Palladium-Catalyzed Enantioselective Cyclization of Silyloxy-1,6-Enynes
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Transition-metal-catalyzed cycloisomerization and cyclization reactions of enynes have emerged as powerful methods for the construction of hetero- and carbocyclic compounds.1 More recently, enantioselective cycloisomerization of 1,6- and 1,7-enynes has been employed in the preparation of enantioenriched 1,4-diene containing structures.2-4 Despite its potential utility, the related enantioselective cycloisomerization of heteroatom-substituted alkenes5 has not been reported. Herein we report the first enantioselective cyclization reactions of 1,6-enynes containing silyloxy-substituted olefins.

On the basis of our recent report on palladium-catalyzed enantioselective 5-exo-dig addition of 1,3-dicarbonyl compounds to alkynes,6 we hypothesized that similar catalysts might promote the enantioselective cycloisomerization of silyl enol ethers. To this end, reaction of silyl enol ethers 1a (3:1 Z:E) and 1b (2:1 Z:E) catalyzed by 10 mol % of ((R)-DTBM-Segphos)Pd(OTf)2 (A) cleanly afforded methylene cycloptrene 2 in 63 and 77% ee, respectively (eq 1). Furthermore, diastereomerically pure (E)-1b afforded 2 with greater enantioselectivity (81% ee) than the corresponding (Z)-isomer (74% ee). The enantioselectivity was further improved to 91% ee by employing tert-butyldimethylsilyl enol ether (E)-1c.

The fact that the silyloxy substituent and the olefin geometry impact the enantioselectivity of the reaction (eq 1) suggests that the silyl enol ether is intact during the enantiodetermining event. We envisioned two potential mechanisms consistent with this observation: (1) enantioselective addition of the enol ether to the electrophilic Pd complex and the resulting C-bonded Pd enolate7 undergoes stereospecific8 insertion into the pendent acetylene or (2) addition of the enol ether onto a Pd(II) activated alkyne.9,10 Given the ease with which Pd enolates undergo protonation,11 the observation that very little hydrolysis of the enol ether occurs during the cyclization reaction suggests these intermediates are not involved in this reaction.12,13 Therefore, we propose that the latter mechanism is operative in the Pd-catalyzed cyclization. Additionally, the proposed transition state (TS)14 for this pathway accounts for the observation that (E)-1d, in which the aryl group is placed under the forming five-membered ring in TS, reacted significantly slower than (Z)-1d.15 Moreover, in TS, the olefin substituents are larger than the alkyl group regardless of the olefin geometry; therefore, the same enantiomer is obtained from either olefin isomer.

Initial investigation of the reaction scope indicated that tert-butyldimethylsilyl enol ethers derived from aryl ketones underwent efficient cyclization giving methylene cycloptrene adducts with good to excellent enantioselectivities (Table 1, entries 1–4). Notably, the potentially enolizable tertiary stereocenter in 4 was formed with good enantioselectivity (entry 2).

Table 1. Enantioselective Pd-Catalyzed Cyclizationa

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions, Time</th>
<th>Product</th>
<th>Yield (ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OTBS</td>
<td>A, 12 h</td>
<td>(2)</td>
<td>93% (91% ee)</td>
</tr>
<tr>
<td>2</td>
<td>OTBS</td>
<td>A, 6 h</td>
<td>(4)</td>
<td>86% (85% ee)</td>
</tr>
<tr>
<td>3</td>
<td>OTBS</td>
<td>A, 12 h</td>
<td>(6)</td>
<td>92% (88% ee)</td>
</tr>
<tr>
<td>4</td>
<td>OTBS</td>
<td>A, 12 h</td>
<td>(8)</td>
<td>70% (73% ee)</td>
</tr>
<tr>
<td>5</td>
<td>OTBS</td>
<td>B, 30 min</td>
<td>(10)</td>
<td>83% (89% ee)</td>
</tr>
<tr>
<td>6</td>
<td>OTBS</td>
<td>B, 30 min</td>
<td>(12)</td>
<td>91% (97% ee)</td>
</tr>
<tr>
<td>7</td>
<td>OTBS</td>
<td>B, 20 min</td>
<td>(14)</td>
<td>80% (98% ee)</td>
</tr>
<tr>
<td>8</td>
<td>OTBS</td>
<td>B, 2 h</td>
<td>(16)</td>
<td>79% (80% ee)</td>
</tr>
<tr>
<td>9</td>
<td>TBSO</td>
<td>B, 20 min</td>
<td>(18)</td>
<td>83% (91% ee)</td>
</tr>
</tbody>
</table>

a Conditions: A: 10% A, rt, 0.02 M Et2O/AcOH; B: 5% B, rt, 0.02 M 100:1 Et2O/AcOH.

While the use of ((R)-DTBM-Segphos)Pd(OTf)2 as a catalyst provided modest enantioselectivities when non-aryl-substituted enol ethers were employed, we were pleased to find that ((R)-Binaphane)-Pd(OH)2(OTf)2 (B) is a highly active and selective catalyst for the cyclization of a greater range of substrates (Table 1, entries 5–10). For example, cyclization of indolyl enol ether 9 catalyzed by 10 mol % of A cleanly afforded 10 but with only 7% ee, whereas the same reaction catalyzed by 5% B gave ketone 10 in 89% ee (entry 5). Moreover, whereas reactions with catalyst A usually required 10% loading and several hours to complete, reactions catalyzed by 5% B generally took place in minutes. Most notably,

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the Pd-catalyzed cyclizations to form amides 14 and 16 represent rare examples of enantioselective catalysis employing O-silyl ketene aminals.17 Catalyst B also allows for the enantioselective preparation of spiro-stereocenters (entries 6, 7, 9, and 10). For example, reaction of 2-silyloxy indole 17a afforded spiro-oxindole 18a in 83% yield and 91% ee (entry 9).

The utility of the Pd-catalyzed method for enantioselective formation of all carbon quaternary centers is illustrated in the total synthesis of (+)-laurebiphenyl (24), a rare example of a dimeric cyclolaurane-type sesquiterpene (Scheme 1). Originally isolated from Laurencia nidifica, laurebiphenyl (24) was recently shown to possess moderate cytotoxicity against a variety of cell lines.18

Ketone 20 was subjected to a reductive Heck cyclization followed by Baeyer–Villiger oxidation to afford lactone 21, which was converted to aldehyde 22 in three steps. Conversion of aldehyde 22 to the corresponding tosyl hydrazone, followed by diazo decomposition, gave the crude cyclopropane product, which was immediately brominated to give 23. Ullman coupling of aryl bromide 23 forged the biaryl bond, and subsequent demethylation furnished (+)-laurebiphenyl (24).21

In conclusion, the first enantioselective Pd-catalyzed addition of silyl enol ethers and silyl ketene aminals onto alkynes has been employed to include heteroatom and tetrasubstituted olefins. Pd-catalyzed cyclizations to form amides 19

References


12. In contrast to reported Pd-catalyzed enantioselective protonolysis of TMS-ene ethers,26 racemic ketone 26 was formed in 5% conversion from the hydrolysis of TBS-ene ether 25.

13. Dihydropyran 27, from which Pd enolate formation is unlikely, undergoes efficient cyclization under similar conditions to afford spiro-bicycle 28.

14. This proposed transition resembles that calculated for the Pt-catalyzed cyclization of enol ether with alkynes.26

15. Pd-catalyzed reactions of (Z)-1b, 1c, and 1d all required 6–8 h to reach completion. In contrast, (E)-1d reached 50% conversion after 8 h. See the Supporting Information for an X-ray structure of complex B.

16. The Supporting Information for an X-ray structure of complex B.


19. Ketone 19 was prepared in four steps from 2-ido-5-methylbenzoic acid (see Supporting Information).

20. The absolute stereochemistry of bromide 23 was determined by X-ray crystallography (see Supporting Information).