Synthesis of Optically Active Oxazolines by an Organocatalytic Isocyanoacetate Aldol Reaction with α-Keto Esters

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Abstract An enantioselective [3+2] cyclization is reported for the construction of a chiral oxazoline skeleton in moderate yield and up to 97% ee. The reactivity and stereochemical discrimination originate from the noncovalent interaction and orientation of a bifunctional catalyst. The novel combination of an α-keto ester and an α-isocyanoacetate establishes an oxazoline which could be a potential chiral ligand for metal-mediated catalysis, and also could be easily converted into an optically active β-hydroxy-α-amino acid.

Key words organocatalysis, bifunctional catalyst, noncovalent interaction, asymmetric cyclization, chiral oxazoline

Nitrogen-containing heterocycles are important in pharmaceutical investigations, especially for small-molecule drug design.1 Aimed at target skeletons of this sort, α-isocyanoacetate has been frequently used as versatile synthon providing dipolar reactivity in a [3+2] cyclization process.2 Mediated by organocatalysis, several prominent manipulations have been used for the construction of analogues of pyrrole3 and imidazole.4 However, the straightforward assembly of optically active oxazolines, which act as ligands for transition metals and are the core framework in numerous natural products, is highly dependent on chiral metal complexes. In 1986, Ito and Hayashi reported the first asymmetric aldol-type reaction for α-isocyanoacetate using a chiral Au(I) complex.5 Subsequent investigations focused on disparate transition metal catalyst systems and often led to the formation of trans-substituted oxazolines.4 In 2011 Dixon et al. utilized a chiral amino phosphine Ag(I) complex to obtain oxazolines with excellent cis selectivity.6 In sharp contrast, the organocatalytic variant for such conversions has been studied and only a single example was presented by Gong et al.8 There has been no report of the combination involving a ketone group, which would afford direct access to oxazolines bearing one or two quaternary asymmetric centers. In this paper, we describe the first asymmetric aldol-type transformation of α-keto esters with α-isocyanoacetate catalyzed by a thiourea/amine bifunctional catalyst and leading to a precursor of β-hydroxy-α-amino acids.9

We began by evaluating the efficiency of the bifunctional catalyst system.10 Progress in noncovalent catalysis furnishes findings, abundant and well-documented, concerning versatile methodologies and selectivities.11 With thiourea/amine-type bifunctional catalysts, the Bronsted basicity of a tertiary amine affords the activation energy for reaction with nucleophilic compounds and simultaneously the thiourea moiety acts as a hydrogen donor to interact with the corresponding electrophile.12 This cooperative mode takes advantage of both the substrate proximity effect and a sterically well-defined transition state rendering high synergy to the catalysis. We hypothesized that the dual carbonyl groups of α-keto esters would permit a well-organized cyclic interaction with the thiourea moiety of the bifunctional catalyst, as shown in Scheme 1. Simultaneously, the acidic C–H bond of α-isocyanoacetate spontaneously enters into a noncovalent interaction with the alkaline site and interacts intramolecularly with the keto group of the α-keto ester.

The inception of the aldol-cyclization cascade is initiated by the reaction of ethyl phenylglyoxylate (1a) with methyl isocyanoacetate (2a) which is promoted by various thiourea amines. Takemoto’s catalyst (3a; Table 1, entry 1), the simplest bifunctional analogue of chiral 1,2-diaminocyclohexane, delivers fair asymmetric induction along with moderate differentiation of diastereoisomers. The results indicate that thioureas containing a strong basic tertiary amine two carbon atoms removed from the thiocarbonyl group could lead to activation and the resulting stereochemistry. The comparable structure in the cinchona alkal-
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Synlett 2017, 28, 1300–1304

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**Table 1** Reaction Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>dr&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>Et</td>
<td>Me</td>
<td>H (2a)</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>53</td>
<td>1.8:1</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>Et</td>
<td>Me</td>
<td>H (2a)</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>48</td>
<td>1.2:1</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>Et</td>
<td>Me</td>
<td>H (2a)</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>53</td>
<td>1.3:1</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>Et</td>
<td>Me</td>
<td>H (2a)</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>58</td>
<td>1.4:1</td>
</tr>
<tr>
<td>5</td>
<td>3d</td>
<td>Et</td>
<td>Me</td>
<td>H (2a)</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>56</td>
<td>1.4:1</td>
</tr>
<tr>
<td>6</td>
<td>3d</td>
<td>Et</td>
<td>Me</td>
<td>H (2a)</td>
<td>THF</td>
<td>trace (n.d.)</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>3d</td>
<td>Et</td>
<td>Me</td>
<td>H (2a)</td>
<td>EtOAc</td>
<td>36</td>
<td>1.5:1</td>
</tr>
<tr>
<td>8</td>
<td>3d</td>
<td>Et</td>
<td>Me</td>
<td>H (2a)</td>
<td>toluene</td>
<td>65</td>
<td>2:1</td>
</tr>
<tr>
<td>9</td>
<td>3c</td>
<td>Et</td>
<td>Me</td>
<td>H (2a)</td>
<td>toluene</td>
<td>70</td>
<td>2:1</td>
</tr>
<tr>
<td>10</td>
<td>3c</td>
<td>Et</td>
<td>t-Bu</td>
<td>H (2d)</td>
<td>toluene</td>
<td>62</td>
<td>2:1</td>
</tr>
<tr>
<td>11</td>
<td>3c</td>
<td>Et</td>
<td>t-Bu</td>
<td>H (2d)</td>
<td>toluene</td>
<td>46</td>
<td>1:7:1</td>
</tr>
<tr>
<td>12</td>
<td>3c</td>
<td>Et</td>
<td>t-Bu</td>
<td>H (2d)</td>
<td>toluene</td>
<td>75</td>
<td>2:1</td>
</tr>
<tr>
<td>13</td>
<td>3c</td>
<td>Me</td>
<td>t-Bu</td>
<td>H (2e)</td>
<td>toluene</td>
<td>67</td>
<td>2:1</td>
</tr>
<tr>
<td>14</td>
<td>3c</td>
<td>Bn</td>
<td>t-Bu</td>
<td>H (2f)</td>
<td>toluene</td>
<td>60</td>
<td>1:1</td>
</tr>
<tr>
<td>15</td>
<td>3e</td>
<td>Et</td>
<td>t-Bu</td>
<td>H (2d)</td>
<td>toluene</td>
<td>75</td>
<td>2:1</td>
</tr>
<tr>
<td>16</td>
<td>3f</td>
<td>Et</td>
<td>t-Bu</td>
<td>H (2d)</td>
<td>toluene</td>
<td>75</td>
<td>2:1</td>
</tr>
<tr>
<td>17</td>
<td>3g</td>
<td>Et</td>
<td>t-Bu</td>
<td>H (2d)</td>
<td>toluene</td>
<td>75</td>
<td>2:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Unless otherwise noted, all reactions were carried out using 1a (0.1 mmol), 2a (0.12 mmol) and the catalyst (10 mol%) in solvent (0.5 mL) at 26 °C for 12 h.

<sup>b</sup> Isolated yield after silica gel chromatography.

<sup>c</sup> The dr was determined by 1H NMR analysis of the crude mixture.

<sup>d</sup> Determined by chiral HPLC.

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**Table 2** Scope of the α-Keto Esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (1a)</td>
<td>75</td>
<td>2:1</td>
<td>94 (81%)</td>
</tr>
<tr>
<td>2</td>
<td>4-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (1b)</td>
<td>73</td>
<td>2:1</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>3-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (1c)</td>
<td>67</td>
<td>2:1</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (1d)</td>
<td>78</td>
<td>2:1</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>3-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (1e)</td>
<td>72</td>
<td>2:1</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (1f)</td>
<td>70</td>
<td>2:1</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>3-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (1g)</td>
<td>76</td>
<td>2:1</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (1h)</td>
<td>73</td>
<td>2:1</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt; (1i)</td>
<td>77</td>
<td>2:1</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>3-F-6-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt; (1j)</td>
<td>75</td>
<td>2:1</td>
<td>97</td>
</tr>
<tr>
<td>11</td>
<td>2-naphthyl (1k)</td>
<td>84</td>
<td>2:1</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>2-thienyl (1l)</td>
<td>80</td>
<td>2:1</td>
<td>89</td>
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</table>

<sup>a</sup> Unless otherwise noted, all reactions were carried out using 1a–i (0.1 mmol), 2d (0.12 mmol) and 3c (10 mol%) in toluene (0.5 mL) at 26 °C for 24 h.

<sup>b</sup> Isolated yield after silica gel chromatography.

<sup>c</sup> The dr was determined by 1H NMR analysis.

<sup>d</sup> Determined by chiral HPLC.

<sup>e</sup> The ee value for minor diastereomer.

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ent effect is consistent with the experimental data and the diastereoselectivity indicates a stepwise approach for the cyclization.

In summary, an asymmetric isocyanoacetate aldol reaction of α-keto esters was realized by a bifunctional catalytic strategy. Aromatic and heteroaromatic α-keto esters are converted into oxazolines in good yield (up to 84%) and with high enantioselectivity (up to 97% ee). This provides practical synthetic access to chiral oxazolines which can be precursors to β-hydroxy-α-amino acids. Further efforts are aimed at improving the diastereoselectivity and elucidating the synthetic utility of the reaction in pharmaceutical chemistry.

**Acknowledgment**

This work was financially supported by the Science and Technology Innovation Committee of Shenzhen Municipality (JCJ20160226105602871), the China Postdoctoral Science Foundation (2016M590009), the Guangdong Province Special Branch Program (2014TX01R111) and the Natural Science Foundation of Guangdong Province (2016A030310243).

**Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588718.
References and Notes

(12) Aliphatic α-keto esters such as ethyl 2-cyclohexyl-2-oxoacetate were also used, but only gave 59% ee.
(13) See the Supporting Information for details.
(15) General Procedure for the Synthesis of Chiral Oxazoline: Phenylglyoxyloxy (1: 0.1 mmol), tert-butyl isoynoatoate (2d: 11.9 mg, 0.12 mmol) and bifunctional catalyst 3c (5.9 mg, 0.01 mmol) were stirred in toluene (0.5 mL) at 26 °C for 24 h. The mixture was separated by silica gel chromatography (10% EtOAc/petroleum ether) and gave product 4.
Analysis data for compound 4a: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.20–1.24 (m, 3 H), 1.52 (s, 9 H), 4.11–4.24 (m, 2 H), 4.88 (d, $J$ = 2.0 Hz, 1 H), 7.14 (d, $J$ = 2.0 Hz, 1 H), 7.31–7.56 (m, 2 H), 7.58–7.60 (m, 2 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 14.0, 28.0, 62.5, 79.7, 83.0, 89.4, 125.3, 129.0, 138.7, 155.5, 168.2, 168.6. HPLC (Chiralcel IB, hexane/i-PrOH = 95:5, flow rate: 1.0 mL/min, $\lambda$ = 210 nm): $t_R$ (major) = 18.08 min, $t_R$ (minor) = 20.22 min. ESI-HRMS: $m/z$ [M + H] calcd for C$_{17}$H$_{21}$NO$_5$: 320.1498; found: 320.1492.