Copper-Catalyzed Enantioselective [1,3]-Rearrangement to Chiral Propargylic Amines

**Significance:** Thermal [3,3]-sigmatropic rearrangements are well precedented and can be achieved at ambient temperature with high levels of enantioselectivity (see, for example: M. P. Watson, L. E. Overman, R. G. Bergman *J. Am. Chem. Soc.* 2007, 129, 5031). In contrast, [1,3]-sigmatropic rearrangements are thermally disallowed, but can be promoted at high temperatures with the use of transition-metal catalysts. No examples of [1,3]-rearrangements affording propargylic products or their enantioselective variants have been previously reported.

**Comment:** The present report details the first example of an enantioselective [1,3]-rearrangement. The alkyne starting materials 1 can be converted into pyridone alkynes 3 with a diverse substrate scope, affording products in high yields with high er. Detaileman studies indicate that the reaction proceeds through allenic intermediate 2 with copper catalysis, followed by a formal [1,3]-rearrangement. The enantioselectivity is derived from a BINAP phosphoryl ligand 2 through CuTC coordination. The synthetic utility of the products was shown by carrying 4 forward to the synthesis of cysteine protease inhibitor 11. This reaction will find utility due to the mild reaction conditions and the ability to modify the pyridine core to generate chiral amines similar to 10.

**Selected examples:**

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>er (as)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂Bn</td>
<td>90%</td>
<td>98.2</td>
</tr>
<tr>
<td>CH₂O-TBS</td>
<td>75%</td>
<td>97.3</td>
</tr>
<tr>
<td>Ph</td>
<td>70%</td>
<td>85.15</td>
</tr>
<tr>
<td>(CH₂)₄CHO</td>
<td>89%</td>
<td>97.3</td>
</tr>
</tbody>
</table>

**Synthetic utility:**

1. HCl
2. Boc₂O

- Products have synthetic utility
- Products have high yield
- Products have moderate to high yields
- Large substrate scope

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Enantioselective Propargylic [1,3]-Rearrangements: Copper-Catalyzed O-to-N Migrations toward C–N Bond Formation