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# Chemo- and Regioselective Palladium-Catalyzed Oxycyclization Reactions of Allendiols: Preparation of Five-, Six-, and Eight-Membered Cycles

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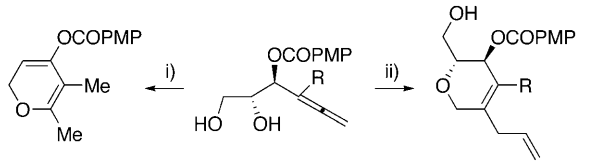
Oxacycles are the major component of many biologically important natural products and functional molecules.[1] Thus, the synthesis of these heterocycles is of current interest. Allenes are a class of compounds with two cumulative carbon–carbon double bonds, which have become more and more interesting not only as targets in natural products synthesis, but also as valuable synthetic precursors for complex molecules.[2] In this context, carbon–heteroatom cyclization is of major interest.[3] However, regioselectivity problems are significant (*endo-trig* versus *endo-dig* versus *exo-dig* versus *exo-trig* cyclization). A cyclization process that involves a selective carbon–heteroatom bond formation, even if the structure of the substrate suggests numerous possibilities for reactivity, represents an attractive strategy. Although many efforts have been made in these fields, metal-catalyzed heterocyclizations of allenes bearing two contiguous nucleophilic centers have rarely been mentioned; only Krause et al. have recently reported the gold-catalyzed 5-*endo* cycloisomerization of both an α,α′-allendiol as well as an α,β-allendiol to give dihydrofurans.[4] The main cause of this relative lack of success might be attributed to additional chemoselectivity problems. Namely, the product distribution depends on the chemo- and regioselectivity of the heterocyclization, but in principle, eight different products are possible. Encouraged by our recent results in heterocyclic and allene chemistry,[5] we thought that chemo- and regioselective palladium-catalyzed cycloetherification of allendiols, namely β,γ- and γ,δ-allendiols, may occur by judicious choice of catalyst owing to their potential ability to discriminate both nucleophilic sites, and the results of our investigations are discussed herein.

β,γ-Allendiol **1a** was chosen as a model substrate for palladium-catalyzed oxycyclization reactions.[6] To screen the reactivity of the β,γ-allendiol moiety, heterocyclization was studied by using **1a** in the presence of a $Pd^0$ catalyst. The 2*H*-pyran **2**, which arises from a totally chemo- and regioselective 6-*exo* oxycyclization of the primary hydroxy group to the central allene carbon with concomitant dehydration, was obtained in moderate yield, together with a complicated mixture of side products (Scheme 1). Next, **1a** was exposed to allyl bromide under $Pd^{II}$ catalysis in DMF. Gratifyingly, the functionalized dihydropyran **3a** was isolated as the sole isomer in 65% yield. Similar behavior was observed for the phenyl derivative **1b** (Scheme 1). This result could be explained through a 6-*endo* cyclization by chemo- and regiospecific attack of the secondary hydroxy group at the terminal allene carbon atom.




**2** (35%) **(–)-1a** R = Me **(–)-1b** R = Ph **(+)-3a** R = Me (65%) **(–)-3b** R = Ph (78%)

Scheme 1. Palladium-catalyzed preparation of dihydropyrans **2** and **3**. Reagents and conditions: i) 5 mol% $[Pd(PPh_3)_4]$, PhI, $K_2CO_3$, toluene, 80°C, 24 h; ii) allyl bromide, 5 mol% $PdCl_2$, DMF, RT, **3a**: 3 h; **3b**: 2 h. PMP = 4-$MeOC_6H_4$.

To probe the feasibility of cycloetherification in β,γ-allendiols by way of palladium-induced oxybromination, allen-

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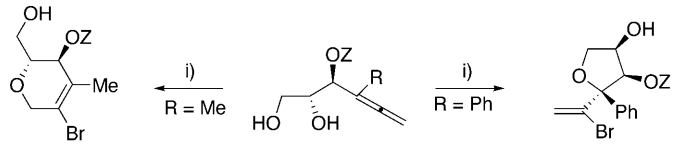
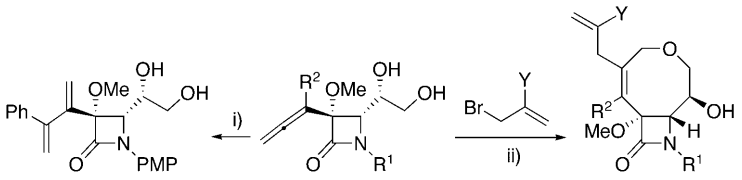
diols **1a** and **1c** were treated with lithium bromide using a Pd–Cu bimetallic catalytic system. Interestingly, the bromoetherification products **4** were observed and, upon further optimization, could be obtained in reasonable yields. These conditions were applied to β,γ-allendiols **1b** and **1d**. To our delight, in contrast to the oxybromination reaction of methyl allendiols **1a** and **1c** which led to a bromodihydropyran, the reaction of phenyl allendiols **1b** and **1d** under identical conditions afforded 2-(1-bromovinyl)tetrahydrofurans **5** (Scheme 2).[7] Thus, by a subtle variation in the substitution pattern of the β,γ-allendiol (Ph versus Me) both the chemo- and the regioselectivity can be completely reversed. The difference in reactivity between both types of allendiols could be explained by considering the electron-withdrawing capacity of the phenyl substituent compared to the electron-donating capacity of the methyl group. Probably, the presence of a Ph substituent in the allene moiety strengthened the electrophilicity of the benzylic-like carbon, favoring the 5-*exo* cyclization of the primary hydroxy group over the 6-*endo* cyclization of the secondary hydroxy group. The *p*-methoxybenzoyloxy group comprises a large substituent; however, the *cis* attack, which would be disfavored with a larger ZO group, increases with **1b** (Z = COPMP) in comparison with **1d** (Z = Me). The reason for the total diastereoselectivity for the 5-*exo* cyclization toward the internal allene carbon atom on phenyl allendiol **1d** to give adduct **5b** compared to the moderate diastereoselectivity of phenyl allendiol **1b** to give adduct **5a** in the examples in Scheme 2, may be related to unfavorable steric interactions between the ZO group and Pd in the π-allylpalladium intermediate derived from **1b**, hampering the required conformation for the *trans* attack.



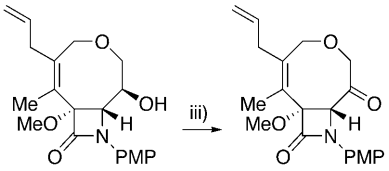

**(+)-4a** Z = COPMP (53%) **(–)-1a** R = Me, Z = COPMP
**(–)-4b** Z = TPS (51%) **(+)-1c** R = Me, Z = TPS
**(–)-1b** R = Ph, Z = COPMP **(+)-5a** Z = COPMP (57%; d.r. = 60:40)
**(+)-1d** R = Ph, Z = Me **(–)-5b** Z = Me (55%; d.r. = 100:0)

Scheme 2. Palladium-catalyzed preparation of dihydropyrans **4** and tetrahydrofurans **5**. Reagents and conditions: i) 7 mol% $Pd(OAc)_2$, LiBr, $Cu(OAc)_2$, $K_2CO_3$, MeCN, $O_2$, RT, 2 h. PMP = 4-$MeOC_6H_4$. TPS = *tert*-butyldiphenylsilyl.

To assess the scope of the reaction, the even more challenging 2-azetidinone-tethered γ,δ-allendiols **6** were tested as cycloetherification substrates. Attempts to generate a bicyclic structure from **6a** by using $Pd^0$ catalysts in the presence of iodobenzene failed, because β-hydride elimination to afford diene **7** competes more effectively.[8] Accordingly, solutions of γ,δ-allendiols **6** were exposed to the above-mentioned conditions for $Pd^{II}$-catalyzed heterocyclizations. Much to our delight, adducts **8a–e** were obtained in good yields in a totally chemo- and regioselective fashion using the $PdCl_2$-catalyzed cyclizative coupling reaction with allyl halides (Scheme 3), through a 8-*endo* cyclization by attack of the primary hydroxy group at the terminal allene carbon atom.[9] To the best of our knowledge, no example of an 8-*endo* cyclization at the terminal allene carbon atom 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. Besides, oxo-

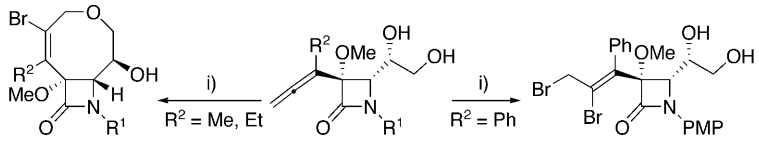



**(+)-7** (45%)
**(+)-6a** $R^1$ = PMP, $R^2$ = Me
**(+)-6a** $R^1$ = PMP, $R^2$ = Me
**(+)-6b** $R^1$ = PMP, $R^2$ = Ph
**(–)-6c** $R^1$ = PMP, $R^2$ = $CH_2OBn$
**(–)-6d** $R^1$ = Bn, $R^2$ = Et
**(+)-8a** Y = H (73%)
**(+)-8b** Y = Br (60%)
**(+)-8c** Y = H (58%)
**(–)-8d** Y = H (60%)
**(+)-8e** Y = H (62%)




**(+)-8a** **(+)-9** (88%)

Scheme 3. Preparation of oxocines **8** and oxocinone **9**. Reagents and conditions: i) 5 mol% $[Pd(PPh_3)_4]$, PhI, $K_2CO_3$, toluene, 80 °C, 120 h; ii) 5 mol% $PdCl_2$, DMF, RT, **8a**: 14 h; **8b**: 16 h; **8c**: 16 h; **8d**: 15 h; **8e**: 15 h; iii) Dess–Martin periodinane, $CH_2Cl_2$, RT, 2 h. PMP = 4-$MeOC_6H_4$.

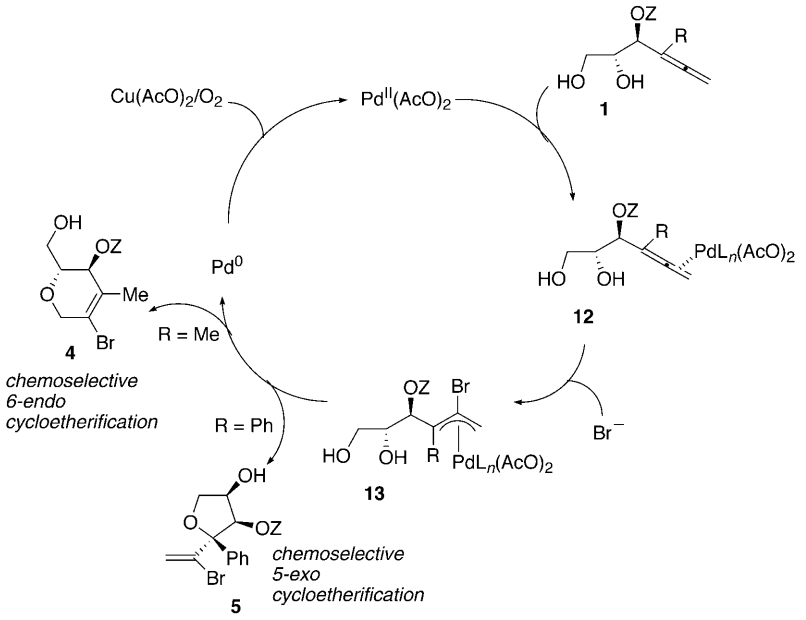



**(+)-10a** (50%)
**(+)-10b** (52%)
**(+)-10c** (44%)
**(+)-6a** $R^1$ = PMP, $R^2$ = Me
**(–)-6e** $R^1$ = Bn, $R^2$ = Me
**(–)-6d** $R^1$ = Bn, $R^2$ = Et
**(+)-6b** $R^1$ = PMP, $R^2$ = Ph
**(+)-11** (43%)

Scheme 4. Preparation of oxocines **10** and dibromide **11**. Reagents and conditions: i) 7 mol% $Pd(OAc)_2$, LiBr, $Cu(OAc)_2$, $K_2CO_3$, MeCN, $O_2$, RT, **10a**: 6 days; **10b**: 7 days; **10c**: 6 days; **11**: 8 days. PMP = 4-$MeOC_6H_4$.

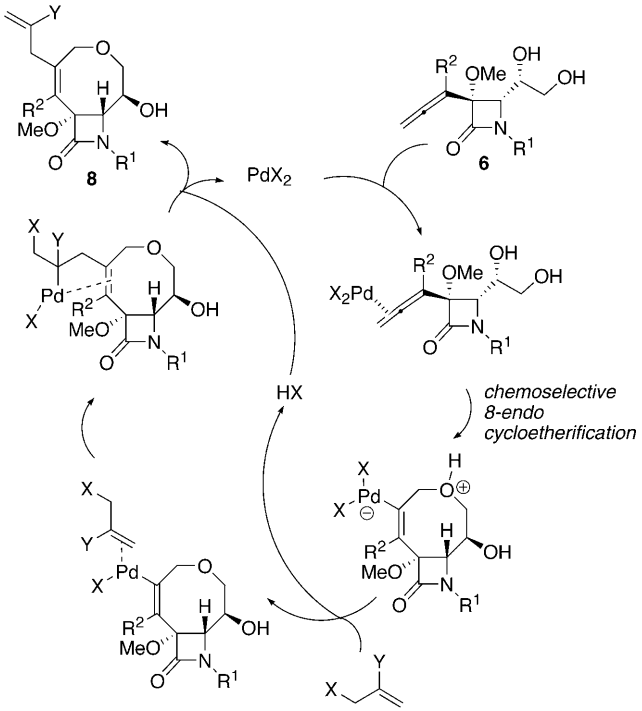
cines **8** are remarkable as they comprise a C3–C4 *trans*-fused β-lactam.[10] HMBC experiments on derivatives **8** established the presence of a new eight-membered oxacycle fused to the β-lactam ring. Chemical evidence was obtained by oxidation of the adduct **8a** with Dess–Martin periodinane, which gave ketone **9** (Scheme 3). Similarly, only the hydroxy group in the δ-position participates in the $Pd(OAc)_2$-catalyzed regiocontrolled oxybromination reaction of methyl- and ethyl-γ,δ-allendiols **6a**, **6d**, and **6e**, giving exclusively the eight-membered fused derivatives **10** (Scheme 4). The use of the above oxybromination reaction conditions on phenyl γ,δ-allendiol **6b** changes the reactivity pattern, suppressing the oxycyclization while retaining the same regioselectivity of the bromination step. Thus, in the case of phenyl allendiol **6b** we observed exclusive formation of the monocyclic dibromide **11**. The divergence between alkyl- and arylallendiols **6** may arise from the different stereolectronic effect imparted by the phenyl group in the oxycyclization step, which directs the reaction toward a new bromide attack at the terminal allene carbon atom rather than toward a cycloetherification.




Scheme 5. Mechanistic explanation for the $Pd^{II}$-catalyzed bromoheterocyclization reaction of β,γ-allendiols **1**.

A likely mechanism for the generation of bromodihydropyrans **4** and tetrahydrofurans **5** should involve the initial formation of a (π-allyl)palladium species.[11] The allenepalladium complex **12** is formed initially and suffers a nucleophilic attack by the bromide to produce σ-allylpalladium species, which rapidly equilibrate to the corresponding (π-allyl)palladium intermediate **13**. Then, a chemo- and regiospecific intramolecular cycloetherification reaction by attack of either the secondary hydroxy group at the terminal allene carbon atom or the primary hydroxy group at the internal allene carbon atom onto the (π-allyl)palladium complex must account for the formation of dihydropyrans **4** or tetrahydrofurans **5** (Scheme 5). Finally, in situ oxidation of $Pd^0$ to $Pd^{II}$ by $Cu(OAc)_2$ completes the catalytic cycle.

The pathway proposed in Scheme 6 appears valid for the formation of products **8**. The oxybromination reaction involves the addition of the halide ion to the allenic moiety to give a (π-allyl)palladium intermediate, whereas the heterocyclizative coupling with allyl halides involves the chemo- and regiocontrolled oxypalladation of the allenic moiety, followed by a Heck-type reaction, and regeneration of the $Pd^{II}$ catalyst through β-halide elimination (Scheme 6).




Scheme 6. Mechanistic explanation for the $Pd^{II}$-catalyzed heterocyclizative coupling reaction of γ,δ-allendiols **6**.

In conclusion, we have demonstrated for the first time that both chemo- and regioselectivity control in the palladium-catalyzed O–C cyclization of allendiols can be achieved. Thus, starting from β,γ- and γ,δ-allendiols this metal-catalyzed methodology provides access to a variety of different-sized (five-, six-, and eight-membered) enantiopure oxacycles.

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**Keywords:** allenes · chemoselectivity · heterocycles · palladium · regioselectivity

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