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Macrolactonization via Hydrocarbon Oxidation

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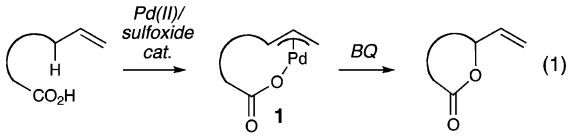
Macrolides are important structural units due to their prevalence in numerous small molecules having significant and diverse biological and medicinal properties. Hydroxyacid lactonization methods are powerful reactions for assembling macrolides, as evidenced by their prevalent use during late stages of total syntheses.[1] Elegant Pd-mediated oxidative cyclizations of linear alkenoic acids to yield five- and six-membered unsaturated lactones have been reported.[2] However, macrolactonizations under these conditions (Pd^{II}/base) have not been demonstrated.[2,3] Herein, we report for the first time a macrolactonization reaction that proceeds via allylic C−H oxidation. Linear ω-alkenoic acids react to furnish 14- to 19-membered alkyl and aryl macrolides with a range of diverse functionalities. In addition to providing greater flexibility in synthetic design, such organometallic C−H to C−O bond-forming methods may streamline synthesis by alleviating some of the requirements for protecting group manipulations and oxidation state changes incurred with ionic processes.[4]

Our group recently reported sulfoxide-promoted, catalytic $Pd(OAc)_2$/BQ α-olefin allylic oxidation systems that furnish branched allylic alkyl and aryl esters from a wide variety of carboxylic acids.[5a,b] These reactions proceed via a novel serial ligand catalysis mechanism in which sulfoxide and BQ interact sequentially with Pd to promote the C−H cleavage and C−O bond-forming steps, respectively.[5b] The C−O bond-forming step may occur via a BQ-promoted inner-sphere reductive elimination of acetate.[6] This suggested to us a novel organometallic macrolactonization strategy proceeding via templated intermediate **1** (eq 1). It was hypothesized



(1)

that Pd templation and activation of the two reacting termini would serve to relieve some constraints of macrocyclization like the use of multiple biasing elements and high-dilution techniques.[7] Herein we report a C−H oxidation macrolactonization method run at 10 mM without the use of high-dilution techniques to prepare 14- to 19-membered macrolides with high levels of regioselectivity and functional group tolerance. Furthermore, we provide evidence in support of a mechanism that proceeds via Pd-templated intermediate **1** (eq 1).

Our study began by examining the cyclization of *o*-(alkenyl)-benzoic acids. We found that 10 mol % $Pd(OAc)_2$/phenyl bis-sulfoxide **2**/BQ (2 equiv) promoted macrolactonizations of linear precursors to furnish 14- to 17-membered macrocyclic benzo-lactones in 52−62% isolated yields (Table 1, entries 1−4) with outstanding regioselectivities (>20:1 by ^{1}H NMR). Macrolacton-ization proceeded at 10 mM substrate concentrations under air with no precautions taken to exclude moisture. The same operational simplicity may be applied to reactions conducted on a *1 g scale* (Table 1, entry 1b).

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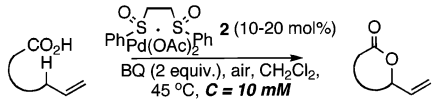
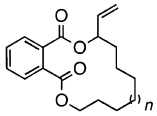
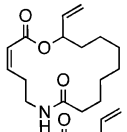
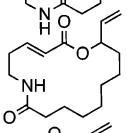
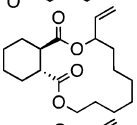
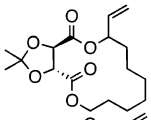
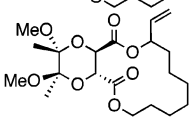
Table 1.



entry	macrolactone product	ring size	isolated yield[a]
1a		14	**3**,61%[b]
1b		**1g scale**	**-->62%**[c]
2		15	**4**,52%
3		16	**5**,60%
4		17	**6**,53%
5		16	**7**,52%[d] 98:2 (*Z*:*E*)[e]
6		16	**8**,63%[d] 99:1 (*E*:*Z*)[e]
7		14	**9**,60% 1.4:1 (d.r.)[f]
8		14	**10**,54%[d,g] 1:1 (d.r.)[f]
9		14	**11**,60%[h] 1.4:1 (d.r.)[e]

[a] Average yields of pure branched isomer for two runs at 0.2 mmol, 72 h. Up to 18% starting material observed (Supporting Information). Some head-to-tail dimerization byproducts have been observed. [b] Higher diultions result in lower macrolide yields. [c] 1 g (3.3 mmol). [d] 20 mol % **2**; 10 mol % **2** gave 17−22% lower yields (Supporting Information). [e] Ratio by GC. [f] Ratio by ^{1}H NMR. [g] C = 20 mM. [h] 15 mol % **2**.

A preliminary study of the scope of the reaction demonstrated that, in addition to aryl acids, vinylic and alkyl acids are competent nucleophiles (Table 1, entries 5−9).[8] Both (*Z*)- and (*E*)-α,β-unsaturated acids undergo cyclization using this allylic C−H oxidation method to furnish 16-membered macrolides **7** and **8** in good yields with *no olefin isomerization* (Table 1, entries 5 and 6). The latter point is significant given that (*Z*)-α,β-unsaturated acids are prone to base-induced olefin isomerization using classical acylation-based macrolactonization methods.[9] Chiral, alkyl acids effectively cyclize and do not appear to significantly influence diastereoselectivity (Table 1, entries 7−9). The mildness of this method is illustrated by macrolactonization of alkenyl acids with densely oxygenated acetonide and acetal moieties (Table 1, entries 8 and 9, respectively). Significantly, the macrolactonization yield of acetonide **10** was improved from 45% to 54% by *increasing* the substrate molarity from 10 to 20 mM (Table 1, entry 8).

Encouraged by the preliminary scope of the reaction, we began to explore the cyclization of substrates incorporating increasing

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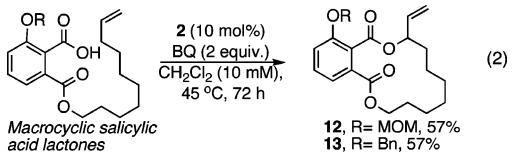
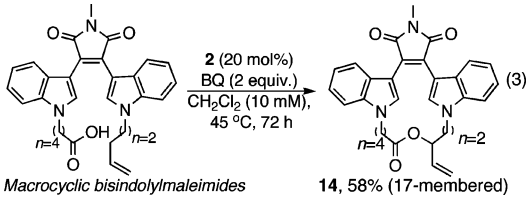
levels of biologically and medicinally relevant functionality. Ortho-substituted salicylate esters are a common structural motif found in a growing number of benzolactone natural products with desirable biological properties (e.g., the antitumor compound radicicol).[10] Acylation-based macrolactonizations of ortho-substituted salicylic acid substrates are challenging due to increased electron density and steric hindrance at the acyl carbon center.[11] Under the allylic oxidation conditions, we found that both MOM- and benzyl-protected, ortho-substituted salicylic acids readily cyclize to afford the corresponding 14-membered ring macrolides **12** and **13** in 57% yields (eq 2).



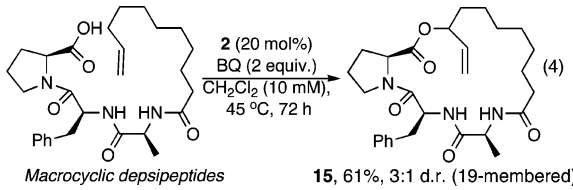
(2)

The indole nucleus is of particular value to the medicinal chemist. For example, a large number of indolocarbazoles of biological interest are known like the PKC inhibitor rebeccamycin[12a] and the related macrocyclic compound LY 333531 developed by Lilly.[12b,c] Using the allylic C−H oxidative macrolactonization, a novel 17-membered bis(indolyl)maleimide macrolide **14** was readily formed in 58% isolated yield (eq 3). Macrolactonization of this nitrogen-rich substrate serves to further highlight the broad functional group compatibility of this C−H oxidation method.



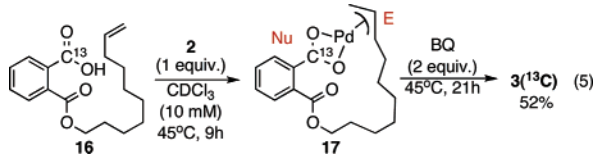
(3)

Macrocyclic depsipeptides have been shown to exhibit potent cytotoxic, antimicrobial, and anti-inflammatory properties.[13] A linear tripeptide containing an α-olefin tether was successfully cyclized under these conditions to provide 19-membered depsipeptide **15** in 61% yield and 3:1 dr (eq 4). This preliminary result suggests that remote chirality can direct the diastereoselectivity of macrolactone formation.



(4)

Mechanistic studies were performed to investigate whether macrolactonization proceeds via C−O bond formation from a templated π-allylPd carboxylate intermediate (eq 5). When stoi-



(5)

chiometric mixtures of ^{13}C-labeled alkenoic acid **16** and bis-sulfoxide/Pd(OAc)$_2$ complex **2** were heated and monitored by ^{1}H NMR spectroscopy, peaks consistent with a π-allylPd complex **17** were observed. Simultaneous monitoring of the C−H cleavage step by ^{13}C NMR spectroscopy showed a Pd-bound carboxylate suggestive of intermediate **17** (^{13}C═O: **16**, δ 170.7; **17**, δ 178.6;[14] **3**, δ 166.6). Evidence for the monomeric nature of **17** was obtained via ESI-HRMS ($C_{18}H_{23}O_4Pd$ $[M + H]^+$, predicted 409.0639, found 409.0598). Addition of BQ to **17** results in formation of macrolide **3** in 52% yield (62% catalytic reaction, Table 1, entry 1). Significantly, in the absence of BQ, reductive elimination is not observed. These studies confirm that macrolactonization proceeds via a serial ligand catalysis mechanism and provide evidence in support of BQ-promoted inner-sphere C−O bond formation from a templated π-allylPd carboxylate intermediate.[5b,6] According to this mechanism, high dilutions are unnecessary because the catalyst dictates that the maximum concentrations of reactive π-allyl and carboxylate moieties are 5−10-fold lower than the substrate concentration.[7]

In summary, this report describes the first examples of Pd-catalyzed macrolactonizations of ω-alkenoic acids via C−H oxidation. These reactions proceed without the use of high-dilution or Schlenk line techniques and display remarkable levels of selectivity and scope. Mechanistic studies support that macrolactonization proceeds via a Pd-templated π-allyl carboxylate intermediate such as **17**. Future studies will explore chemoselectivity issues with respect to internal olefins[5b] and the effects of substrate and reagent chirality on diastereoselectivity in the context of complex molecule synthesis.

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Supporting Information Available: Detailed experimental procedures, full characterization, and a complete list of authors for ref 12b. This material is available free of charge via the Internet at http://pubs.acs.org.

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