from each complex. Thus, the possible processes imply 9-*endo-trig*, 8-*exo-dig*, 10-*endo-trig*, 9-*exo-dig* (from **36**), 8-*endo-dig*, 7-*exo-trig*, 9-*endo-dig*, and 8-*exo-trig* (from **37**) intramolecular oxycyclizations. Moreover, we have also take into account the formation of both the isomers *cis* and *trans* of the endocyclic C=C double bond (see Table S3, the Supporting Information).

The computed results (Figure 6) indicate that the lowest-energy transition structure is $\mathbf{TS}_{9-endo-trig}$ (14.5 kcal mol^{-1} above **36**), which involves the nucleophilic addition of the secondary hydroxylic oxygen to the activated terminal allene carbon. A strong H-bond is observed between the endocyclic oxygen and the attacking OH, which likely enhances the nucleophilicity of the alcohol and stabilizes the transition structure. It has been reported that metal-catalyzed cyclizations of allenols[57] and closely related palladium-catalyzed cyclizative coupling reactions[11,58] favor an *endo-trig* cyclization mode. Noteworthy, the analogous transition structure by attack of the primary OH ($\mathbf{TS}_{10endo-trig}$), which would also eventually afford products of type oxecine, is 5.9 kcal mol^{-1} higher in energy. It makes that pathway very unlikely because of enthalpic penalty of the longer chain and probably because it lacks the stabilizing intramolecular H-bond and requires a higher structural distortion of the allenic group (dihedral angle of 20.9 vs. 9.4° for $\mathbf{TS}_{9-endo-trig}$).

The alternative transition structures for the intramolecular nucleophilic attack of the alcohol to the activated allene, which involve the ε- or ζ-allenol moiety and/or other allenic positions, show higher activation energy values than $\mathbf{TS}_{9-endo-trig}$ ($\Delta\Delta G^{\#}$ = 2.0–21.4 kcal mol^{-1}). These energy differences are high enough to support the kinetic preference for the chemo- and regioselective formation of the dioxonine framework, in full agreement with the experimental observations.

The formation of the *exo*-cyclized products is slightly exergonic, likely due to the higher flexibility to form the stabilizing H-bond between the attacking alcohol and the chloride ligand for the subsequent HCl displacement step. On the contrary, the formation of the *endo*-intermediates is slightly endergonic, such as for $\mathbf{I}_{8-endo-dig}$, in which there is no possibility to form this H-bond interaction.

The experimental results have shown a different selectivity as function of the chain length (**2** vs. **4**). Thus, upon exposure to a catalytic amount of [$PdCl_2$] in the presence of allyl bromide, these precursors yield oxocines **10** (Scheme 4) and oxonines **16** (Scheme 8), respectively, therefore showing the same regioselectivity but a divergent chemoselectivity. To get insights into this issue, we have performed further calculations with **37** as a model substrate (Scheme 14).

Amazingly, the computed results (Table 1) indicate that the lowest-energy transition structure is $\mathbf{TS}_{8-endo-trig}$ (13.2 kcal mol^{-1} above the reactant complex **38**), which involves the nucleophilic addition of the primary hydroxylic oxygen to the activated terminal allene carbon. These results confirm the same regioselective *endo-trig* cyclization mode for these precursors. However, regarding the chemoselectivity, the substitution and configuration at the β-lactam carbons, as well as the shorter tether, involves a higher tension for the nucleophilic addition of the secondary hydroxylic functionality on the ter-

Table 1. Free-energy differences (in solution) of the computed structures.

Structure	Alcohol	ΔG [kcal mol^{-1}]
38		0.0
39		11.4
$\mathbf{TS}_{8-endo-trig}$	δ	13.2
$\mathbf{TS}_{7-exo-dig}$	δ	21.8
$\mathbf{TS}_{7-endo-trig}$	γ	22.3
$\mathbf{TS}_{6-exo-dig}$	γ	28.9
$\mathbf{TS}_{7-endo-dig}$	δ	38.2
$\mathbf{TS}_{6-exo-trig}$	δ	22.7
$\mathbf{TS}_{5-exo-trig}$	γ	39.4
$\mathbf{TS}_{6-endo-dig}$	γ	42.9

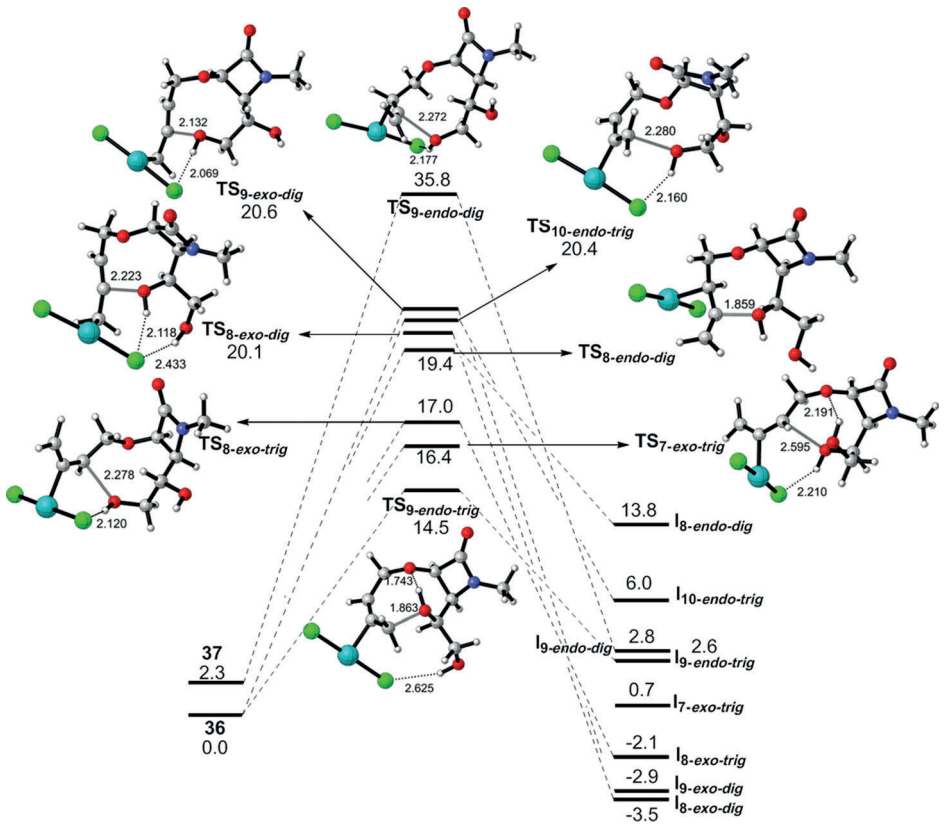
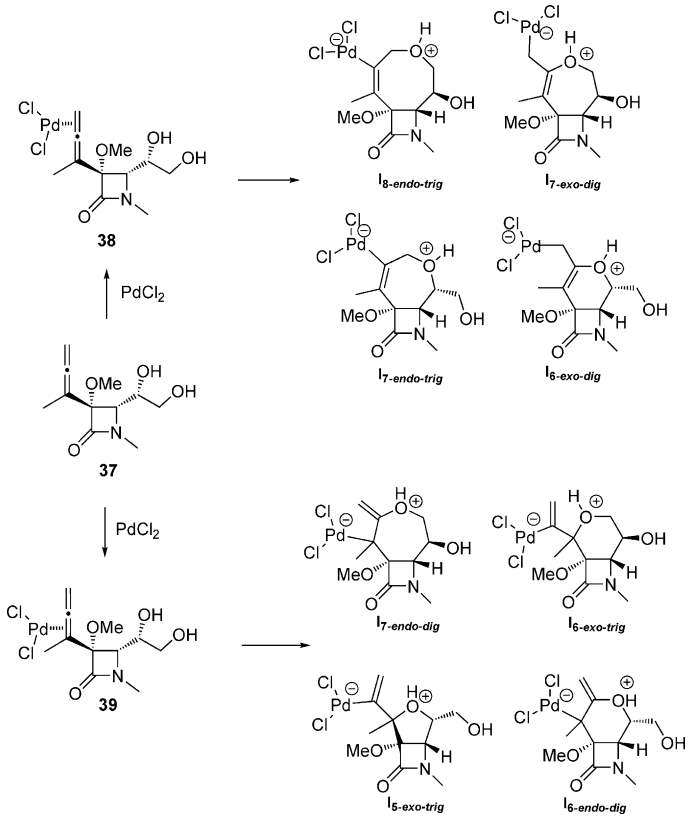


Figure 6. Computed free-energy profile (in kcal mol^{-1}) for the possible Pd-catalyzed heterocyclizations of **35**.



Scheme 14. Plausible [$PdCl_2$]-catalyzed heterocyclization routes.

minal allene carbon, as the computed barrier suggests (**TS**$_{7-endo-trig}$ 22.3 kcal mol^{-1}). Likewise, **TS**$_{7-exo-dig}$, which implies the same chemoselectivity and different regioselectivity as **TS**$_{8-endo-trig}$, also involves a markedly higher energy barrier (21.8 kcal mol^{-1}).

Other alternative transition structures leading to smaller heterocycles also show even higher activation barriers than **TS**$_{8-endo-trig}$ ($\Delta\Delta G^{\#} = 9.5$–$29.7$ kcal mol^{-1}) due to the more severe steric tension to reach the pertinent transition states. These energy differences clearly support the kinetic preference for the chemo- and regioselective formation of the oxocine skeleton, in harmony with the experimental observations.

Conclusion

The chemo-, regio-, and diastereocontrolled cicloetherification of 2-azetidinone-tethered γ,δ-, δ,ε- and ε,ζ-allenic diols into morpholines, oxocines, and dioxonines has been realized by using various palladium-catalyzed cyclizative coupling reactions. Chemo- and regiocontrol issues are mainly influenced by the length of the tether rather than by the nature of the metal catalysts and substituents. Besides, to understand this difference in reactivity, a DFT study has been performed. We hope that these selective cyclization reactions can be used in the selective preparation of other types of heterocyclic compounds.

Computational Details

All the calculations reported in this paper were performed with the Gaussian 09 suite of programs.[59] All species were optimized with Truhlar's dispersion-corrected meta hybrid exchange-correlation functional M06, which has been recommend for species involving transition metals,[60] in combination with 6-311g(2d,p) basis sets for all atoms except Pd and I, which were treated with the LANL2DZ electron core potential,[61] and associated basis set with the correction factors proposed by Frenking.[62] The stationary points thus obtained were characterized by means of harmonic analysis. It was verified that for all the transition structures, the normal mode related to the imaginary frequency corresponds to the nuclear motion along the reaction coordinates under study. In several significant cases, intrinsic reaction coordinate (IRC) calculations were performed to unambiguously connect transition structures with reactants and products. Solvents effects were taken into account by use of the Polarizable Continuum Model (PCM).[63] Single-point calculations on the gas-phase optimized geometries were performed

to estimate the changes in the Gibbs energies in the presence of DMF as solvent. The natural bond orbital analysis (NBO)[64] were carried on the optimized structures.

Experimental Section

General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, $\delta=0.0$ ppm), or $CDCl_3$ (^{13}C, $\delta=76.9$ ppm). Low- and high-resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Specific rotation $[\alpha]_D$ is given in $10^{-1}\,^\circ\,cm^2\,g^{-1}$ at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

General procedure for the Pd^{II}-catalyzed cyclization of allenic diols in presence of allyl bromide: **Preparation of oxocines 10, morpholines 14, and dioxonines 16**: Palladium(II) chloride (0.005 mmol) was added to a stirred solution of the corresponding allenic diol **2–4** (0.10 mmol) and allyl bromide (0.50 mmol) in *N*,*N*-dimethylformamide (0.6 mL). The reaction was stirred under 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 adducts 10, 14, or 16.[65]

Oxocine (+)-10a: From γ,δ-allendiol (+)-**2a** (45 mg, 0.14 mmol), and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound (+)-**10a** (37 mg, 73%) as a colorless oil; $[\alpha]_D=+21.9$ ($c=0.4$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta=7.66$ and 6.86 (d, each 2H, $J=9.2$ Hz), 5.10 (dd, 1H, $J=6.3$, 1.8 Hz), 5.03 (t, 2H, $J=1.5$ Hz), 4.35 and 3.88 (d, each 1H, $J=10.5$ Hz), 4.30 (m, 4H), 3.78 (s, 3H), 3.53 (s, 3H), 2.80 (d, 2H, $J=4.9$ Hz), 2.40 (br s, 1H), 1.97 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta=165.4$, 156.5, 137.4, 134.1, 131.1, 129.2, 120.4, 116.1, 114.0, 90.0, 80.4, 76.6, 72.8, 69.5, 55.5, 53.5, 37.6, 17.8 ppm; IR ($CHCl_3$,): $\tilde{\nu}=3430$, 1745 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{20}H_{25}NO_5$: 359.1733 $[M]^+$; found: 359.1740.

Oxocine (+)-10b: From γ,δ-allendiol (+)-**2a** (40 mg, 0.125 mmol), and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound (+)-**10b** (33 mg, 60%) as a colorless oil. $[\alpha]_D=+18.8$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.67$ and 6.88 (d, each 2H, $J=9.3$ Hz), 5.68 and 5.51 (m, each 1H), 5.24 (d, 1H, $J=6.1$ Hz,), 4.38 (m, 4H), 4.32 and 3.97 (d, each 1H, $J=10.5$ Hz), 3.94 (s, 3H), 3.58 (s, 3H), 3.20 (d, 2H, $J=24.0$ Hz,), 2.01 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=164.9$, 156.6, 139.3, 135.2, 130.9, 130.3, 120.4, 118.1, 114.1, 90.0, 80.9, 75.8, 73.3, 69.5, 55.5, 53.8, 45.3, 18.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=3435$, 1746 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{20}H_{24}BrNO_5[M]^+$: 437.0838; found: 437.0843.

Oxocine (+)-10c: From γ,δ-allendiol (−)-**2b** (43 mg, 0.14 mmol), and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound (+)-**10c** (27 mg, 56%) as a colorless oil; $[\alpha]_D=+89.0$ ($c=2.2$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.33$ (m, 5H), 5.70 (m, 1H), 5.05 (m, 1H), 4.98 (m, 1H), 4.57 and 4.47 (d, each 1H, $J=15.0$ Hz), 4.17 (m, 4H), 3.74 (d, 1H, $J=8.5$ Hz), 3.64 (d, 1H, $J=9.0$ Hz), 3.51 (s, 3H), 2.75 (d, 2H, $J=6.1$ Hz), 1.99 (s, 3H), 1.65 ppm (d, 1H, $J=6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=168.0$, 137.1, 136.5, 134.1, 129.4, 128.8, 128.2, 127.7, 116.0, 90.8, 79.8, 76.8, 71.9, 68.6, 53.8, 45.2, 37.4, 17.8 ppm; IR ($CHCl_3$,): $\tilde{\nu}=3435$, 1746 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{20}H_{25}NNaO_4$: 366.1681 $[M+Na]^+$; found: 366.1687.

Oxocine (+)-10d: From γ,δ-allendiol (−)-**2c** (56 mg, 0.18 mmol), and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound (+)-**10d** (40 mg, 62%) as a colorless oil. $[\alpha]_D=+7.5$ ($c=0.3$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.23$ (m, 5H), 5.64 (m, 1H), 4.98 (m, 1H), 4.93 (dd, 1H, $J=3.1$, 1.7 Hz), 4.53 and 4.38 (d, each 1H, $J=14.8$ Hz), 4.06 (m, 4H), 3.71 (dd, 1H, $J=12.7$, 2.2 Hz), 3.66 (d, 1H, $J=8.5$ Hz), 3.41 (s, 3H), 2.70 (m, 2H), 2.41 and 2.15 (m, each 1H), 0.91 ppm (t, 3H, $J=7.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=167.5$, 136.8, 136.2, 136.0, 134.9, 128.7, 128.5, 127.7, 116.3, 90.7, 80.5, 76.2, 72.9, 69.5, 53.6, 45.1, 37.3, 24.3, 13.9 ppm; IR ($CHCl_3$): $\tilde{\nu}=3429$, 1747 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{21}H_{27}NNaO_4$: 380.1838 $[M+Na]^+$; found: 380.1831.

Oxocine (−)-10e: From γ,δ-allendiol (−)-**2d** (38 mg, 0.089 mmol) and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound (−)-**10e** (25 mg, 60%) as a colorless oil. $[\alpha]_D=-1.5$ ($c=2.5$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.59$ and 6.83 (d, each 2H, $J=9.0$ Hz), 7.10 (m, 5H), 5.74 (m, 1H), 5.06 (m, 2H), 4.44 and 4.40 (d, each 1H, $J=5.3$ Hz), 4.33 (m, 7H), 3.97 (dd, 1H, $J=12.4$, 1.9 Hz), 3.80 (s, 3H), 3.55 (s, 3H), 2.89 ppm (dd, 2H, $J=5.1$, 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=165.4$, 156.2, 142.3, 137.7, 134.5, 131.4, 130.9, 128.0, 127.7, 127.2, 120.4, 116.8, 113.9, 88.3, 81.1, 76.1, 73.3, 72.8, 70.3, 67.6, 55.4, 53.4, 37.4 ppm; IR ($CHCl_3$,): $\tilde{\nu}=3432$, 1746 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{27}H_{31}NNaO_6$: 488.2049 $[M+Na]^+$; found: 488.2041.

Oxocine (+)-10f: From γ,δ-allendiol (+)-**2e** (47 mg, 0.125 mmol) and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound (+)-**10f** (31 mg, 58%) as a colorless oil. $[\alpha]_D=+14.3$ ($c=0.4$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.59$ and 6.82 (d, each 2H, $J=9.2$ Hz), 7.31 (m, 5H), 5.68 (m, 1H), 5.08 (dd, 1H, $J=3.4$, 1.7 Hz,), 5.00 (dd, 1H, $J=9.5$, 1.7 Hz,), 4.68 (d, 1H, $J=7.8$ Hz,), 4.52 and 4.15 (d, each 1H, $J=12.7$ Hz), 4.39 (d, 2H, $J=2.2$ Hz), 4.31 (m, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 2.66 (m, 2H), 2.16 ppm (d, 1H, $J=6.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=167.3$, 156.4, 140.5, 138.5, 135.1, 131.1, 128.4, 127.5, 120.4, 116.7, 114.0, 81.8, 75.1, 74.1, 71.1, 55.4, 54.0, 39.3 ppm; IR ($CHCl_3$,): $\tilde{\nu}=3432$, 1744 cm^{-1}; MS (ES): *m/z*: 421 ($[M^+]$, 17), 420 ($[M^+-1]$, 100).

Oxocine (+)-10g: From γ,δ-allendiol (−)-**2f** (42 mg, 0.13 mmol) and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound (+)-**10g** (30 mg, 57%) as a colorless oil. $[\alpha]_D=+50.0$ ($c=2.5$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.25$ (m, 10H), 5.61 (m, 1H), 5.02 (dd, 1H, $J=6.0$, 1.7 Hz,), 4.95 (dd, 1H, $J=12.7$, 1.7 Hz,), 4.61 and 4.18 (d, each 1H, $J=14.8$ Hz), 4.30 (s, 2H), 4.13 (m, 4H), 3.69 (s, 3H), 2.58 (m, 2H), 2.82 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=166.3$, 139.9, 138.4, 137.0, 136.0, 135.9, 135.1, 128.7, 128.6, 128.2, 127.7, 127.5, 116.7, 90.8, 81.5, 75.0, 73.9, 69.2, 54.1, 44.9, 39.2 ppm; IR ($CHCl_3$,): $\tilde{\nu}=3434$, 1745 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{25}H_{28}NO_4$: 406.2018 $[M+H]^+$; found: 406.2014.

Morpholine (+)-14a: From δ,ε-allendiol (+)-**3a** (51 mg, 0.24 mmol), and after chromatography of the residue using hexanes/ethyl acetate (1:3) as eluent gave compound (+)-**14a** (30 mg, 50%) as a colorless oil. $[\alpha]_D=+4.9$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta=5.78$ (m, 1H), 5.13 (m, 2H), 5.08 (m, 1H), 5.01 (m, 1H), 4.54 (dd, 1H, $J=4.5$, 1.2 Hz), 3.92 (dd, 1H, $J=11.1$, 3.1 Hz), 3.80 (m, 2H), 3.66 (m, 2H), 3.58 (s, 3H), 3.56 (dd, 1H, $J=9.5$, 4.5 Hz), 2.84 (m, 2H), 2.72 ppm (ddd, 1H, $J=13.7$, 10.7,

1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 168.3, 144.5, 135.3, 117.2, 112.9, 83.8, 77.7, 77.4, 63.1, 59.3, 50.5, 42.0, 37.2 ppm; IR ($CHCl_3$,): $\tilde{\nu}$ = 3435, 1744 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{13}H_{20}NO_4$: 254.1392 $[M+H]^+$; found: 254.1401.

Morpholine (+)-14b: From δ,ε-allendiol (+)-**3b** (72 mg, 0.25 mmol) and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound (+)-**14b** (51 mg, 62%) as a colorless oil. $[\alpha]_D$ = +5.0 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.34 (m, 5H), 5.80 (m, 1H), 5.13 (m, 1H), 5.08 (m, 1H), 5.00 (m, 1H), 4.94 and 4.68 (d, each 1H, *J* = 11.8 Hz), 4.73 (dd, 1H, *J* = 4.4, 0.9 Hz), 3.94 (dd, 1H, *J* = 10.5, 3.1 Hz), 3.82 (m, 2H), 3.66 (m, 2H), 3.56 (dd, 1H, *J* = 9.5, 4.7 Hz), 2.83 (m, 2H), 2.73 ppm (ddd, 1H, *J* = 13.1, 10.7, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 168.7, 144.8, 136.9, 135.5, 128.5, 128.4, 128.2, 117.4, 113.2, 81.6, 77.6, 77.5, 73.4, 63.3, 50.8, 42.3, 37.4 ppm; IR ($CHCl_3$,): $\tilde{\nu}$ = 3438, 1746 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{19}H_{24}NO_4$: 330.1705 $[M+H]^+$; found: 330.1711.

Dioxonine (+)-16a: From ε,ζ-allendiol (+)-**4a** (51 mg, 0.17 mmol), and after chromatography of the residue using hexanes/ethyl acetate (1:2) as eluent gave compound (+)-**16a** (36 mg, 61%) as a colorless oil; $[\alpha]_D$ = +2.3 (*c* = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.40 and 6.87 (d, each 2H, *J* = 9.1 Hz), 5.80 (m, 2H), 5.13 (m, 2H), 4.77 (d, 1H, *J* = 5.3 Hz), 4.45 (m, 3H), 4.17 (m, 1H), 4.00 (m, 2H), 3.79 (s, 3H), 3.69 (m, 2H), 3.04 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 164.9, 156.8, 138.8, 134.0, 130.0, 126.0, 120.0, 117.1, 114.3, 80.6, 77.2, 67.8, 67.6, 63.5, 58.0, 55.5, 32.6 ppm; IR ($CHCl_3$,): $\tilde{\nu}$ = 3440, 1742 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{19}H_{24}NO_5$: 346.1654 $[M+H]^+$; found: 346.1638.

Dioxonine (+)-16b: From ε,ζ-allendiol (−)-**4b** (70 mg, 0.24 mmol), and after chromatography of the residue using hexanes/ethyl acetate (1:2) as eluent gave compound (+)-**16b** (46 mg, 58%) as a colorless oil. $[\alpha]_D$ = +0.9 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.20 (m, 5H), 5.67 (m, 2H), 5.03 (m, 2H), 4.70 and 4.20 (d, each 1H, *J* = 15.0 Hz), 4.53 (d, 1H, *J* = 5.1 Hz), 4.40 (dd, 1H, *J* = 12.4, 6.0 Hz), 4.24 (dd, 1H, *J* = 12.6, 7.0 Hz), 3.98 (s, 1H), 3.88 (m, 1H), 3.55 (m, 2H), 2.91 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.6, 138.5, 135.6, 134.1, 128.9, 128.3, 127.9, 126.3, 117.0, 81.4, 71.1, 67.4, 67.0, 63.9, 58.1, 45.6, 32.7 ppm; IR ($CHCl_3$, cm^{-1}): $\tilde{\nu}$ = 3442, 1743; HRMS (ES): *m/z* calcd for $C_{19}H_{24}NO_4$: 330.1705 $[M+H]^+$; found: 330.1706.

General procedure for the Pd^{II}-catalyzed cyclization of γ,δ-allenic diols 2 in presence of lithium bromide: Preparation of bromooxocines 12: 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 γ,δ-allendiol 2 (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 adducts **12**.

Oxocine (+)-12a: From γ,δ-allendiol (+)-**2a** (53 mg, 0.17 mmol) and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound (+)-**12a** (34 mg, 50%) as a pale-yellow oil. $[\alpha]_D$ = +25.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.63 and 6.88 (d, each 2H, *J* = 9.2 Hz), 4.63 (d, 2H, *J* = 1.7 Hz), 4.39 (m, 3H), 3.86 (dd, 1H, *J* = 11.0, 2.2 Hz), 3.57 (s, 3H), 2.20 ppm (t, 3H, *J* = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 164.1, 156.7, 133.4, 130.6, 127.0, 120.5, 114.1, 90.0, 88.7, 80.7, 80.2, 72.1, 68.9, 55.5, 54.1, 23.2 ppm; IR ($CHCl_3$,): $\tilde{\nu}$ = 3426, 1742 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{17}H_{20}BrNO_5$: 397.0525 $[M]^+$; found: 397.0519.

Oxocine (+)-12b: From γ,δ-allendiol (−)-**2b** (51 mg, 0.16 mmol), and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound (+)-**12b** (32 mg, 52%) as a pale-yellow oil; $[\alpha]_D$ = +6.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.33 (m, 5H), 4.62 and 4.45 (d, each 1H, *J* = 16.1 Hz), 4.52 (s, 2H), 4.17 (m, 2H), 3.74 (d, 1H, *J* = 8.8 Hz), 3.59 (d, 1H, *J* = 8.1 Hz), 3.55 (s, 3H), 2.20 (t, 3H, *J* = 1.6 Hz), 1.52 ppm (d, 1H, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.9, 136.3, 133.5, 129.0, 128.1, 127.9, 126.9, 80.8, 79.7, 71.0, 68.2, 54.3, 45.3, 23.1 ppm; IR ($CHCl_3$,): $\tilde{\nu}$ = 3427, 1743 cm^{-1}; MS (ES): *m/z*: 382 ($[M^+ + 1]$, 98), 380 ($[M^+ - 1]$, 100).

Oxocine (+)-12c: From γ,δ-allendiol (−)-**2c** (67 mg, 0.21 mmol), and after chromatography of the residue using hexanes/ethyl acetate (2:1) as eluent gave compound (+)-**12c** (37 mg, 44%) as a pale-yellow oil. $[\alpha]_D$ = +7.0 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.34 (m, 5H, Ar), 4.60 and 4.47 (d, each 1H, *J* = 14.7 Hz), 4.57 and 4.48 (d, each 1H, *J* = 15.8 Hz), 4.14 (m, 2H), 3.70 (d, 1H, *J* = 8.6 Hz), 3.68 (dd, 1H, *J* = 12.2, 3.4 Hz), 3.53 (s, 3H, OMe), 2.70 (m, 1H), 2.47 (m, 1H),1.00 ppm (t, 3H, *J* = 7.53 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 166.5, 139.5, 135.9, 128.8, 128.5, 127.9, 126.5, 89.3, 80.8, 80.0, 71.6, 68.8, 54.1, 45.3, 29.4, 11.8 ppm; IR ($CHCl_3$,): $\tilde{\nu}$ = 3431, 1745 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{18}H_{22}BrNO_4$: 395.0732 $[M]^+$; found: 395.0739.

Procedure for the Pd^0-catalyzed cyclization of δ,ε-allenic diols 3 in the presence of iodobenzene: Preparation of morpholines 15: $[Pd(PPh_3)_4]$ (11 mg, 0.0093 mmol) was added to a mixture of the corresponding δ,ε-allendiol **3** (0.18 mmol), iodobenzene (22 μL, 0.19 mmol), and silver carbonate (99 mg, 0.36 mmol) in DMF (1.5 mL) under argon, and the resulting mixture was heated at 80 °C until disappearance of the starting material (TLC, 15 h). The reaction was then quenched with brine (1.8 mL) and the mixture was extracted with ethyl acetate (3×3 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure adducts **15**.

Morpholine (+)-15a: From δ,ε-allendiol (+)-**3a** (11 mg, 0.52 mmol), and after chromatography of the residue using hexanes/ethyl acetate (1:2) as eluent gave compound (+)-**15a** (78 mg, 61%) as a colorless oil. $[\alpha]_D$ = +5.0 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.34 (m, 5H), 5.42 (m, 2H), 4.55 (dd, 1H, *J* = 4.7, 1.3 Hz), 4.44 (dd, 1H, *J* = 10.7, 3.1 Hz), 3.94 (m, 2H), 3.77 (m, 3H), 3.60 (s, 3H), 3.59 (m, 1H), 2.67 ppm (ddd, 1H, *J* = 13.4, 10.7, 1.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 168.2, 146.0, 138.4, 128.6, 128.1, 126.6, 114.3, 83.7, 77.7, 76.5, 63.1, 59.3, 50.5, 42.6 ppm; IR ($CHCl_3$,): $\tilde{\nu}$ = 3442, 1747 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{16}H_{20}NO_4$: 290.1392 $[M+H]^+$; found: 290.1397.

Morpholine (+)-15b: From δ,ε-allendiol (+)-**3b** (36 mg, 0.12 mmol) and after chromatography of the residue using hexanes/ethyl acetate (1:1) as eluent gave compound (+)-**15b** (24 mg, 55%) as a colorless oil. $[\alpha]_D$ = +3.3 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.35 (m, 10H), 5.42 (m, 2H), 4.95 and 4.70 (d, each 1H, *J* = 11.7 Hz), 4.74 (dd, 1H, *J* = 4.7, 1.2 Hz), 4.46 (dd, 1H, *J* = 10.7, 3.2 Hz), 4.01 (m, 1H), 3.83 (dd, 1H, *J* = 5.4, 3.4 Hz), 3.79 (m, 1H), 3.71 (dd, 1H, *J* = 11.8, 5.7 Hz), 3.59 (dd, 1H, *J* = 9.6, 4.7 Hz), 2.69 ppm (ddd, 1H, *J* = 13.4, 10.7, 1.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 168.3, 146.0, 138.4, 136.6, 128.6, 128.5, 128.2, 128.1, 128.0, 126.6, 114.3, 81.3, 77.8, 77.2, 73.1, 63.1, 50.5, 42.7 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3444, 1746 cm^{-1}; HRMS (ES): *m/z* calcd for $C_{22}H_{24}NO_4$: 366.1705 $[M+H]^+$; found: 366.1703.

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[1] The β-lactam nucleus is the key structural motif in biologically relevant compounds such as antibiotics, enzyme inhibitors, neurotherapeutics, antitumorals, and gene activators. For selected references, see: a) *Chemistry and Biology of β-Lactam Antibiotics, Vols. 1–3* (Eds.: R. B. Morin, M. Gorman), Academic press, New York, **1982**; b) R. Southgate, C. Branch, S. Coulton, E. Hunt in *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products* (Ed.: G. Lukacs), Springer, Berlin, **1993**, p. 621; c) G. Veinberg, M. Vorona, I. Shestakova, I. Kanepe, E. Lukevics, *Curr. Med. Chem.* **2003**, *10*, 1741; d) J. D. Rothstein, S. Patel, M. R. Regan, C. Haenggeli, Y. H. Huang, D. E. Bergles, L. Jin, M. D. Hoberg, S. Vidensky, D. S. Chung, S. V. Toan, L. I. Bruijn, Z.-z. Su, P. Gupta, P. B. Fisher, *Nature* **2005**, *433*, 73; e) T. M. Miller, D. W. Cleveland, *Science* **2005**, *307*, 361; f) M. Feledziak, C. Michaux, A. Urbach, G. Labar, G. G. Muccioli, D. M. Lambert, J. Marchand-Brynaert, *J. Med. Chem.* **2009**, *52*, 7054; g) B. Alcaide, P. Almendros, C. Aragoncillo, *Curr. Opin. Drug. Disc.* **2010**, *13*, 685; h) B. K. Banik, E. Banik, F. F. Becker in *Topics in Heterocyclic Chemistry, Vol. 22* (Ed.: B. K. Banik), Springer, Berlin, Heidelberg, **2010**, p. 349; i) S. A. Testero, J. F. Fisher, S. Mobashery, *β-Lactam Antibiotics in Burger's Medicinal Chemistry, Drug Discovery and Development, Vol. 7* (Eds.: D. J. Abraham, D. P. Rotella), Wiley, Hoboken, **2010**, pp 259–404.

[2] For selected reviews, see: a) A. Kamath, I. Ojima, *Tetrahedron* **2012**, *68*, 10640; b) B. Alcaide, P. Almendros, *Chem. Rec.* **2011**, *11*, 311; c) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437; d) B. Alcaide, P. Almendros, *Curr. Med. Chem.* **2004**, *11*, 1921; e) A. R. A. S. Deshmukh, B. M. Bhawal, D. Krishnaswamy, V. V. Govande, B. A. Shinkre, A. Jayanthi, *Curr. Med. Chem.* **2004**, *11*, 1889; f) B. Alcaide, P. Almendros, *Synlett* **2002**, 381; g) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Synlett* **2001**, 1813; h) B. Alcaide, P. Almendros, *Chem. Soc. Rev.* **2001**, *30*, 226; i) I. Ojima, F. Delaloge, *Chem. Soc. Rev.* **1997**, *26*, 377; j) M. S. Manhas, D. R. Wagle, J. Chiang, A. K. Bose, *Heterocycles* **1988**, *27*, 1755.

[3] For selected reviews, see: a) A. S. Kleinke, D. Webb, T. F. Jamison, *Tetrahedron* **2012**, *68*, 6999; b) I. Larrosa, P. Romea, F. Urpí, *Tetrahedron* **2008**, *64*, 2683; c) J. B. Bremner, S. Samosorn in *Progress in Heterocyclic Chemistry, Vol. 18* (Eds.: G. W. Gribble, J. A. Joule), Elsevier, Oxford, **2007**, pp. 402–429; d) G. R. Newkome in *Progress in Heterocyclic Chemistry, Vol. 18* (Eds.: G. W. Gribble, J. A. Joule), Elsevier, Oxford, **2007**, pp. 430–448; e) J. P. Wolfe, M. B. Hay, *Tetrahedron* **2007**, *63*, 261; f) N. L. Snyder, H. M. Haines, M. W. Peczuh, *Tetrahedron* **2006**, *62*, 9301; g) P. A. Clarke, S. Santos, *Eur. J. Org. Chem.* **2006**, 2045; h) J. W. Blunt, B. R. Copp, W.-P. Hu, M. H. G. Munro, P. T. Northcote, M. R. Prinsep, *Nat. Prod. Rep.* **2007**, *24*, 31; i) M. saleem, H. J. Kim, M. S. Ali, Y. S. Lee, *Nat. Prod. Rep.* **2005**, *22*, 696; j) M. M. Faul, B. E. Huff, *Chem. Rev.* **2000**, *100*, 2407; k) D. J. Faulkner, *Nat. Prod. Rep.* **1996**, *13*, 75.

[4] For reviews on allene chemistry, see: a) Special issue on *Progress in Allene Chemistry* (Eds.: B. Alcaide, P. Almendros): *Chem. Soc. Rev.* **2014**, *43*, Issue 9; b) T. Lechel, F. Pfrengle, H.-U. Reissig, R. Zimmer, *ChemCatChem* **2013**, *5*, 2100; c) S. Yu, S. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 3074; *Angew. Chem.* **2012**, *124*, 3128; d) P. Rivera-Fuentes, F. Diederich, *Angew. Chem. Int. Ed.* **2012**, *51*, 2818; *Angew. Chem.* **2012**, *124*, 2872; e) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994; f) B. Alcaide, P. Almendros, *Adv. Synth. Catal.* **2011**, *353*, 2561; g) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Soc. Rev.* **2010**, *39*, 783; h) M. Brasholz, H.-U. Reissig, R. Zimmer, *Acc. Chem. Res.* **2009**, *42*, 45; i) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382; j) N. Bongers, N. Krause, *Angew. Chem. Int. Ed.* **2008**, *47*, 2178; *Angew. Chem.* **2008**, *120*, 2208; k) R. A. Widenhoefer, X. Han, *Eur. J. Org. Chem.* **2006**, 4555; l) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; m) A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387; n) *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**; o) B. Alcaide, P. Almendros, *Eur. J. Org. Chem.* **2004**, 3377; p) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701; q) R. W. Bates, V. Satcharoen, *Chem. Soc. Rev.* **2002**, *31*, 12; r) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3590; *Angew. Chem.* **2000**, *112*, 3737; s) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067.

[5] a) B. Alcaide, P. Almendros, J. M. Alonso, I. Fernández, G. Gómez-Campillos, M. R. Torres, *Chem. Commun.* **2014**, *50*, 4567; b) B. Alcaide, P. Almendros, M. T. Quirós, *Chem. Eur. J.* **2014**, *20*, 3384; c) B. Alcaide, P. Almendros, J. M. Alonso, I. Fernández, S. Khodabakhshi, *Adv. Synth. Catal.* **2014**, *356*, 1370; d) B. Alcaide, P. Almendros, M. T. Quirós, R. López, M. I. Menéndez, A. Sochacka-Ćwikła, *J. Am. Chem. Soc.* **2013**, *135*, 898; e) B. Alcaide, P. Almendros, T. Martínez del Campo, M. T. Quirós, E. Soriano, J. L. Marco-Contelles, *Chem. Eur. J.* **2013**, *19*, 14233.

[6] B. Alcaide, P. Almendros, R. Carrascosa, M. C. Redondo, *Chem. Eur. J.* **2008**, *14*, 637.

[7] Terminal alkynyldioxolanes **5** and **6** were prepared from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde as we previously described: a) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Commun.* **1999**, 1913; b) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, C. Pardo, E. Sáez, M. R. Torres, *J. Org. Chem.* **2002**, *67*, 7004.

[8] a) P. Crabbé, H. Fillion, D. André, J. L. Luche, *J. Chem. Soc. Chem. Commun.* **1979**, 860; b) J. Kuang, S. Ma, *J. Org. Chem.* **2009**, *74*, 1763.

[9] To the best of our knowledge, the Pd-catalyzed cyclizative coupling reaction of δ-allenols with allyl or aryl halides has not yet been reported. For its pioneered used in α-allenols, see: D. Xu, Z. Li, S. Ma, *Chem. Eur. J.* **2002**, *8*, 5012.

[10] For Pd-catalyzed 5-*exo* and 6-*exo* haloetherifications, see: C. Jonasson, A. Horváth, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2000**, *122*, 9600.

[11] B. Alcaide, P. Almendros, T. Martínez del Campo, E. Soriano, J. L. Marco-Contelles, *Chem. Eur. J.* **2009**, *15*, 1909.

[12] L. Xue, Z. Lin, *Chem. Soc. Rev.* **2010**, *39*, 1692.

[13] P. Fitton, M. P. Johnson, J. E. McKeon, *Chem. Commun.* **1968**, 6.

[14] E. A. Mitchell, M. C. Baird, *Organometallics* **2007**, *26*, 5230.

[15] a) D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722; b) U. Christmann, R. Vilar, *Angew. Chem. Int. Ed.* **2005**, *44*, 366; *Angew. Chem.* **2005**, *117*, 370.

[16] a) M. Ahlquist, P. Fristrup, D. Tanner, P.-O. Norrby, *Organometallics* **2006**, *25*, 2066; b) M. Ahlquist, P.-O. Norrby, *Organometallics* **2007**, *26*, 550.

[17] J. P. Stambuli, M. Bühl, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 9346.

[18] a) K. C. Lam, T. B. Marder, Z. Lin, *Organometallics* **2007**, *26*, 758; b) F. Barrios-Landeros, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 6944.

[19] A. A. C. Braga, G. Ujaque, F. Maseras, *Organometallics* **2006**, *25*, 3647.

[20] P. Vidossich, G. Ujaque, A. Lledós, *Chem. Commun.* **2014**, *50*, 661.

[21] S. Ma, *Top. Organomet. Chem.* **2005**, *14*, 183.

[22] For details, see the Supporting Information.

[23] a) I. Shimizu, J. Tsuji, *Chem. Lett.* **1984**, 233; b) N. Vicart, B. Cazes, J. Gore, *Tetrahedron Lett.* **1995**, *36*, 5015.

[24] a) R. C. Larock, S. Varaprath, H. H. Lau, C. A. Fellows, *J. Am. Chem. Soc.* **1984**, *106*, 5274; b) J. H. Groen, C. J. Elsevier, K. Vrieze, W. J. J. Smeets, A. L. Spek, *Organometallics* **1996**, *15*, 3445; c) T. Yagyu, M. Hamada, K. Osakada, T. Yamamoto, *Organometallics* **2001**, *20*, 1087; d) L. Canovese, F. Visentin, G. Chessa, C. Santo, P. Uguagliati, G. Bandoli, *J. Organomet. Chem.* **2002**, *650*, 43.

[25] T. Bai, S. Ma, G. Jia, *Coord. Chem. Rev.* **2009**, *253*, 423.

[26] a) M. Gardiner, R. Grigg, V. Sridharan, N. Vicker, *Tetrahedron Lett.* **1998**, *39*, 435; b) I.-Y. Jeong, Y. Nagao, *Tetrahedron Lett.* **1998**, *39*, 8677; c) J. M. Zenner, R. C. Larock, *J. Org. Chem.* **1999**, *64*, 7312; d) S. Ma, D. Duan, Z. Shi, *Org. Lett.* **2000**, *2*, 1419; e) L. Yet, *Chem. Rev.* **2000**, *100*, 2963; f) S. Ma, D. Duan, Y. Wang, *J. Comb. Chem.* **2002**, *4*, 239; g) S. Ma, J. Zhang, L. Lu, *Chem. Eur. J.* **2003**, *9*, 2447; h) X. Gai, R. Grigg, I. Köppen, J. Marchbank, V. Sridharan, *Tetrahedron Lett.* **2003**, *44*, 7445; i) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644; j) J. J. H. Diederen, R. W. Sinkeldam, H.-W. Frühauf, H. Hiemstra, K. Vrieze, *Tetrahedron Lett.* **1999**, *40*, 4255; k) R. Grigg, W. S. MacLachlan, D. T. MacPherson, V. Sridharan, S. Suganthan, M. Thornton-Pett, J. Zhang, *Tetrahedron* **2000**, *56*, 6585; l) R. Grigg, M. Kordes, *Eur. J. Org. Chem.* **2001**, 707; m) S. Ma, W. Gao, *Org. Lett.* **2002**, *4*, 2989; n) R. C. Larock, C. Tu, P. Pace, *J. Org. Chem.* **1998**, *63*,

6859; o) C. Sirlin, J. Chengebroyen, R. Konrath, G. Ebeling, I. Raad, J. Dupont, M. Paschaki, F. Kotzyba-Hibert, C. Harf-Monteil, M. Pfeffer, *Eur. J. Org. Chem.* **2004**, 1724.

[27] a) J. F. Hartwig, *Inorg. Chem.* **2007**, *46*, 1936; b) K. Tatsumi, R. Hoffmann, A. Yamamoto, J. K. Stille, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857.

[28] a) T. Bai, J. Zhu, P. Xue, H. H.-Y. Sung, I. D. Williams, S. Ma, Z. Lin, G. Jia, *Organometallics* **2007**, *26*, 5581; b) T. Bai, L. Xue, P. Xue, J. Zhu, H. H.-Y. Sung, S. Ma, I. D. Wiliams, Z. Lin, G. Jia, *Organometallics* **2008**, *27*, 2614.

[29] a) R. J. Wu, Y. H. Liu, H. Z. Yuan, X. A. Mao, *J. Organomet. Chem.* **1996**, *519*, 237; b) M. Kawatsura, Y. Uozumi, T. Hayashi, *Chem. Commun.* **1998**, 217.

[30] A. Grabulosa, G. Muller, J. I. Ordinas, A. Mezzetti, M. A. Maestro, M. Font-Badia, X. Solans, *Organometallics* **2005**, *24*, 4961.

[31] a) W. F. Karstens, M. Stol, F. J. T. Rutjes, H. Hiemstra, *Synlett* **1998**, 1126; b) W. F. Karstens, F. J. T. Rutjes, H. Hiemstra, *Tetrahedron Lett.* **1997**, *38*, 6275; c) C. Shin, Y. Oh, Y. J. H. Cha, A. N. Pae, H. Choo, Y. S. Cho, *Tetrahedron* **2007**, *63*, 2182; d) W. Oppolzer, A. Pimm, B. Stammen, W. E. Hume, *Helv. Chim. Acta* **1997**, *80*, 623.

[32] a) K. J. Szabó, *Chem. Soc. Rev.* **2001**, *30*, 136; b) V. Branchadell, M. Moreno-Mañas, F. Pajuelo, R. Pleixats, *Organometallics* **1999**, *18*, 4934.

[33] G. C. Lloyd-Jones, S. C. Stephen, *Chem. Eur. J.* **1998**, *4*, 2539.

[34] M. Sjögren, S. Hansson, P.-O. Norrby, B. Akermark, M. E. Cucciolito, A. Vitagliano, *Organometallics* **1992**, *11*, 3954.

[35] S. Hansson, P.-O. Norrby, M. Sjogren, B. Akermark, M. E. Cucciolito, F. Giordano, A. Vitagliano, *Organometallics* **1993**, *12*, 4940.

[36] U. Kazmaier, D. Stolz, K. Kraemer, F. L. Zumpe, *Chem. Eur. J.* **2008**, *14*, 1322.

[37] a) Z. Lu, S. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 258; *Angew. Chem.* **2008**, *120*, 264; b) M. Kranenburg, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **1998**, 25; c) A. Frölander, S. Lutsenko, T. Privalov, C. Moberg, *J. Org. Chem.* **2005**, *70*, 9882; d) T. Hayashi, A. Yamamoto, Y. Ito, E. Nishioka, H. Miura, K. Yanagi, *J. Am. Chem. Soc.* **1989**, *111*, 6301.

[38] J. Kleimark, C. Johansson, S. Olsson, M. Hakansson, S. Hansson, B. Akermark, P.-O. Norrby, *Organometallics* **2011**, *30*, 230.

[39] B. Åkermark, K. Zetterberg, S. Hansson, B. Krakenberger, A. Vitagliano, *J. Organomet. Chem.* **1987**, *335*, 133.

[40] B. M. Trost, X. Ariza, *J. Am. Chem. Soc.* **1999**, *121*, 10727.

[41] a) C. Goux, P. Lhoste, D. Sinou, *Synlett* **1992**, 725; b) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1999**, *121*, 4545; c) I. Dubovyk, I. D. G. Watson, A. K. Yudin, *J. Org. Chem.* **2013**, *78*, 1559.

[42] M. H. Katcher, P.-O. Norrby, A. G. Doyle, *Organometallics* **2014**, *33*, 2121.

[43] B. Goldfuss, U. Kazmeier, *Tetrahedron* **2000**, *56*, 6493.

[44] P. Fristrup, T. Jensen, J. Hoppe, P.-O. Norrby, *Chem. Eur. J.* **2006**, *12*, 5352.

[45] J. Hartwig, *Organotransition Metal Chemistry*, University Science Books, Sausalito, **2010**.

[46] N. Svensen, P. Fristrup, D. Tanner, P.-O. Norrby, *Adv. Synth. Catal.* **2007**, *349*, 2631.

[47] For instance, the transition structure for the 6-*exo*-*trig* cyclization from a *syn* conformation of the [Pd(η^3-allyl)] complex is 24.1 kcal mol^{-1} higher in energy than $\mathbf{TS}_{31'-30''}$. See the Supporting Information for details.

[48] a) F. Delbecq, C. Lapouge, *Organometallics* **2000**, *19*, 2716; b) M. D. Curtis, O. Eisenstein, *Organometallics* **1984**, *3*, 887; c) T. R. Ward, *Organometallics* **1996**, *15*, 2836.

[49] J. D. Oslob, B. Akermark, P. Helquist, P.-O. Norrby, *Organometallics* **1997**, *16*, 3015.

[50] J. A. García-López, I. Saura-Llamas, J. E. McGrady, D. Bautista, J. Vicente, *Organometallics* **2012**, *31*, 8333.

[51] For some reviews, see ref. [3a] and the following: a) S. K. Chattopadhyay, S. Karmakar, T. Biswas, K. C. Majumdar, H. Rahaman, B. Roy, *Tetrahedron* **2007**, *63*, 3919; b) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; c) M. Inoue, *Chem. Rev.* **2005**, *105*, 4379; d) T. Nakata, *Chem. Rev.* **2005**, *105*, 4314.

[52] E. Soriano, J. Marco-Contelles, *Synthesis of Eight- to Ten-Membered Ring Ethers* In *Topics in Heterocyclic Chemistry (Synthesis of Saturated Oxygenated Heterocycles II*; Ed.: J. Cossy*), Vol. 36,* Springer, Heidelberg, **2014**, pp. 321 – 368.

[53] C. Mukai, M. Ohta, H. Yamashita, S. Kitagaki, *J. Org. Chem.* **2004**, *69*, 6867.

[54] M. A. Tarselli, J. L. Zuccarello, S. J. Lee, M. R. Gagné, *Org. Lett.* **2009**, *11*, 3490.

[55] a) K. C. Majumdar, B. Chattopadhyay, A. Taher, *Synthesis* **2007**, 3647; b) K. C. Majumdar, A. K. Pal, A. Taher, P. Debnath, *Synthesis* **2007**, 1701; c) K. C. Majumdar, B. Chattopadhyay, *Synlett* **2008**, 979; d) K. C. Majumdar, B. Chattopadhyay, S. Nath, *Tetrahedron Lett.* **2008**, *49*, 1609.

[56] K. C. Majumdar, B. Chattopadhyay, *Synthesis* **2009**, 2385.

[57] See, for instance: a) M. Asikainen, N. Krause, *Adv. Synth. Catal.* **2009**, *351*, 2305; b) D. Eom, D. Kang, P. H. Lee, *J. Org. Chem.* **2010**, *75*, 7447; c) M. Brasholz, B. Dugovič, H.-U. Reissig, *Synthesis* **2010**, 3855; d) S. Ma, Z. Yu, S. Wu, *Tetrahedron* **2001**, *57*, 1585; e) A. V. Kelin, V. Gevorgyan, *J. Org. Chem.* **2002**, *67*, 95.

[58] a) B. Alcaide, P. Almendros, T. Martínez del Campo, E. Soriano, J. L. Marco-Contelles, *Chem. Eur. J.* **2009**, *15*, 9127; b) B. Alcaide, P. Almendros, J. M. Alonso, I. Fernández, *Chem. Commun.* **2012**, *48*, 6604.

[59] Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fuku-da, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2010**.

[60] a) Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008**, *41*, 157; b) Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.

[61] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 270.

[62] A. W. Ehlers, M. Bçhme, S. Dapprich, A. Gobbi, A. Hçllwarth, V. Jonas, K. F. Kçhler, R. Stegmann, A. Veldkamp, G. Frenking, *Chem. Phys. Lett.* **1993**, *208*, 111.

[63] a) S. Miertuš, E. Scrocco, J. Tomasi, *J. Chem. Phys.* **1981**, *55*, 117; b) J. L. Pascual-Ahuir, E. Silla, I. Tuñón, *J. Comput. Chem.* **1994**, *15*, 1127; c) V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995.

[64] a) A. E. Reed, F. J. Weinhold, *J. Chem. Phys.* **1985**, *83*, 1736; b) A. E. Reed, R. B. Weinstock, F. J. Weinhold, *J. Chem. Phys.* **1985**, *83*, 735; c) A. E. Reed, L. A. Curtiss, F. J. Weinhold, *Chem. Rev.* **1988**, *88*, 899.

[65] Experimental procedures as well as full spectroscopic and analytical data for compounds that are not included in the Experimental Section are described in the Supporting Information. It contains compound characterization data, experimental procedures, Cartesian coordinates, and copies of NMR spectra for all new compounds.

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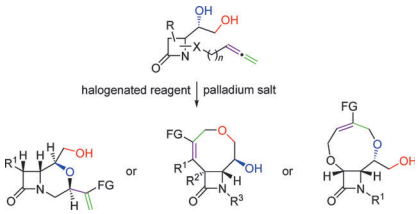
FULL PAPER

Joy of cyclization: A chemo-, regio-, and stereoselective methodology for the preparation of a variety of diversely functionalized enantiopure morpholines, oxocines, and dioxonines involves the controlled palladium-catalyzed cyclizative coupling reaction of 2-azetidinone-tethered γ,δ-, δ,ε- and ε,ζ-allenic diols (see scheme).



Synthetic Methods

B. Alcaide, P. Almendros,* R. Carrascosa, L. Casarrubios, E. Soriano*

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A Versatile Synthesis of β-Lactam-Fused Oxacycles through the Palladium-Catalyzed Chemo-, Regio-, and Diastereoselective Cyclization of Allenic Diols