Asymmetrical Henry reaction using copper (II)/2-oxazoline complex.

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INTRODUCTION

The Henry reaction or nitro aldol reaction is one of the most versatile methods to obtain a new C-C bond. The asymmetric version of this reaction has been used to generate a variety of useful building blocks\[1\] for organic synthesis. The catalytic asymmetric Henry reaction uses chiral ligands as a source of asymmetry and amino alcohols have found applications as catalysts in asymmetric reactions\[3-5\]. Among several asymmetric ligands, several 2-oxazolines derivatives have been used as metal ligands in this type of reaction\[3-5\]. In this context, the asymmetrical catalyst copper/2-oxazoline chiral derivative was studied using a new class of chiral 2-oxazoline compounds.

RESULTS AND DISCUSSION

After some optimization studies compounds 1, 3, and 4 were obtained. These 2-oxazoline compounds were mixed with copper (II) acetate and submitted to EPR analysis in frozen ethanol. Scheme 1 outlines the synthesis of 2-oxazoline ether derivatives:

![Scheme 1. Synthesis of 2-oxazolines ligands.](image)

Compound 1 shows a Cu(II) spectrum, characteristic of a tetragonal elongated geometry, additionally modulated by a superhyperfine signal originated from two chemically equivalent nitrogen nuclei. These observations were further confirmed upon spectral simulation. Moreover, the ratio between the hyperfine parallel splitting and the parallel g-factor points to a 2N2O coordination scheme.\[6\] Compound 3 has no signal in EPR analysis, indicating that no complex was formed, while for compound 4 EPR analyses shows a spectrum of two species in equilibrium, with a ratio of 47% to 53%.

To optimize the Henry reaction, a solvent screening was performed using dichloromethane, water, isopropanol, ethanol and THF. The best solubility result was obtained using ethanol and THF.

The nitro aldol reactions were also performed without any ligand, to verify its influence in the reaction kinetics. In THF without ligand the yield was significantly lower furnishing 15%. Using ethanol yields 65% of nitro aldol product. Having selected the best solvent, the asymmetrical Henry reaction was performed using 1 as a ligand. The reaction conditions are shown in the Table 1 below.

![Scheme 2. Asymmetrical Henry reaction with [Cu(OAc)_2]/1.](image)

Table 1. Nitro-aldol reaction using compound 1 as ligand

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield</th>
<th>e.e.</th>
<th>% cat.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>120</td>
<td>81.4%</td>
<td>26.8 (R)</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>120</td>
<td>78.5%</td>
<td>27.3 (R)</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>120</td>
<td>71.4%</td>
<td>22.7 (R)</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>120</td>
<td>81.2%</td>
<td>26.1 (R)</td>
<td>30%</td>
</tr>
<tr>
<td>5</td>
<td>EtOH</td>
<td>120</td>
<td>98%</td>
<td>13.3 (S)</td>
<td>5%</td>
</tr>
<tr>
<td>6</td>
<td>EtOH</td>
<td>120</td>
<td>97.1%</td>
<td>13.7 (S)</td>
<td>10%</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
<td>120</td>
<td>97.3%</td>
<td>15.9 (S)</td>
<td>20%</td>
</tr>
<tr>
<td>8</td>
<td>EtOH</td>
<td>120</td>
<td>91.3%</td>
<td>12.3 (S)</td>
<td>30%</td>
</tr>
</tbody>
</table>

a The results (only 120 hours) are shown in table 1. mol (%) of catalyst.
b The enantiomeric excess was determined using a chiral HPLC analysis.

CONCLUSION

Using copper (II)/1 as a catalyst and ethanol as solvent asymmetrical nitro aldol reaction was performed in good yields although in lower enantiomeric excess. However, changing the solvent promoted an unexpected inversion\[7\] in the configuration of product 6. More experimental data are needed to elucidate this intriguing effect and to increase the enantiomeric excess.

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REFERENCES