Alkoxy- and hydroxycyclization of enynes catalyzed by Pd(II) and Pt(II) catalysts*

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Abstract: The development of a novel reaction ideal in terms of atom economy was achieved. The scope of the reaction was evaluated in the presence of Pd and Pt catalysts. The first enantioselective Pt-promoted enyne carboalkoxycyclization was developed in up to 85% stereoselectivity. This ideal atom-economical reaction afforded the corresponding functionalized five-membered carbo- and heterocycles in good to excellent yields. The use of silver salts combined with \((R)-\text{Ph}-\text{BINEPINE}\), a monophosphane atropisomeric ligand, was found to be the best-suited combination for moderate to high enantioselectivities on carbonated and nitrogenated substrates.

Keywords: platinum; cycloisomerization; asymmetric catalysis; palladium; atom economy.

INTRODUCTION

Over the past few years, significant research has been directed toward the development of new methodologies for synthetic efficiency and atom-economy processes [1]. Among them, tandem reactions that allow the formation of several new bonds in a single step from readily available materials are of particular interest [2]. Moreover, the potential of transition-metal-catalyzed cyclization reactions of unsaturated substrates has been steadily demonstrated, as they give a direct way toward the synthesis of highly valuable precursors of natural products or biologically active compounds [3,4]. Palladium catalysis, in particular, has been the driver of many advances, and the seminal and elegant work of Trost has placed 1,6-enynes as excellent partners for cycloisomerization reactions. These unsaturated derivatives participate in cycloisomerization reactions leading to 1,4- or 1,3-dienes (eq. 1) [1,5]. When performing the well-known cycloisomerization reaction in organoaqueous medium in the presence of the system \(\text{PdCl}_2/\text{TPPTS}\) (TPPTS = trisodium salt of 3,3',3''-phosphanetriylbenzenesulfonic acid [6]), we discovered a novel reaction, which allows for the simultaneous and stereoselective formation of a C–C and a C–O bond from enynes (eq. 2) [7].

\[
\text{Z} = \begin{array}{c}
\text{R} \\
\text{MX}_n
\end{array} \rightarrow \begin{array}{c}
\text{Z} \\
\text{R}
\end{array} \text{or} \ \begin{array}{c}
\text{Z} \\
\text{R}
\end{array}
\]


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The hydroxyl- and alkoxycyclization reactions were then developed with various 1,6-enynes and other nucleophiles in the presence of Pd and Pt catalysts (eq. 3) [8]. The scope of this new reaction has also been assessed on some oxygenated enynes in view of its utilization in the synthesis of natural compounds of biological interest such as Podophyllum lignans where the accessibility of the aryltetralin fragment via this route has been already demonstrated [9]. The asymmetric version of alkoxy- or hydroxycyclization would provide a valuable synthetic tool for natural or biologically active product syntheses.

**Pd- VS. Pt-CATALYZED HYDROXY- AND METHOXYCYCLIZATION REACTIONS**

Aiming to examine the influence of allylic side chain, we prepared several oxygenated compounds 1a–d via Williamson reactions of the corresponding allylic alcohols with propargyl bromide (Scheme 1). The system PdCl₂/TPPTS was highly efficient for the synthesis of various alcohols 2a–c. We observed a high dependence of the electronic features as higher isolated yields were obtained for the propargylic enynes bearing electron-rich aromatic substrates. No reactivity of the nitro-substituted derivative 2d was observed. The functionalized alcohol 2c was a key intermediate in the synthesis of a precursor of podophyllotoxin [9]. The reactions were also conducted in MeOH at 65 °C, and the corresponding ethers were formed in 60–77 %. Once again, better results were obtained for electron-rich substituted enynes (Scheme 1).
The Pd-catalyzed mechanism of this highly atom-economical reaction was found to be similar to platinum catalysts [8d,e]. The reaction of propargyl cinnamyl ether 1a with PdCl$_2$ and TPPTS as the ligand in a 1,4-dioxane/D$_2$O mixture at 80 °C afforded selectively deuterated 2-d$_2$ (Scheme 2). We have also prepared the deuterated alkyne 1-d$_1$ by n-BuLi deprotonation followed by D$_2$O quenching. The reaction of 1-d$_1$ with PdCl$_2$ and TPPTS afforded the corresponding adduct 2-d$_1$ [8a].

A reasonable hypothesis for the mechanism is based on the Lewis acidic character of the Pd and Pt catalysts (Scheme 3). The reaction may be initiated by the formation of the π-alkynyl complex A through the complexation of the unsaturated triple bond to the metal catalyst. The π-alkynyl complex A would then evolve to give a cyclopropyl metal carbene complex C, which would be opened by an external nucleophile such as methanol or water and would give rise to the vinylmetallate B. Further protonolysis of this intermediate would form the desired cycloadduct and would regenerate the catalyst. This mechanism accounts for the deuteration pattern found in the reactions of 1 and 1-d$_1$. The Pd carbene has not been isolated: therefore, the concerted addition of nucleophiles on intermediate A and formation of the C–C bond is possible too.
The carbonated and nitrogenated 1,6-enynes behaved differently in the presence of the PdCl₂/TPPTS system (Scheme 4). The reaction of 4a led to a mixture of the desired alcohol 5a and the diene 6a, resulting from the classic cycloisomerization reaction followed by an isomerization of the exomethylene double bond. The same trend was observed when the reaction was conducted in MeOH, despite the fact that compounds 7a and 6a were this time inseparable by chromatography on silica gel. This lack of selectivity for the system was also observed in the case of the dimethylated substrate 4b or the nitrogenated derivative 4c, which were transformed to the corresponding dienes 6b and 6c in 65–72 % yield.

The efficiency of the system could be switched to the desired alkoxycyclization reaction in the presence of the PtCl₂/TPPTS system. No traces of the dienes were detected when the ligand TPPTS was added to the reaction mixture. Various alcohols and methoxyethers were, therefore, prepared in good to excellent isolated yield (Scheme 5).

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We then turned our attention to platinum chemistry for the asymmetric version and investigated the functionalization of enyne 1a with platinum in the presence of several chiral phosphane ligands (Table 1) [10]. Preliminary tests were performed in dioxane/water 6:1 using 10 mol % Pt catalyst and 15 mol % of bidentate or 30 mol % of mono-dentate phosphine. Even if under these conditions long reaction times are required for the alcohol 2a to be obtained in high yield, the accelerating effect induced by the phosphorus ligand is quite evident from the fact that only traces of 2a can be detected when the reaction is run in the absence of any phosphane (entry 1). The stereoselectivities obtained in the first batch of experiments were, however, disappointingly low [11]. The use of the well-known atropisomeric ligands (R)-BINAP [12] or (R)-MeO-BIPHEP [13] afforded the alcohol 2a in respectively 0 and 5 % enantiomeric excess (entries 2 and 3). Other ligands such as (–)-DIOP [14], (R,R)-DIPAMP [15] or (S,S)-Et-FerroTANE [16] or (S,S)-MeDuPHOS [17] (entries 4–6) did not give better results. Interestingly, two-digit values were recorded only in three cases with (R)-Ph-BINEPINE [(R)-phenyl-binaphtophoshepine] [18] (entry 7), with (R,S)-JOSIPHOS [19] (entry 8), and with (+)-BIPNOR [20], a ligand with stereogenic phosphorus centers (entry 9). The last one was the best chiral inducer of this set, but the enantiomeric excess (ee) did not exceed 25 %. Further improvements were attempted using other chiral ligands, in different cosolvents (acetone, toluene, ethylene glycol, dimethylformamide, dimethylacetamide, dimethylsulfoxide, 1,2-dichloroethane…) at various temperature without success [11].
Table 1 Ligand and silver salt effect on PtCl$_2$-promoted enyne hydroxycyclization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Ag salts (0.25 equiv)</th>
<th>Time [d]</th>
<th>Yield [%]</th>
<th>ee [%]</th>
<th>ee [%]$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-BINAP</td>
<td>/</td>
<td>5</td>
<td>100</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(R)-MeO-BIPHEP</td>
<td>/</td>
<td>4.5</td>
<td>100</td>
<td>5 (+)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(--)-DIOP</td>
<td>/</td>
<td>5</td>
<td>72</td>
<td>8 (+)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(R,R)-DIPAMP</td>
<td>/</td>
<td>5</td>
<td>70</td>
<td>5 (–)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(S,S)-Et-FerroTANE</td>
<td>/</td>
<td>5</td>
<td>97</td>
<td>6 (+)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(S,S)-MeDuPHOS</td>
<td>/</td>
<td>5</td>
<td>98</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(R)-Ph-BINEPINE</td>
<td>/</td>
<td>6.5</td>
<td>91</td>
<td>20 (–)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(R,S)-JOSIPHOS</td>
<td>/</td>
<td>4</td>
<td>91</td>
<td>13 (–)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(+)-BIPNOR</td>
<td>/</td>
<td>3</td>
<td>79</td>
<td>25 (–)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>(R,S)-JOSIPHOS</td>
<td>AgPF$_6$</td>
<td>4</td>
<td>58</td>
<td>35 (–)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>(R,S)-JOSIPHOS</td>
<td>AgBF$_4$</td>
<td>2</td>
<td>65</td>
<td>38 (–)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>(R,S)-JOSIPHOS</td>
<td>AgSbF$_6$</td>
<td>2.5</td>
<td>62</td>
<td>41 (–)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>(+)-BIPNOR</td>
<td>AgSbF$_6$</td>
<td>3</td>
<td>53</td>
<td>33 (–)</td>
<td></td>
</tr>
<tr>
<td>14$^b$</td>
<td>(R)-Ph-BINEPINE</td>
<td>AgSbF$_6$</td>
<td>4</td>
<td>94</td>
<td>85 (+)</td>
<td></td>
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<tr>
<td>15$^c$</td>
<td>(R)-Ph-BINEPINE</td>
<td>AgSbF$_6$</td>
<td>4</td>
<td>60$^d$</td>
<td>85 (+)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ The ee value was determined by HPLC [Chiralcel OD-H, hexane/propan-2-ol (95:5)].

$^b$5 mol % PtCl$_2$, 60 °C.

$^c$5 mol % PtCl$_2$, aqueous acetone, 60 °C.

$^d$Conversion.

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As it was our feeling that the catalytic performance of our Pt-derivative should have gained from an increased electrophilicity at the metal center (Scheme 3), we undertook to remove the chloride ligands from the coordination sphere of the Pt-phosphane complexes. The activation of Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1). With the Pt(II) complexes with silver salts had previously been used with high success for asymmetric Diels–Alder reactions, Friedel–Crafts acylations, and Bayer-Villiger oxidations [21]. To this purpose, various silver salts with poorly coordinating counterions were added to our catalytic system (Table 1).
Table 2 PtCl₂-promoted enyne hydroxy- and alkoxycyclizations.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enyne</th>
<th>Time [d]</th>
<th>Yield [%]</th>
<th>Product</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>4</td>
<td>94</td>
<td>MeO₂C</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ph</td>
<td>(+)-5a</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>3.5</td>
<td>87</td>
<td>MeO₂C</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OH</td>
<td>(+)-5b</td>
</tr>
<tr>
<td>3</td>
<td>4b</td>
<td>5.5</td>
<td>100</td>
<td>MeO₂C</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OH</td>
<td>(+)-7b</td>
</tr>
<tr>
<td>4</td>
<td>4c</td>
<td>6.5</td>
<td>57</td>
<td>TsN</td>
<td>56</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OH</td>
<td>(+)-5c</td>
</tr>
<tr>
<td>5</td>
<td>4d</td>
<td>7</td>
<td>86</td>
<td>TsN</td>
<td>84</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Ph</td>
<td>(+)-7d</td>
</tr>
</tbody>
</table>

Z = CO₂Me₂, R¹ = Ph, R² = H, 4a
Z = CO₂Me₂, R¹ = R² = Me, 4b
Z = NTs, R¹ = R² = Me, 4c
Z = NTs, R¹ = Ph, R² = H, 4d

The ee value was determined by HPLC (Chiralcel OD-H or Chiralpak AS-H).

Reaction at 80 °C in screw-capped tube.

This asymmetric reaction is still highly challenging as no general metal/chiral ligand association is available. The group of Echavarren showed that Au catalysts may also be suitable for an asymmetric induction at room temperature or 60 °C [23a] and observed that AgSbF₆ salts, as in the platinum case, were highly beneficial in the AuCl/(R)-TolBINAP system to induce promising ee's. A unique example based on the methoxycyclization of a substituted sulfonated substrate was described so far in an excellent 94 % ee. Our ongoing studies on the Au-catalyzed hydroxy- and alkoxycyclization reactions are quite promising too, as the alcohol 2a was prepared at room temperature in the presence of AuCl₃/AgSbF₆ associated with an analog of (R)-MeO-BIPHEP ligand in 78 % ee [24]. Moreover, recent years witnessed tremendous growth in the number of Au-catalyzed reactions for carbon–carbon and carbon-heteroatom bond formations [23,25]. In pursuit of investigation on atom-economical metal-catalyzed cycloisomerization reactions [8a,10,26], we recently showed that 1,6-enynes bearing alcohols 8a–c might undergo clean Au-catalyzed cyclization under extremely mild conditions [27]. No alkoxy-
cyclization or reactivity of the allylic side chain was observed (Scheme 6), as the bicyclic ketals 9a–c were isolated in high yields. This demonstrates the opened reactivity of all 1,6-enynes and, therefore, the difficulty to discover a general and universal system.

![Scheme 6](image)

In conclusion, we have developed the first enantioselective Pt-promoted enyne alkoxycyclization in up to 85% stereoselectivity. This ideal atom-economical reaction leads to the corresponding functionalized five-membered carbo- and heterocycles in good to excellent yields. The use of silver salts combined with (R)-Ph-BINEPINE, a monophosphane atropisomeric ligand, is by now the best-suited combination for moderate to high enantioselectivities on carbonated and nitrogenated substrates, and the first C–C application with this ligand. Further improvements are still needed for this reaction. The higher catalyst activity of Au catalysts would probably allow further applications toward the synthesis of a broader range of substrates and other structurally original polycyclic derivatives.

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REFERENCES AND NOTES


