Asymmetric Organocatalytic Synthesis of Lactams and Lactones

**Significance:** The reported method for the synthesis of lactams and lactones 4 employs quinine- and quinidine-derived catalysts 3 to activate α,β-unsaturated acid chlorides 1 toward reaction with bisnucleophiles 2. A variety of heterocycles relevant to medicinal and natural product chemistry were obtained, including 2-pyrrolidinones, 2-piperidinones, enol δ-valerolactones, and 3,4-dihydro-2-pyridinones. The yields are modest to good and enantioselectivity is good to excellent.

**Comment:** For success of the reported method, significant tuning of the reaction conditions to the substrate, including the use of excess reactant; the choice of base, catalyst, and temperature; and the use of additives, is required. Catalyst 3b affords products of opposite configuration to those obtained using 3a or 3c; although, in our opinion, the publication relies too heavily on assumptions in drawing this conclusion. In the synthesis of piperidinones, a retro-aza Michael side reaction results in low yields of the desired product.

**Selected examples:**

**Pyrrolidinones and Piperidinones**

- **Catalyst:** 3b
- **Bases:** LiHMDS (1 equiv), DBU (1 equiv)
- **Solvent:** THF
- **Conditions:** –30 °C, 18 h

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>ee</th>
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<tbody>
<tr>
<td>Bz</td>
<td>78%</td>
<td>86%</td>
</tr>
<tr>
<td>Ts</td>
<td>73%</td>
<td>93%</td>
</tr>
</tbody>
</table>

**Enol δ-lactones**

- **Catalyst:** 3a, 3c
- **Bases:** LiHMDS (1 equiv), DBU (1 equiv)
- **Solvent:** THF
- **Conditions:** –30 °C, 18 h

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
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<tr>
<td>4-ClC₆H₄</td>
<td>40%</td>
<td>93%</td>
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**Example:**

- **Catalyst:** 3b
- **Base:** DIPEA (3 equiv), LiCl (1 equiv)
- **Additive:** LiHMDS and DIPEA
- **Solvent:** PhMe
- **Conditions:** 23 °C, 20 h

- **Yield:** 80% yield, 93% ee

**3,4-Dihydro-2-pyridinones**

- **Catalyst:** 3c
- **Base:** DIPEA, HCO₂NH₄
- **Additive:** LiCl (1 equiv)
- **Solvent:** 4 Å MS
- **Conditions:** 23 °C, 20 h

- **Yield:** 52% yield, 90% ee

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