A Catalytic Asymmetric Chlorocyclization of Phenol Compounds
Meghan Richardson, Nastaran Salehi Marzijarani, Arvind Jaganathan, Babak Borhan
Department of Chemistry, Michigan State University, East Lansing, MI 48824

Abstract
The purpose of this experiment is to find the proper conditions of a chlorocyclization of a phenol derivative to create a substrate that will be used in total synthesis of Napyradiomycin A1 (Fig. 1). To optimize the synthesis of the compound, temperature, reaction time, chlorine source, catalyst, solvent, and R-group on the phenol derivative were all modified to select for both high ee percentage and high yield.

Introduction
- Enantioselective halocyclizations are a relatively new field of research that have been becoming more important recently.
- Optimizing the synthesis of the compound with high yields and high percent ee will allow it to be used as a substrate in total synthesis of natural products like Napyradiomycin A1 in an asymmetric fashion.
- Napyradiomycin A1 has antibacterial properties and some anticancer properties.
- Enantioselective total synthesis of Napyradiomycin A1 has already been achieved, but use of the phenol derivative as a substrate will allow the synthesis to be approached in an entirely new manner.

Table 1: Results of Chlorocyclization of substrate A

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cl source (eq)</th>
<th>Cat (eq)</th>
<th>Solvent (M)</th>
<th>Temp</th>
<th>time</th>
<th>Yield</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCDMH (1.1 eq)</td>
<td>(DHQD)_2PHAL (0.1 eq)</td>
<td>TFE:DCM (1.1) (0.025 M)</td>
<td>-30 °C</td>
<td>30 min</td>
<td>98%</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>DCDP (1.2 eq)</td>
<td>(DHQD)_2PHAL (0.1 eq)</td>
<td>TFE (0.025 M)</td>
<td>-30 °C</td>
<td>120 min</td>
<td>35%</td>
<td>64%</td>
</tr>
<tr>
<td>3</td>
<td>DCDMH* (1.2 eq)</td>
<td>(DHQD)_2PHAL (0.1 eq)</td>
<td>TFE (0.025 M)</td>
<td>-30 °C</td>
<td>30 min</td>
<td>82%</td>
<td>64%</td>
</tr>
<tr>
<td>4</td>
<td>DCDMH (1.1 eq)</td>
<td>(DHQD)_2PHAL (0.1 eq)</td>
<td>TFE (0.025 M)</td>
<td>-30 °C</td>
<td>110 min</td>
<td>18%</td>
<td>66%</td>
</tr>
<tr>
<td>5</td>
<td>Dich.T (1.1 eq)</td>
<td>(DHQD)_2PHAL (0.1 eq)</td>
<td>TFE (0.025 M)</td>
<td>-30 °C</td>
<td>30 min</td>
<td>68%</td>
<td>69%</td>
</tr>
<tr>
<td>6</td>
<td>Dich.T (1.1 eq)</td>
<td>(DHQD)_2PHAL (0.1 eq)</td>
<td>TFE (0.025 M)</td>
<td>-30 °C</td>
<td>45 min</td>
<td>89%</td>
<td>70%</td>
</tr>
</tbody>
</table>

* Regular DCDMH from the bottle; all other DCDMH was recrystallized

Results & Discussion
- Using a 1:1 mixture of TFE and DCM as a solvent has a much higher yield than TFE alone, but a much lower ee%.
- When concentration of (DHQD)_2PHAL is lowered to ten mole percent from 20 mole percent, ee % increases.
- The smaller the R’-group on the chlorine source, the higher the ee %; lower bulk decreases steric hindrance.

Conclusions
- 1.2 eq DCH, 0.1 eq (DHQD)_2PHAL, and 0.025 TFE give the best results.
- 70% ee is not perfect, but it indicates that enantioselectivity is possible; the relatively high % ee indicates good interaction between catalyst and substrate, and suggests promising future results.
- For further studies, Dichloramine T and DCH should be considered as a chlorine sources, different phenol derivatives should be pursued, and reaction times should be more closely monitored.

Citations