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A catalytic and iterative route to β-substituted esters via highly enantioselective conjugate addition of dimethylzinc to unsaturated malonates†

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Using the chiral phosphoramidite ligand (S,R,R)-L1 in the conjugate addition of dimethylzinc to acyclic unsaturated malonates, enantioselectivities of up to 98% have been obtained for the first time. An iterative and stereoconvergent route to 3,5-dimethyl esters that takes advantage of this asymmetric catalysis has been developed.

Among several methods for catalytic asymmetric carbon–carbon bond formation, the copper-catalyzed conjugate addition of organozinc reagents to unsaturated carbonyl compounds is a widely used key transformation. To date, efficient protocols for the conversion of both cyclic and acyclic enones, as well as nitroalkenes, have been developed featuring excellent stereocontrol. High enantioselective additions have also been reported for lactones. On the other hand, similar conjugate addition to acyclic unsaturated esters remains a major challenge, in particular, realizing the synthetic potential of optically active β-substituted esters as chiral building blocks in organic synthesis. In earlier studies, only moderate stereocontrol was achieved in the 1,4-addition of diethylzinc to nitro-substituted unsaturated esters and malonates. Recently, Hird and Hoveyda described the addition of diphosphine ligands to cyclic and acyclic unsaturated esters featuring excellent enantioselectivity applying peptide-based phosphine ligands. We wish to report the development of a highly enantioselective, copper-catalyzed 1,4-addition to acyclic esters employing monodentate phosphoramidite ligands. Furthermore, an iterative and stereodivergent route to 3,5-dimethyl esters is presented.

Since simple acyclic unsaturated esters are not reactive in the conjugate addition of diethylzincs, we focused on unsaturated malonates 1 (Scheme 1). The products 2 can easily be converted into the monoesters 3 by dealkoxycarbonylation. In view of the prominent role of the resulting structural motif in numerous natural products, the enantioselective introduction of a methyl substituent using Me2Zn is considered the most important goal.

Diethyl isopentylidene malonate (1a) was chosen as a model substrate and a variety of phosphoramidite ligands were screened using 2 mol% of catalyst (Cu : L ratio 1 : 2 ; Scheme 2). The best results were obtained with ligands L1, L2 and L3. Full conversion was reached within 1–2 h, producing ees of up to 94% (Table 1). These three ligands share the same amine part, but differ in the diol part. Converting the configuration of the major product, (S,R,R)-2a, was determined by comparison of the optical rotation with literature data (see ESI†). R-Enantiomer of 2a obtained.

To further optimize the reaction conditions, L1 and L2 were tested in different solvents (Table 2). In toluene, an ee of 95% was obtained for both ligands. This could be improved to an excellent value of 97% ee by using heptane as the solvent. Diethyl ether and

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
1a & \quad 1a \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Et} & \quad \text{Et} \\
2a & \quad 2a \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
3a & \quad 3a \\
\end{align*}
\]

\[
\begin{align*}
\text{L1} & \quad \text{L1} \\
\text{L2} & \quad \text{L2} \\
\text{L3} & \quad \text{L3} \\
\end{align*}
\]

\[
\begin{align*}
\text{L4} & \quad \text{L4} \\
\text{L5} & \quad \text{L5} \\
\text{L6} & \quad \text{L6} \\
\text{L7} & \quad \text{L7} \\
\text{L8} & \quad \text{L8} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{S} & \quad \text{S} \\
\text{S} & \quad \text{S} \\
\text{S} & \quad \text{S} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{Et} & \quad \text{Et} \\
\text{Et} & \quad \text{Et} \\
\text{Et} & \quad \text{Et} \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

Scheme 2 Conjugate addition of dimethylzinc to unsaturated malonic ester 1a.

Table 1 Effect of the ligand in asymmetric conjugate addition of Me2Zn to 1a at –40 °C in toluene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion (%)</th>
<th>Time/h</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>100</td>
<td>2</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>100</td>
<td>1</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>100</td>
<td>2</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>99</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>84</td>
<td>21</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>L6</td>
<td>41</td>
<td>2</td>
<td>59</td>
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<tr>
<td>7</td>
<td>L7</td>
<td>22</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>L8</td>
<td>92</td>
<td>21</td>
<td>26</td>
</tr>
</tbody>
</table>

* The configuration of the major product, (S)-2a, was determined by comparison of the optical rotation with literature data (see ESI†). † R-Enantiomer of 2a obtained.

Table 2 Effect of the solvent in asymmetric conjugate addition of Me2Zn to 1a at –60 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Time/h</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>Toluene</td>
<td>4</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>Toluene</td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>Heptane</td>
<td>24</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>L2</td>
<td>Heptane</td>
<td>20</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>L1</td>
<td>Diethyl ether</td>
<td>20</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>L2</td>
<td>Diethyl ether</td>
<td>4</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>L1</td>
<td>CH3Cl</td>
<td>20</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>L2</td>
<td>CH3Cl</td>
<td>4</td>
<td>88</td>
</tr>
</tbody>
</table>

* All conjugate additions were run to complete conversion.

† Electronic supplementary information (ESI) available: experimental procedures and spectral data for all products. See http://www.rsc.org/ suppdata/cc/b3/b315871c/
dichloromethane also lead to full conversion within 20 h, somewhat lower ees were observed. As a general trend, it was found that longer reaction times were required to reach full conversion when using L1 as compared to L2, whereas the ees were similar with both ligands.

Under the optimized conditions, a number of unsaturated malonates were tested (Table 3). For linear alkyl substituents, excellent ees of up to 96% and full conversion within 25 h were achieved (entries 1–13). A second substituent at the γ-position lowers the reactivity of the system (entries 14–19); however, for the isopropyl-substituted malonic ester 1e, an excellent ee of 98% was obtained using ligand L1 in toluene. With the exception of substrate 1f, in general, L1 gave slightly higher ees than L2.

**Table 3** Asymmetric conjugate addition of dimethylzinc to unsaturated malonic esters 1b–1f

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diester</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Time/ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b Pr</td>
<td>L1</td>
<td>Toluene</td>
<td>100</td>
<td>21/95</td>
</tr>
<tr>
<td>2</td>
<td>1b Pr</td>
<td>L2</td>
<td>Toluene</td>
<td>98</td>
<td>4/94</td>
</tr>
<tr>
<td>3</td>
<td>1b Pr</td>
<td>L1</td>
<td>Heptane</td>
<td>98</td>
<td>21/96</td>
</tr>
<tr>
<td>4</td>
<td>1b Pr</td>
<td>L2</td>
<td>Heptane</td>
<td>100</td>
<td>20/96</td>
</tr>
<tr>
<td>5</td>
<td>1b Pr</td>
<td>L1</td>
<td>Diethyl ether</td>
<td>100</td>
<td>21/94</td>
</tr>
<tr>
<td>6</td>
<td>1c Et</td>
<td>L1</td>
<td>Toluene</td>
<td>100</td>
<td>24/96</td>
</tr>
<tr>
<td>7</td>
<td>1c Et</td>
<td>L2</td>
<td>Toluene</td>
<td>100</td>
<td>24/92</td>
</tr>
<tr>
<td>8</td>
<td>1c Et</td>
<td>L1</td>
<td>Heptane</td>
<td>80</td>
<td>24/92</td>
</tr>
<tr>
<td>9</td>
<td>1c Et</td>
<td>L2</td>
<td>Heptane</td>
<td>45</td>
<td>24/90</td>
</tr>
<tr>
<td>10</td>
<td>1d (CH3)2Ph</td>
<td>L1</td>
<td>Toluene</td>
<td>98</td>
<td>2/86</td>
</tr>
<tr>
<td>11</td>
<td>1d (CH3)2Ph</td>
<td>L2</td>
<td>Toluene</td>
<td>100</td>
<td>25/82</td>
</tr>
<tr>
<td>12</td>
<td>1d (CH3)2Ph</td>
<td>L1</td>
<td>Heptane</td>
<td>98</td>
<td>25/66</td>
</tr>
<tr>
<td>13</td>
<td>1d (CH3)2Ph</td>
<td>L2</td>
<td>Heptane</td>
<td>97</td>
<td>25/42</td>
</tr>
<tr>
<td>14</td>
<td>1e iPr</td>
<td>L1</td>
<td>Toluene</td>
<td>60</td>
<td>68/98</td>
</tr>
<tr>
<td>15</td>
<td>1e iPr</td>
<td>L2</td>
<td>Toluene</td>
<td>42</td>
<td>68/96</td>
</tr>
<tr>
<td>16</td>
<td>1e iPr</td>
<td>L1</td>
<td>Heptane</td>
<td>10</td>
<td>68 n.d.</td>
</tr>
<tr>
<td>17</td>
<td>1e iPr</td>
<td>L2</td>
<td>Heptane</td>
<td>8</td>
<td>68 n.d.</td>
</tr>
<tr>
<td>18</td>
<td>1f 1-Furyl</td>
<td>L1</td>
<td>Toluene</td>
<td>80</td>
<td>25/90</td>
</tr>
<tr>
<td>19</td>
<td>1f 1-Furyl</td>
<td>L2</td>
<td>Toluene</td>
<td>57</td>
<td>25/94</td>
</tr>
</tbody>
</table>

* All conjugate additions run at ~60 °C. † The configuration of the major product was determined by comparison of the optical rotation with literature data (see ESI†). n.d.: not determined.

An attractive aspect of the new methodology is that it provides the basis for an iterative catalytic protocol (Scheme 3). In this way, the stereoselective construction of 3,5-dimethyl carbonyl motifs can be achieved, which are common in numerous naturally occurring compounds.

![Scheme 3 Iterative 1,4-addition](image)

Thus, diethyl propylidene malonate (1e) was subjected to an asymmetric conjugate addition providing, after decarbonylation, (S)-ethyl 3-methylpentanoate (3e) in excellent yield and enantiomeric excess (Scheme 3). A sequence involving reduction of the ester moiety to the corresponding alcohol, oxidation to the aldehyde and subsequent Knovenagel condensation gave access to unsaturated moieties to the corresponding alcohol, oxidation to the aldehyde and subsequent Knoevenagel condensation gave access to unsaturated products (Scheme 4). In summary, we have shown that excellent stereocontrol can be achieved in the catalytic conjugate addition of dimethylzinc to unsaturated malonic esters and that the methodology can be applied iteratively, thus allowing the construction of either syn- or anti-3,5-dimethyl carbonyl compounds.

This project was financially supported by the European Network COMBICAT (HPRN-CT-2000-00014).

**Notes and references**

8. In accordance with observations made by Alexakis et al. (see ref. 5), we found modest ees for the addition of Et2Zn to malonates 1, attributed to a significant uncatalyzed reaction.