Enantioselective synthesis of (−)-chloramphenicol via silver-catalysed asymmetric isocyanoacetate aldol reaction†

Allegra Franchino, Pavol Jakubec and Darren J. Dixon*

The highly enantio- and diastereoselective aldol reaction of isocyanoacetates catalysed by Ag₂O and cinchona-derived amino phosphines applied to the synthesis of (−)- and (+)-chloramphenicol is described. The concise synthesis showcases the utility of this catalytic asymmetric methodology for the preparation of bioactive compounds possessing α-amino-β-hydroxy motifs.

Chiral vicinal amino alcohols represent a very important class of compounds, which are of interest to synthetic chemists not only as valuable building blocks and chiral auxiliaries, but also by virtue of their pharmacological properties.1 Bioactive vicinal amino alcohols of differing complexity include the broad spectrum antibiotics chloramphenicol2 (1) and thiamphenicol1 (2), the protease inhibitor for HIV treatment saquinavir4 (3) and the antihypertensive drug aliskiren5 (4, Fig. 1). Among others,1,6 a privileged access to these structures is offered by the aldol reaction of glycine equivalents,7 including isocyanoacetates,8 followed by reduction of the carboxylic group. Recently, our group developed a cooperative catalytic system consisting of a Lewis acid (Ag⁺) and a cinchona-derived amino phosphine ligand, bearing both Brønsted and Lewis basic sites, for the activation of isocyanoacetate pronucleophiles towards electrophiles, such as aldehydes,9 ketimines10 and ketones.11

As a direct demonstration of the utility of this asymmetric methodology, herein we report a short asymmetric synthesis of (−)-chloramphenicol12 which is the first one relying on a catalytic enantio- and diastereoselective aldol reaction.13 According to our retrosynthetic plan, outlined in Scheme 1, (−)-chloramphenicol would be derived through standard chemical manipulations from the trans oxazoline (4S,5R)-6.14 It was envisioned that the latter could be obtained via the Ag-catalysed asymmetric isocyanoacetate aldol reaction (IAR) between a suitable isocyanoacetate ester7 and 4-nitrobenz-
aldehyde (8). Specifically, on the basis of our previous work it was anticipated that the use of cinchonine-derived amino phosphine L-1 as chiral ligand in the IAR would provide oxazoline 6 with the desired absolute configuration for the preparation of (−)-chloramphenicol (Table 1).

Our investigation thus began by performing the reaction between 8 and tert-butyl isocyanoacetate 7a under the conditions where the enantiomeric purity could be improved to 98% e.e. by a chemoselective reduction of the ester group with excess sodium borohydride delivered (−)-chloramphenicol in 80% yield and 99% e.e.17 (+)-Chloramphenicol was prepared in an analogous manner from oxazoline (4R,5S)-6f in slightly lower yield (68%) and better stereocontrol (92 : 8 d.r., 93% e.e., entry 10).

Finally, catalyst loading studies confirmed the ideal Ag/ligand ratio to be 1 : 1, specifically with 2.5 mol% Ag2O and 5 mol% L-2 (see ESI, Table S2†).

After having successfully improved yield and stereocontrol for the isocyanoacetate aldol reaction, oxazoline (4S,5R)-6f was prepared on 2.5 mmol scale with 72% yield and 89% e.e.,16 and then was readily elaborated to the target molecule (Scheme 2). Ring opening of 6f using thionyl chloride in methanol proceeded with 75% yield to afford the amino alcohol whose enantiomeric purity could be improved to 98% e.e. by a single recrystallisation from toluene (61% yield, first crop). The amino alcohol was then acylated with dichloroacetyl chloride to provide dichloroacetamide 9 in 83% yield. Finally, chemo-selective reduction of the ester group with excess sodium borohydride delivered (−)-chloramphenicol in 80% yield and 99% e.e.17 (+)-Chloramphenicol was prepared in an analogous manner from oxazoline (4R,5S)-6f.

In summary, a catalytic asymmetric synthesis of (−)-chloramphenicol has been accomplished, delivering the target molecule in 4 steps and 22% yield calculated from 4-nitrobenzaldehyde. The concise synthetic route relies on the enantio- and diastereoselective aldol reaction of isocyanoacetates catalysed by Ag2O and cinchona-derived amino phosphine ligands. Extensive screening of the reaction parameters...
Table 2  Pronucleophile and ligand screening in the isocyanoacetate aldol reaction between 8 and 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>7</th>
<th>Ligand</th>
<th>Time (min)</th>
<th>Yield (a) (%)</th>
<th>d.r. (trans : cis)</th>
<th>e.e. (d) (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>(CH₃)₃C</td>
<td>7a</td>
<td>L-1</td>
<td>30</td>
<td>70</td>
<td>91 : 9</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>7b</td>
<td>L-1</td>
<td>100</td>
<td>80</td>
<td>88 : 12</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>PhCH₂</td>
<td>7c</td>
<td>L-1</td>
<td>180</td>
<td>61</td>
<td>90 : 10</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>PhCH₂</td>
<td>7c</td>
<td>L-2</td>
<td>80</td>
<td>64</td>
<td>90 : 10</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>4-(OCH₃)C₆H₄CH₂</td>
<td>7d</td>
<td>L-2</td>
<td>60</td>
<td>63</td>
<td>89 : 11</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>3,5-(CF₃)₂C₆H₃CH₂</td>
<td>7e</td>
<td>L-2</td>
<td>60</td>
<td>56</td>
<td>90 : 10</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>PhCH</td>
<td>7f</td>
<td>L-1</td>
<td>100</td>
<td>81</td>
<td>93 : 7</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
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<td>7f</td>
<td>L-2</td>
<td>45</td>
<td>78</td>
<td>91 : 9</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>Ph₂CH</td>
<td>7f</td>
<td>L-3</td>
<td>200</td>
<td>82</td>
<td>93 : 7</td>
<td>88d</td>
</tr>
<tr>
<td>10</td>
<td>Ph₂CH</td>
<td>7f</td>
<td>L-4</td>
<td>60</td>
<td>68</td>
<td>92 : 8</td>
<td>93e</td>
</tr>
</tbody>
</table>

a Reaction performed on 0.25 mmol of 7 (0.01 M in AcOEt) using 1.1 eq. of 8. Configuration of 6 assigned by analogy with previous work.9
b Isolated yield of trans diastereomer after FCC. c d.r. determined by 1H NMR analysis of the crude reaction mixture. d e.e. of trans diastereomer determined by HPLC on chiral stationary phase. e Opposite enantiomer obtained.

Scheme 2  Synthesis of (−)- and (+)-chloramphenicol.
has been undertaken to optimise the key step, eventually achieving the formation of the two contiguous stereocentres of the target molecule with good enantiocontrol. The present work demonstrates the utility of this asymmetric methodology for the preparation of bioactive molecules bearing an α-amino-β-hydroxy motif.

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Notes and references

1 S. C. Bergeimeier, Tetrahedron, 2000, 56, 2561.


15 The preparation of isocyanoacetates 7a-f from commercial reagents over three steps is detailed in the ESI.

16 Removal of 4 Å molecular sieves had no detrimental effect on the reaction.

17 The observed slight upgrade in e.e. between 9 and 1 is linked to the chromatographic purification process.