Enantioselective Michael addition and Henry reaction catalyzed by a new heterobimetallic aluminum-lithium complex derived from (+)-2,3-O-isoproplidin e threitol

Ch V Rajasekhar & H Maheswaran

Indian Institute of Chemical Technology,
Hyderabad 500 007, India

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A heterobimetallic catalyst obtained by the reaction of LiAlH₄ with (+)-2,3-O-isoproplidin e threitol promotes asymmetric Michael reaction (between malonic esters, and thiophenols to cyclic enones) as well as Henry reaction (between aliphatic and aromatic aldehydes and nitromethane) with excellent yields albeit low enantiomeric excesses.

The synthesis of optically active chiral compounds, which play an important role in the development of medicines, is one of the most fascinating aspects of modern organic synthesis. Of the methods that are available for preparing such compounds, catalytic asymmetric synthesis involving main-group organometallic complexes has received much attention in recent years. This is clearly seen from the discovery of a heterobimetallic multifunctional complexes bringing about highly enantioselective Michael addition, and Henry (nitroaldol) reactions reported by Shibasaki et al. The most important aspect of these catalytic systems is the use of axially chiral 2,2'-binaphthols as chiral auxiliary in effecting enantioselective organic transformation.

It is of interest to evaluate the utility of heterobimetallic multifunctional catalysts containing non-axially chiral diols in these reactions. This is important for two reasons. First reason is that these chiral diols derived ligands (DIOP or TADDOL for example) has already shown to afford high enantiomeric excesses for a variety of organic transformations. Another reason is that they are readily accessible from a large chiral pool of natural products such as (+)-tartaric acid, and thus less expensive in comparison to 2,2'-binaphthols. In this note, we report the synthesis of new aluminum-lithium-heterobimetallic complex containing natural tartaric acid derived (+)-2,3-O-isoproplidin e threitol for use in enantioselective Michael addition and Henry reactions with excellent yields albeit low enantiomeric excesses.

Experimental

All chemicals used were of analytical grade. (+)-2,3-O-isoproplidin e threitol was synthesized in two steps from natural (+)-tartaric acid following the reported procedure. Freshly distilled solvents were used in all the reactions.

The new heterobimetallic catalyst was synthesized in three steps from readily available natural (+)-tartaric acid as shown above. (+)-2,3-O-isoproplidin e threitol reacts readily with LiAlH₄ (0.5 eq) in THF to give a heterobimetallic complex in situ with the evolution of hydrogen. This solution was used as catalyst for enantioselective Michael and Henry reactions. The enantiomeric excess of the products were calculated with the specific rotation values available in the literature.

Typical reaction procedure

To a solution of LiAlH₄ (0.19 g, 5.0 mmol) in THF (5 mL) was added a solution of (+)-2,3-O-isoproplidin e threitol (20 mL, 10 mmol, 0.5 M in THF) at room temperature (RT). After 1 h of stirring at RT, this solution of the catalyst I (0.2 M in THF) was filtered, and directly used for both Michael addition and Henry reactions.

Michael reaction—To a stirred solution of the catalyst I (1.0 mmol) in THF (5 mL) was added either cyclohexone (10.0 mmol) or cyclopentenone (10.0 mmol), and either diethyl malonate (1.6 g, 10.0 mmol) or p-chlorothiophenol (1.4 g, 10.0 mmol) at RT. After 10 h of stirring at RT, the reaction mixture was treated with 1 N HCl (2.0 mL), and extracted with EtOAc (3×20 mL). The combined organic extracts were dried using Na₂SO₄ and concentrated to give an oily residue. Purification by flash chromatography (SiO₂, 60-120), 5% EtOAc/hexanes) gave the Michael adducts listed in Table 1 (entries 1-4) in good yields. The product was characterized by ¹H-NMR spectroscopy.

Henry reaction—To a stirred solution of the catalyst I (1.0 mmol) in THF (5 mL) was successfully...
Table I—Michael addition of malonic esters, thiophenols to cyclic enones in the presence of heterobimetallic catalyst.

<table>
<thead>
<tr>
<th>Acceptor</th>
<th>Donor</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield(%)</th>
<th>(\delta_{D}^{25})</th>
<th>ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>![Image 1]</td>
<td>![Image 2]</td>
<td>8</td>
<td>![Image 3]</td>
<td>95 (67)</td>
<td>+3.5 (c=1, CHCl(_3))</td>
<td>10</td>
</tr>
<tr>
<td>![Image 4]</td>
<td>![Image 5]</td>
<td>8</td>
<td>![Image 6]</td>
<td>95 (60)</td>
<td>+1.5 (c=2.5, CHCl(_3))</td>
<td>36</td>
</tr>
<tr>
<td>![Image 7]</td>
<td>![Image 8]</td>
<td>7</td>
<td>![Image 9]</td>
<td>98 (54)</td>
<td>+0.3 (c=1, CHCl(_3))</td>
<td>&lt;1</td>
</tr>
<tr>
<td>![Image 10]</td>
<td>![Image 11]</td>
<td>7</td>
<td>![Image 12]</td>
<td>98 (87)</td>
<td>+0.4 (c=1, CHCl(_3))</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

\(\text{Yield}\) determined by \(\text{\(^1\)H NMR spectroscopy (200 MHz, CDCl}_3\)); isolated yields are given in parenthesis.

\(\text{ee}\) 's: Based on the specific rotation values

Absolute configuration is R

Add corresponding aldehydes (10.0 mmol), and nitromethane (6.1 g, 100 mmol) at RT. After 10 h of stirring at RT, the reaction mixture was treated with 1 \(N\) HCl (2.0 mL), and extracted with EtOAc (3x20 mL). The combined organic extracts were dried using \(\text{Na}_2\text{SO}_4\), and concentrated to give an oily residue. Purification by flash chromatography (SiO\(_2\), 5% EtOAc/Hexanes) gave the nitroaldol products listed in Table 2 (entries 1-4) in good yields. The product was characterized by \(\text{\(^1\)H-NMR spectroscopy.}\)
Table 2—Henry reaction (nitro aldo reaction) of nitromethane to both aliphatic and aromatic aldehydes in the presence of heterobimetallic catalyst.

<table>
<thead>
<tr>
<th>Acceptor</th>
<th>Donor</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>( [\alpha]_{D}^{25} )</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH₂CH₂CHO</td>
<td>CH₃NO₂</td>
<td>8</td>
<td>![Product Image]</td>
<td>(92)70</td>
<td>+1.23</td>
<td>(c=1, CHCl₃)</td>
</tr>
<tr>
<td>PhCHO</td>
<td>CH₃NO₂</td>
<td>8</td>
<td>![Product Image]</td>
<td>99(81)</td>
<td>+1.5</td>
<td>(c=1, CHCl₃)</td>
</tr>
<tr>
<td>CH₃CH₂CHO</td>
<td>CH₃NO₂</td>
<td>7</td>
<td>![Product Image]</td>
<td>(90)72</td>
<td>+3.02</td>
<td>(c=1, CHCl₃)</td>
</tr>
<tr>
<td>p-Me(C₆H₄)CHO</td>
<td></td>
<td>7</td>
<td>![Product Image]</td>
<td>98(87)</td>
<td>+2.0</td>
<td>(c=1, CHCl₃)</td>
</tr>
</tbody>
</table>

\(^{1}\) Determined by \(^{1}H\) NMR spectroscopy (200 MHz, CDCl₃); isolated yields are given in parenthesis.

**Results and discussion**

The results shown in Tables 1 and 2 reveal that yields are almost quantitative and the reaction time for the formation of Michael adducts and nitroaldol is much less in comparison to those involving axially chiral 2,2'-binaphthol systems reported by Shibasaki *et al.* However, the observed low specific rotation values for these compounds clearly indicate that only a little asymmetric induction has occurred. This is particularly the case with Henry reaction wherein very low specific rotation values are observed. Another tartaric acid derived chiral diol ligand (3,4-bis(hydroxy)pyrrolidine) also results, it gave very low ee's for Michael addition reactions.

These results are consistent with the earlier observation of Shibasaki *et al.* that there could be an undesired exchange between the asymmetric ligand for (acidic) nitromethane occurring during the course of the reaction so as to produce an achiral nitronate, resulting in only a low asymmetric induction. More acidic chiral diols are required to suppress this ligand exchange. Also, our results clearly demonstrate that heterobimetallic bifunctional catalysts derived from highly acidic 2,2'-binaphthol is much more superior than those containing (+)-2,3-O-isoproylidine threitol and 3,4-bis(hydroxy)pyrrolidine.

In conclusion, we have developed a new heterobimetallic catalyst for asymmetric Michael addition and Henry reactions. This catalyst gives excellent yields albeit low enantiomeric excess. Use of more acidic non-axially chiral diols containing (+)-2,3-O-isoproylidine threitol structural unit may be helpful in order to obtain high enantiomeric excesses. The structural modification of containing (+)-2,3-O-isoproylidine threitol is currently under progress in order to increase both the acidity of the chiral diols and to improve the enantiomeric excesses of Michael adducts and nitroaldol.

**Acknowledgement**

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References


