New Synthetic Methodology toward Macrolides/Macrolactams via Palladium-Catalyzed Carbon-Heteroatom Bond-Forming Reactions

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Abstract: A concise and versatile syntheses of 11-16 membered macrolides and 13-15 membered macrolactams have been achieved using a Tsuji-Trost type reaction. This approach is composed of intramolecular cyclization employing ethyl carbonate with carboxylic acids and catalytic amount of Pd(PPh3)4 to form carbon-heteroatom covalent bonds with no use of stoichiometric reagents.

Key words: macrolactones, macrolactams, palladium-catalyzed reaction, carbon-heteroatom bond-formation

Macrocyclic lactones so-called macrolides are important molecules in biological and medicinal chemistries, because they often show notable bioactivities as represented by erythromycins1 and epothilones.2 In addition, their intriguing structures have also attracted considerable attention from the synthetic community, and numerous efforts have been devoted to synthesize macrolides and their derivatives.3 The conventional synthetic approaches constructing macrolides involve carbon-oxygen bond formation by the use of condensing agents such as bis(4-pyridyl)disulphide (PySSPy);4 2,4,6-trichlorobenzoyl chloride;5 and 2-methyl-6-nitrobenzoic anhydride (NMBA).6 Although they have been also used for the synthesis of macrocyclic natural products, it is indispensable to use stoichiometric reagents for achievement of macrolactonization.

Thus, along these lines the development of a variety of the stoichiometric macrolactonization has been accompanied up to date,3a however, catalytic reactions for the construction of macrolides have not so far been established. Recently, White and co-workers have reported an example of macrolactonization employing catalytic Pd(OAc)2/BQ α-olefin allylic oxidation system, expanding the utility of transition-metal-catalyzed reaction for macrocyclic carbon-oxygen bond formation.7 Considering that the reaction proceeds via a Pd-templated π-allyl carboxylate intermediate, intramolecular Tsuji-Trost type reaction with carboxylic acids bearing allylic leaving groups would be expected to afford macrolides. To the best of our knowledge, only one example of this type of reaction has been reported by Trost in his review and the catalytic synthesis remained undeveloped.8 In this paper, we report an efficient and general method for constructing 11-16 membered macrolides with Pd(0) catalyst and further extension of this method to the synthesis of 13-15 membered macrolactams. For the purpose of the construction of macrocycles, we use ethyl carbonate as the leaving group, because cleavage of the allylic carbon-oxygen bond in allylic carbonate would provide π-allylpalladium intermediate, readily giving rise to cyclization under base free conditions (Scheme 1).

Scheme 2 Reagents and conditions: a: n = 1, b: n = 2, c: n = 3, d: n = 4, e: n = 5, f: n = 6: (a) (i) (EtO)2P(O)CH2CO2Et, t-BuOK, THF, -78 °C; (ii) DIBAL-H, CH2Cl2, -78 °C; (b) (i) ethyl chlorocarbonate, pyridine; (ii) PPTS, EtOH; (c) (i) PDC, MS4A, CH2Cl2; (ii) NaClO2, NaH2PO4·2H2O, 2-methyl-2-butene, t-BuOH; (d) vinyl magnesium chloride, THF, 0 °C.

The preparation of cyclization precursors 4a-f (n = 1-6) were shown in Scheme 2. Linear aldehydes9 1a-f underwent Horner-Emmons reaction and DIBAL-H reduction to give E-allyl alcohols 2a-f, respectively. Allylic alcohol moieties were then converted into

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corresponding allyl ethyl carbonates followed by deprotection of TBS protecting groups to afford 3a-f, respectively. The resulting primary hydroxy groups were subsequently oxidized in a stepwise manner to give 4a-f.

Meanwhile, we also prepared regioisomeric ethyl carbonate 6. Thus, addition of vinylmagnesium chloride to 1c gave allyl alcohol 5 in 74% yield. This intermediate was readily converted to 6c through the same sequence as used for the synthesis of 4.

In an initial series of experiments, we examined the formation of 13-membered macroclide α-7c upon treatment of 4c in the presence of palladium catalyst. After screening the detailed reaction conditions using a variety of phosphine-ligands and solvents, we found that the reaction using 20 mol% of Pd(PPh3)4 in a highly diluted CH2Cl2 solution (c = 2.0 mM) at room temperature afforded the optimal result. Under these conditions, lactone α-7c was formed in 51% yield as an E/Z mixture (83:17), while its regioisomer γ-7c was not at all formed from observation of its 1H NMR spectroscopy (Table 1, Entry 3). Alternatively, Boc- and Cbz-protected amides 9c and 10c prepared from 8c12 were found to undergo efficient macrocyclization in the presence of Pd(PPh3)4 and t-BuOK13 to give 13-membered lactams 12c and 13c with complete regioselectivities in favor of the E-isomers (Entries 2 and 3). Furthermore, 9d,e also cyclized to yield 14- and 15-membered lactams 12d,e with high regioselectivities, respectively (Entries 4 and 5).

Encouraged by this successful implementation of the Pd-catalyzed macrocyclization of carboxylic acids 4, we turned our attention to the synthesis of corresponding nitrogen-containing heterocycles (Scheme 3, Table 2). Although carboxylic acid 4c could be smoothly converted to the corresponding amide 8c, subsequent attempts to perform the Pd(PPh3)4-catalyzed macrocyclization unfortunately resulted in decomposition of the starting material (Entry 1). Alternatively, Boc- and Cbz-protected amides 9c and 10c prepared from 8c12 were found to undergo efficient macrocyclization in the presence of Pd(PPh3)4 and t-BuOK13 to give 13-membered lactams 12c and 13c with complete regioselectivities in favor of the E-isomers (Entries 2 and 3). Furthermore, 9d,e also cyclized to yield 14- and 15-membered lactams 12d,e with high regioselectivities, respectively (Entries 4 and 5).

### Table 1 Pd(0)-catalyzed macrocyclization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield/%a</th>
<th>α:γb</th>
<th>E/Zc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a (n = 1)</td>
<td>6 (7a)</td>
<td>100.0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>4b (n = 2)</td>
<td>31 (7b)</td>
<td>97:3</td>
<td>64:36</td>
</tr>
<tr>
<td>3</td>
<td>4c (n = 3)</td>
<td>51 (7c)</td>
<td>100.0</td>
<td>83:17</td>
</tr>
<tr>
<td>4</td>
<td>4d (n = 4)</td>
<td>70 (7d)</td>
<td>99:1</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>4e (n = 5)</td>
<td>64 (7e)</td>
<td>86:14</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>4f (n = 6)</td>
<td>73 (7f)</td>
<td>67:33</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>55 (7e)</td>
<td>99:1</td>
<td>86:14</td>
</tr>
</tbody>
</table>

a Isolated and combined yields. 
b Ratios were determined by 1H NMR analysis (300 MHz, CDCl3). 
c E/Z ratios could not be determined.

In summary, we demonstrated the new synthetic methodology for catalytic macrocyclizations associated with carbon-oxygen and carbon-nitrogen bond formations. Compared to the conventional macrocyclizations, this approach is advantageous in that only easily removable alcohols and CO2 were formed as side-products during the course of the reactions. The success of this diverse and efficient
macrocyclization could show broader applicability of this methodology to the synthesis of macrocyclic natural products, and, in addition, represents the first example of Pd-catalyzed macrolactamization to generate 13-15 membered lactams.

Supporting Information for this article is available online at http://www.thieme-connect.de/ejournals/toc/synlett.

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References

(10) We observed that the reaction with the isolated single E-α-7c under the same reaction conditions afforded a 90:10 mixture of E/Z-isomers without production of γ-7c (Scheme 4).

(11) This would be attributed to the strain based on the ring size.

(13) The macrolactamization of 9c in the absence of t-BuOK resulted in α-12c in 44% yield (Scheme 5).
Palladium-Catalyzed Macrolactonization/Macrolactamization

Graphical abstract

11-16 membered macrocycles