Enantioselective palladium catalyzed allylic substitution of acyloxy pyrrolinones by alcohols

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Chiral non-racemic acyloxy pyrrolinones are converted into alkoxypyrrrolinones with retention of configuration by a palladium catalyzed allylic substitution; this comprises a key step in a short chemo-enzymatic route to acyliminium ion precursors.

Enantiothermically pure alkoxypyrrrolinones have been shown to be facile building blocks for a diversity of stereoselective syntheses involving Diels–Alder cycloadditions, 1,3-dipolar reactions, conjugate additions and acyliminium ion intermediates.

In particular application in the asymmetric synthesis of alkaloids, based on the synthesis of gelsemine.3 However, the stereoselective synthesis from hydroxypyrrolinones is unknown. We now report that the enzymatic method can be combined with a palladium catalyzed allylic substitution to generate optically active alkoxypyrrrolinones, which can readily be transformed to acyliminium ion precursors.

When a solution of (R)–(−)–2a (R1 = Me) in PrOH is stirred at room temperature for 7 h in the presence of 0.5 mol% Pd(PPh3)2, 5-isopropoxy derivative (R)–(−)–3a (R2 = Pr) is obtained in 99% yield with 95% ee (Table 1, entry 1).† The optically active acyloxy pyrrolinone is thus converted into optically active alkoxypyrrrolinone, via Pd catalyzed allylic substitution with PrOH as the nucleophile, with nearly complete retention of configuration. An allyl palladium intermediate 5 (Scheme 2) is presumably involved. When the reaction was performed in the presence of Pd(OAc)2 (5 mol%) and PPh3 (20 mol%) the reaction rate was appreciably lower (90% conversion after 3 d at 20 °C, > 95% ee). An essential feature is that the nucleophile PrOH is also used as a solvent (roughly 13 μl). In the presence of an additional solvent like THF (PrOH ca. 10−1 μl) no product was obtained after 18 h at room temp. When the allylic substitution was performed at higher temperatures, the reaction was very fast, but the enantioselectivity decreased in the course of the reaction (Table 2). This depletion of ee might be due either to loss of stereochemical integrity of the allyl palladium intermediate or partial racemization of acyloxy pyrrolinone 1 or alkoxypyrrrolinone 3.

The substitution using Pd(PPh3)4 can easily be performed on a gram scale with equal efficiency (99%) and selectivity (94% ee). A lower rate was observed in the presence of additional PPh3, probably because the equilibrium for the oxidative addition of the palladium complex is shifted to the left (Scheme 2). The effect on the enantioselectivity is negligible.

When EtOH was used instead of PrOH as a nucleophile the reaction was much faster, probably because of the higher rate of the nucleophilic substitution. In this case the reaction was much faster, probably because of the lower rate of the nucleophilic substitution.

Table 1 Pd catalyzed nucleophilic substitution of (−)-2 (> 99% ee)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>T°C</th>
<th>Catalyst</th>
<th>t/h</th>
<th>Conversion (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Pr</td>
<td>25</td>
<td>Pd(PPh3)4 (0.5%)</td>
<td>7</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Pr</td>
<td>25</td>
<td>Pd(PPh3)4 (0.5%)</td>
<td>5.5</td>
<td>72</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Et</td>
<td>18</td>
<td>Pd(PPh3)4 (5%)</td>
<td>1</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>4a</td>
<td>Allyl</td>
<td>Pr</td>
<td>20</td>
<td>Pd(OAc)2 + PPh3 (5%)</td>
<td>63</td>
<td>100</td>
<td>83</td>
</tr>
<tr>
<td>5a</td>
<td>C6H5</td>
<td>Pr</td>
<td>20</td>
<td>Pd(OAc)2 + PPh3 (10%)</td>
<td>63</td>
<td>40</td>
<td>84</td>
</tr>
<tr>
<td>6a</td>
<td>Bu</td>
<td>Pr</td>
<td>20</td>
<td>Pd(OAc)2 + PPh3 (5%)</td>
<td>48</td>
<td>29</td>
<td>95</td>
</tr>
<tr>
<td>7a</td>
<td>Ph</td>
<td>Pr</td>
<td>20</td>
<td>Pd(OAc)2 + PPh3 (5%)</td>
<td>18</td>
<td>33</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>Pr</td>
<td>25</td>
<td>Pd(MeCN)2Cl2 + PPh3 (5%)</td>
<td>21</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>Pr</td>
<td>25</td>
<td>Pd(MeCN)2Cl2 (5%)</td>
<td>3</td>
<td>99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>Et</td>
<td>25</td>
<td>Pd(MeCN)2Cl2 (5%)</td>
<td>3</td>
<td>94</td>
<td>99</td>
</tr>
</tbody>
</table>

* The conversion was determined by GC. † The ee of 3 was determined by chiral GC; > 99% indicates that the other enantiomer could not be detected. ‡ (+)-2 (> 99% ee) was used as starting material. § The ee of starting material 2 is unknown.

Chem. Commun., 1998 655
With this catalyst the reaction is fast, quantitative and proceeds with complete stereoselectivity (Table 1, entries 9, 10). On 0.5 g scale with 5 mol% PdII catalyst, 96% yield of \( \text{R}^2\text{OH} \) was obtained. Palladium(II) complexes such as Pd(OAc) \(_2\) were also tested without PPh \(_3\). In this case the reaction did not proceed, but surprisingly when LiCl was added 22% conversion was found after 23 h (42% ee). A mixture of Pd(MeCN)\(_2\)Cl \(_2\) (5 mol%) and PPh \(_3\) (20 mol%) was also used, but although this reaction was faster than with Pd(OAc) \(_2\) and PPh \(_3\) (100% conversion in 21 h), the selectivity was not improved (Table 1, entry 8). A remarkable improvement was achieved when Pd(MeCN)\(_2\)Cl \(_2\) (5 mol%) was used without PPh \(_3\). With this catalyst the reaction is fast, quantitative and proceeds with complete stereoselectivity (Table 1, entries 9, 10). On 0.5 g scale with 5 mol% PdII catalyst, 96% yield of (S)-3a (\( \text{R}^2 = \text{Pr} \), 99% ee) was obtained.

Palladium catalyzed nucleophilic substitution reactions of allylic substrates have found widespread use in organic synthesis and although a variety of nucleophiles has been employed emphasis has been on carbon–carbon bond formation. On the contrary the use of alcohols as nucleophiles in Pd catalyzed allylic substitution is rare, because alcohols are generally considered poor nucleophiles. The few reported examples are often either intramolecular substitutions or make use of derivatives of alcohols. The quantitative and stereoselective Pd catalyzed allylic substitution of 5-acyloxypyrrolinones by alcohols provides a key step in the new catalytic enantioselective, lipase and palladium based methodology for the preparation of enantiopure alkoxyxypyrrolinones.

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**Notes and References**

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‡ Ee’s were determined with a Hewlett Packard 5890 GC, equipped with a capillary column coated with CP cyclohexedrin B-2,3,6-M-19 (for 3a, \( \text{R} = \text{Pr} \)) or with a 30 m \( \times 0.25 \) mm capillary column (ASTEC Q0409-15) coated with B-TA (\( \beta \)-cyclohexedrin, trifluoroacetyl) (for 3b, \( \text{R} = \text{Et} \)).

Selected data for 3a: \( \delta^o_{\text{H}} (\text{CDCl} \text{3}) -149 (\text{s, CHCl} \text{3}); \delta^o_{\text{H}} (\text{CDCl} \text{3}) 1.15 (\text{d, } 3 \text{ H, J} 2.0); 6.15 (\text{d, } 1 \text{ H, J} 2.0); 6.97 (\text{dd, } 1 \text{ H, J} 6.1); 6.97 (\text{dd, } 1 \text{ H, J} 2.0, 6.1); \delta^o_{\text{H}} (\text{CDCl} \text{3}) 22.8 (\text{q}, 23.0 (\text{q}), 24.9 (\text{q}), 73.0 (\text{d}), 86.3 (\text{d}), 126.8 (\text{d}), 147.7 (\text{d}), 168.7 (\text{s}), 170.0 (\text{s})).


6 A. D. Cuiper, R. M. Kellogg and B. L. Feringa, unpublished work.


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