Asymmetric Schmidt Reaction of Hydroxyalkyl Azides with Ketones

*J. Am. Chem. Soc.* 2003, 125, 7914-7922

Kiran Sahasrabudhe, Vijaya Gracias, Kelly Furness, Brenton T. Smith, Christopher E. Katz, D. Srinivasa Reddy, and Jeffrey Aubé

![Chemical structure](image)
Methods for Asymmetric Conversion of Ketones to Lactams

- Photochemical rearrangement of chiral oxaziridines

\[
\text{Ketone} \xrightarrow{1. (S)-\alpha\text{-MBA}, 2. oxidation} \text{Oxaziridine} \xrightarrow{\text{hv}} \text{Lactam} + \text{Lactam (and diastereomers)}
\]

- Schmidt reaction using chiral alkyl azides

\[
\text{Ketone} + \text{Alkyl azide} \xrightarrow{\text{BF}_3\cdot\text{OEt}_2} \text{Nitrile oxide} \xrightarrow{\text{hydrolysis}} \text{Lactam}
\]

**Comparison of Two Methods**

<table>
<thead>
<tr>
<th>Oxaziridines</th>
<th>Asymmetric Schmidt reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>A chiral methylbenzylamine as a stereocontrolling group</td>
<td>Using a chiral alkyl azide</td>
</tr>
<tr>
<td>Three discrete steps and moderate overall yield (around 70%)</td>
<td>One-pot, one-workup procedure and higher overall yield (85%-100%)</td>
</tr>
<tr>
<td>Relatively low stereoselectivity (88:12 as the best result)</td>
<td>Considerably greater stereoselectivity (49:1 as the best result)</td>
</tr>
</tbody>
</table>
Selection and Synthesis of Hydroxyalkyl Azides – 1,2-azido alcohol

- Mitsunobu procedure:
  - Using activated diols:
  - Ring opening of epoxides:

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{AD-mix-} \alpha} \text{Ph} \xrightarrow{\text{SOCl}_2} \text{Ph} \xrightarrow{\text{NaN}_3, \text{DMF}, 70 \, ^\circ\text{C}} \text{Ph} \\
1 & \xrightarrow{85\%, >99\% \, \text{ee}} \xrightarrow{92\%} \xrightarrow{74\%, >99.5\% \, \text{ee}} 2 \\
\text{Ph} & \xrightarrow{\text{NaN}_3} (\pm)-1 + (\pm)-3 \
\end{align*}
\]

80%, 75:25 mixture of isomers
**Selection and Synthesis of Hydroxyalkyl Azides – 1,3-azido alcohol**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td><img src="image" alt="Structure 5" /></td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Structure 6" /></td>
</tr>
<tr>
<td>(±)-7</td>
<td><img src="image" alt="Structure (±)-7" /></td>
</tr>
<tr>
<td>8, R₁ = Me, R₂ = H</td>
<td><img src="image" alt="Structure 8" /></td>
</tr>
<tr>
<td>9, R₁ = H, R₂ = Ph</td>
<td><img src="image" alt="Structure 9" /></td>
</tr>
<tr>
<td>(±)-10</td>
<td><img src="image" alt="Structure (±)-10" /></td>
</tr>
<tr>
<td>11, R₁ = Me, R₂ = H</td>
<td><img src="image" alt="Structure 11" /></td>
</tr>
<tr>
<td>12, R₁ = H, R₂ = Me</td>
<td><img src="image" alt="Structure 12" /></td>
</tr>
</tbody>
</table>

- **Simple azide displacement:** (compound 5 and 8)

- **Mitsunobu reactions:** (compound 6, 7, 10 and 11)

- **Multistep pathways:** (compound 9 and 12)
Table 1. Reactions of 1 with 4-Methylcyclohexanone

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>$T$ (°C)</th>
<th>time (h)</th>
<th>yield (%)$^a$</th>
<th>ratio of 14a: 14b$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>$-78 \rightarrow$ rt</td>
<td>36</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Et₂O</td>
<td>0</td>
<td>21</td>
<td>3$^c$</td>
<td>73:27</td>
</tr>
<tr>
<td>3</td>
<td>cyclohexane</td>
<td>3</td>
<td>18</td>
<td>74</td>
<td>73:27</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN</td>
<td>$-30$</td>
<td>18</td>
<td>41</td>
<td>69:31</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>$-30$</td>
<td>18</td>
<td>15$^c$</td>
<td>83:17</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>100</td>
<td>62</td>
<td>70:30</td>
</tr>
<tr>
<td>7</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>21</td>
<td>86</td>
<td>69:31</td>
</tr>
<tr>
<td>8</td>
<td>CCl₄</td>
<td>$-20$</td>
<td>18</td>
<td>97</td>
<td>78:22</td>
</tr>
<tr>
<td>9</td>
<td>$n$-pentane</td>
<td>$-20$</td>
<td>23</td>
<td>100</td>
<td>78:22</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields except where noted. $^b$ Ratios determined by HPLC of crude reaction mixtures. $^c$ Yield for this example estimated from HPLC trace.
Effects of Substituents on Ketones and 1,2-Hydroxyalkyl Azides

![Chemical Reaction Diagram]

1: $R_1 = H$, $R_2 = Ph$
2: $R_1 = Ph$, $R_2 = Ph$
3: $R_1 = Ph$, $R_2 = H$

**Table 2. Reactions of 1,2-Hydroxyethyl Azides with 4-substituted Ketones**

<table>
<thead>
<tr>
<th>entry</th>
<th>azide</th>
<th>ketone $R$</th>
<th>major product</th>
<th>yield (%)$^a$</th>
<th>ratio $a:b$</th>
<th>$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Me</td>
<td>14a</td>
<td>97</td>
<td>78:22</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>$t$-Bu</td>
<td>15a</td>
<td>83</td>
<td>85:15</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Me</td>
<td>16a</td>
<td>51</td>
<td>87:13</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>$t$-Bu</td>
<td>17a</td>
<td>64</td>
<td>88:12</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3$^c$</td>
<td>$t$-Bu</td>
<td>18a or 18b$^d$</td>
<td>73</td>
<td>56:44</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Isolated yield. $^b$ Ratio determined by HPLC trace of the crude reaction mixture. $^c$ This experiment was done using a racemic hydroxyalkyl azide. $^d$ Not assigned for this example.
Reactions of 1,3-Hydroxyalkyl Azides

Table 3. Reactions of Monosubstituted 1,3-Hydroxyalkyl Azides with 4-Substituted Cyclohexanones

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone R</th>
<th>azide</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
<th>products</th>
<th>ratio&lt;sup&gt;a&lt;/sup&gt;:b&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>5</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>19</td>
<td>93:7</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>5</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>20</td>
<td>96:4</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>t-Bu</td>
<td>5</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>21</td>
<td>95:5</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>22&lt;sup&gt;e&lt;/sup&gt;</td>
<td>89:11</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>t-Bu</td>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>23&lt;sup&gt;e&lt;/sup&gt;</td>
<td>90:10</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H(OMe)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>H</td>
<td>24&lt;sup&gt;d&lt;/sup&gt;</td>
<td>90:10&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>8</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>25</td>
<td>78:22</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>t-Bu</td>
<td>8</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>26</td>
<td>74:26</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>27&lt;sup&gt;e&lt;/sup&gt;</td>
<td>60:40</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>t-Bu</td>
<td>9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>28&lt;sup&gt;e&lt;/sup&gt;</td>
<td>60:40</td>
<td>98</td>
</tr>
<tr>
<td>11</td>
<td>Me</td>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>H</td>
<td>i-Pr</td>
<td>H</td>
<td>29&lt;sup&gt;d&lt;/sup&gt;</td>
<td>88:12&lt;sup&gt;d&lt;/sup&gt;</td>
<td>88</td>
</tr>
<tr>
<td>12</td>
<td>t-Bu</td>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>H</td>
<td>i-Pr</td>
<td>H</td>
<td>30&lt;sup&gt;d&lt;/sup&gt;</td>
<td>88:12&lt;sup&gt;d&lt;/sup&gt;</td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratio determined by HPLC of crude reaction mixtures, except where noted.  
<sup>b</sup> Total yields of isolated purified lactams.  
<sup>c</sup> This reaction was done in the enantiomeric series to that shown in this table.  
<sup>d</sup> This experiment was done using a racemic hydroxyalkyl azide.  
<sup>e</sup> Ratio estimated by 1H NMR examination of the crude reaction mixture.
Other Effects of the Ketones

➤ Meso disubstituted cyclohexanone

![Meso disubstituted cyclohexanone reaction](image)

➤ 3-Substituted cyclohexanone

![3-Substituted cyclohexanone reaction](image)

➤ Alternative ring sizes

![Alternative ring sizes reaction](image)
N-Dealkylation of the Lactams

- Dissolving metal reduction: (for benzylic lactams)

- Oxidation and elimination: (for nonbenzylic lactams)
Mechanistic Hypotheses

(a) Equatorial vs. axial addition

(b) Conformation of the new ring

(c) Relationship between leaving group and the migrating bond (the migrating bond is darkened)

Either darkened bond is synplanar to the leaving group in this example.
Addition of Azides

Example with 1,2-azido alcohol

\[
\begin{align*}
\text{Ketone} \quad &\xrightarrow{\text{N}_3\text{-OH, BF}_3\cdot\text{OEt}_2, \text{Ph}} \quad \text{39 (major isomer shown)} \\
&\quad \quad \text{90\% overall yield of 4 isomers} \\
&\quad \quad \text{a : b = 10 : 1}
\end{align*}
\]
Example 1:
Difference in the reaction of cis- and trans-1,3-azide

Example 2:
The size of the substituent on azides affects the selectivity.
Lower selectivity of the 2-substituted azidopropanols. (table 3)
Conformation of the New Ring- B

![Chemical Structure](image)

**Table 3.** Reactions of Monosubstituted 1,3-Hydroxyalkyl Azides with 4-Substituted Cyclohexanones

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone R</th>
<th>azide</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>products</th>
<th>ratio</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>5</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>19</td>
<td>93:7</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>5</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>20</td>
<td>96:4</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>t-Bu</td>
<td>5</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>21</td>
<td>95:5</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>22&lt;sup&gt;c&lt;/sup&gt;</td>
<td>89:11</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>t-Bu</td>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>23&lt;sup&gt;c&lt;/sup&gt;</td>
<td>90:10</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-C₆H(OMe)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>H</td>
<td>24&lt;sup&gt;d&lt;/sup&gt;</td>
<td>90:10&lt;sup&gt;d,c&lt;/sup&gt;</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>8</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>25</td>
<td>78:22</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>t-Bu</td>
<td>8</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>26</td>
<td>74:26</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>27&lt;sup&gt;c&lt;/sup&gt;</td>
<td>60:40</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>t-Bu</td>
<td>9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>28&lt;sup&gt;c&lt;/sup&gt;</td>
<td>60:40</td>
<td>98</td>
</tr>
<tr>
<td>11</td>
<td>Me</td>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>H</td>
<td>i-Pr</td>
<td>H</td>
<td>29&lt;sup&gt;d&lt;/sup&gt;</td>
<td>88:12&lt;sup&gt;d&lt;/sup&gt;</td>
<td>88</td>
</tr>
<tr>
<td>12</td>
<td>t-Bu</td>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>H</td>
<td>i-Pr</td>
<td>H</td>
<td>30&lt;sup&gt;d&lt;/sup&gt;</td>
<td>88:12&lt;sup&gt;d&lt;/sup&gt;</td>
<td>85</td>
</tr>
</tbody>
</table>
Rationale of Migration

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.

- Antiperiplanar rearrangements of leaving group relative to the migrating bond were supported by numerous literatures.
Mechanistic Hypotheses for Three-Carbon Tethers

\[
\text{t-Bu} \quad \text{Ph} \\
\text{O} + \text{N}_3 \text{CH} \text{OH} \xrightarrow{\text{BF}_3 \cdot \text{OEt}_2} \quad \text{N}_3 \\
\text{t-Bu} \\
\text{[reversible]} \quad \text{[reversible]} \\
\text{t-Bu} \\
\text{Ph} \\
\text{OH}^{-} \\
\text{[major product]} \\
\text{t-Bu} \\
\text{Ph} \\
\text{HO} \quad \text{N} \\
\text{t-Bu} \\
\text{[minor product]}
\]
Mechanistic Hypotheses for Two-Carbon Tethers

\[
\text{Ketone} + \text{Phenyl azide} \rightarrow \text{Nitrone} \rightarrow \text{Product}
\]

\( \text{anti} \) migration of \( \text{back bond} \)

 major product
An asymmetric equivalent of the Schmidt reaction permits the stereocontrol in ring expansions of symmetrical cyclohexanones. Selectivities can be as high as ca. 98:2.

1,3-azido alcohols are generally more reactive and provide superior selectivities than 1,2-azido alcohols.

Some initial suggestions were proposed as to how the selectivity obtained in the overall process might be achieved.