Chiral Phosphine…The Nucleophilic Trigger

3+2 Cycloaddition
4+2 Annulation

Wilson, J. E.; Fu, G. C. Angew. Chem. Int. Ed. 2006, 45, 1426-1429 (3+2)

Cory Newman
February 17, 2006
3+2 Cycloaddition Reaction

3+2 Cycloaddition using Alkynoates

Nucleophilic Trigger
3+2 Cycloaddition Mechanism

Uses of non-Chiral Phosphorus

\[ R\text{CO}_2\text{Et} + \text{N}^\text{Ts} \xrightarrow{(20 \text{ mol}\% \text{ PbU}_3, \text{C}_6\text{H}_6, \text{rt})} \text{R}_\text{N}^\text{Ts} \text{CO}_2\text{Et} \]

a) \( R = \text{n-Pr}, \text{R}^1 = \text{Ph}, 63\% \)
b) \( R = \text{Et}, \text{R}^1 = \text{piperonyl}, 65\% \)
c) \( R = \text{n-Pr}, \text{R}^1 = 2\text{-furyl}, 33\% \)
d) \( R = \text{THPO}(\text{CH}_2)_7, \text{R}^1 = 1\text{-naphthyl}, 75\% \)


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First Example of Chiral Phosphorus

And the Best Chiral Phosphorus is......

And the Best Chiral Phosphorus is…….
Proposed Transition State
3+2 Cycloaddition of Allenes & Enones

Wilson, J. E.; Fu, G. C. Angew. Chem. Int. Ed. 2006, 45, 1426-1429
Survey of Chiral Phosphorus

\[ \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \]

\[ \begin{align*}
\text{313} & \quad \text{P} & \quad \text{P} & \quad \text{2} \\
\text{334} & \quad \text{A} & \quad \text{Ph} & \quad \text{B} & \quad \text{Ph} \\
\text{581} & \quad \text{P} & \quad \text{P} & \quad \text{2} \\
\text{627} & \quad (R)-\text{BINAP} & \\
\text{673} & \\
\text{734} & \\
\end{align*} \]

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Phosphine}^{[b]} & \text{Yield [%]}^{[c]} & \text{ee [%]}^{[d]} & \text{A:B} \\
\hline
(R)-2 & 64 & 88 & 13:1 \\
(S)-binapine & 0 & \text{--} & \text{--} \\
(R)-binap & 2 & 50 & >20:1 \\
(R)-nmdpp & 4 & -4 & 11:1 \\
(R,R)-Me-bpe & 61 & -4 & 6:1 \\
(R,R)-ferrotane & 64 & 11 & 7:1 \\
(R,R)-Et-DuPhos & 61 & 58 & 7:1 \\
\hline
\end{array}
\]
Survey of Chiral Phosphorus

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Phosphine[^b]</th>
<th>Yield [%][^c]</th>
<th>ee [%][^d]</th>
<th>A:B</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-2</td>
<td>64</td>
<td>88</td>
<td>13:1</td>
</tr>
<tr>
<td>(S)-binapine</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>(R)-binap</td>
<td>2</td>
<td>50</td>
<td>&gt; 20:1</td>
</tr>
<tr>
<td>(R)-nmdpp</td>
<td>4</td>
<td>-4</td>
<td>11:1</td>
</tr>
<tr>
<td>(R,R)-Me-bpe</td>
<td>61</td>
<td>-4</td>
<td>6:1</td>
</tr>
<tr>
<td>(R,R)-ferrotane</td>
<td>64</td>
<td>11</td>
<td>7:1</td>
</tr>
<tr>
<td>(R,R)-Et-DuPhos</td>
<td>61</td>
<td>58</td>
<td>7:1</td>
</tr>
</tbody>
</table>

[^b]: [Phosphine](#)
[^c]: Yield in percentage
[^d]: ee in percentage
## Scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R¹</th>
<th>Yield [%][b]</th>
<th>ee [%][c]</th>
<th>A:B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>64</td>
<td>88</td>
<td>13:1</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>4-chlorophenyl</td>
<td>76</td>
<td>82</td>
<td>7:1</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>4-methylphenyl</td>
<td>61</td>
<td>87</td>
<td>20:1</td>
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<td>Ph</td>
<td>4-methoxy-phenyl</td>
<td>54</td>
<td>88</td>
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<tr>
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<td>Ph</td>
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<td>87</td>
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<tr>
<td>6</td>
<td>4-methoxy-phenyl</td>
<td>Ph</td>
<td>67</td>
<td>87</td>
<td>10:1</td>
</tr>
<tr>
<td>7</td>
<td>2-furyl</td>
<td>Ph</td>
<td>69</td>
<td>88</td>
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<tr>
<td>8[d]</td>
<td>2-quinolyl</td>
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<td>52</td>
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<tr>
<td>9[d]</td>
<td>4-chlorophenyl</td>
<td>2-(5-methyl-furyl)</td>
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<td>89</td>
<td>&gt;20:1</td>
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<tr>
<td>10</td>
<td>Ph</td>
<td>2-thienyl</td>
<td>74</td>
<td>90</td>
<td>6:1</td>
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<tr>
<td>11</td>
<td>C≡CC₅H₁₁</td>
<td>Ph</td>
<td>65</td>
<td>85</td>
<td>6:1</td>
</tr>
<tr>
<td>12</td>
<td>C≡CTES</td>
<td>Ph</td>
<td>70</td>
<td>87</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>13</td>
<td>C₅H₁₁</td>
<td>Ph</td>
<td>39[e]</td>
<td>75</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

Wilson, J. E.; Fu, G. C. Angew. Chem. Int. Ed. 2006, 45, 1426-1429
Spiro Example

Dienones

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{Ph} \quad \text{CO}_2\text{Et} \\
\begin{array}{c}
\text{Ph} \quad \text{CO}_2\text{Et} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph}
\end{array} & \quad \text{CO}_2\text{Et} \\
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph}
\end{array}
\end{align*}
\]

\[
\begin{align*}
10\% \text{ (R)-2} & \quad \text{toluene} \\
\text{RT} & \quad \text{RT}
\end{align*}
\]

<table>
<thead>
<tr>
<th>( n )</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>93</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{Ph} \quad \text{CO}_2\text{Et} \\
\begin{array}{c}
\text{Ph} \quad \text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph}
\end{array} & \quad \text{Ph} \\
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{yield (%)} \quad \text{ee (%)} \\
\text{Ph} & \quad 75 \quad 89 \\
\text{2,6-dichlorophenyl} & \quad 68 \quad 73
\end{align*}
\]

4+2 Cycloaddition Reaction...

Kwon Reaction

\[
\text{Me} \quad \text{CO}_2\text{Et} + \text{R} \equiv \text{N} \equiv \text{Ts} \xrightarrow{\text{PBU}_3 (20 \text{ mol}\%)} \xrightarrow{\text{CH}_2\text{Cl}_2, \text{RT}} \text{R} \quad \text{CO}_2\text{Et}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>product</th>
<th>yield (%)</th>
<th>R</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph ((2a))</td>
<td>3a(^c)</td>
<td>98</td>
<td>4-pyridyl ((2k))</td>
<td>3k</td>
<td>92(^d)</td>
</tr>
<tr>
<td>4-OMeC(_6)H(_4) ((2b))</td>
<td>3b</td>
<td>99</td>
<td>4-NO(_2)C(_6)H(_4) ((2l))</td>
<td>3l</td>
<td>86</td>
</tr>
<tr>
<td>4-CH(_3)C(_6)H(_4) ((2c))</td>
<td>3c</td>
<td>95</td>
<td>2-OH(_2)C(_6)H(_4) ((2m))</td>
<td>3m</td>
<td>0</td>
</tr>
<tr>
<td>3-ClC(_6)H(_4) ((2d))</td>
<td>3d</td>
<td>96</td>
<td>2-OTBS(_2)C(_6)H(_4) ((2n))</td>
<td>3n</td>
<td>93</td>
</tr>
<tr>
<td>2-ClC(_6)H(_4) ((2e))</td>
<td>3e</td>
<td>93</td>
<td>2-pyrrolyl ((2o))</td>
<td>3o</td>
<td>0</td>
</tr>
<tr>
<td>4-FC(_6)H(_4) ((2f))</td>
<td>3f</td>
<td>95</td>
<td>N-Boc-2-pyrrolyl ((2p))</td>
<td>3p</td>
<td>99</td>
</tr>
<tr>
<td>4-CN(_6)H(_4) ((2g))</td>
<td>3g</td>
<td>98</td>
<td>trans-styrenyl ((2q))</td>
<td>3q</td>
<td>trace(^e)</td>
</tr>
<tr>
<td>2-CF(_3)C(_6)H(_4) ((2h))</td>
<td>3h</td>
<td>98</td>
<td>(t)-butyl ((2r))</td>
<td>3r</td>
<td>86(^f)</td>
</tr>
<tr>
<td>1-naphthyl ((2i))</td>
<td>3i</td>
<td>96</td>
<td>(n)-propyl ((2s))</td>
<td>3s</td>
<td>0(^g)</td>
</tr>
<tr>
<td>2-furyl ((2j))</td>
<td>3j</td>
<td>97</td>
<td>2-furyl ((2j))</td>
<td>3j</td>
<td>97</td>
</tr>
</tbody>
</table>

4+2 Cycloaddition Mechanism

# Additional Substrates

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\[
\begin{align*}
R & \quad \text{Ts} \quad \text{R}^' \\
\text{2} & \quad + \quad 12 \\
P\text{Bu}_3 (20 \text{ mol%}) & \quad \text{CH}_2\text{Cl}_2, \text{ RT} \\
\end{align*}
\]

\[
\begin{align*}
R & \quad \text{product} \\
\text{13} & \quad \text{yield (%)}^b \quad \text{dr}^c \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R'</th>
<th>product</th>
<th>yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (2a)</td>
<td>4-ClC\text{6}H\text{4} (12a)</td>
<td>13a</td>
<td>99</td>
<td>98:2</td>
</tr>
<tr>
<td>2</td>
<td>Ph (2a)</td>
<td>2-FC\text{6}H\text{4} (12b)</td>
<td>13b</td>
<td>99</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td>Ph (2a)</td>
<td>3-OMeC\text{6}H\text{4} (12c)</td>
<td>13c</td>
<td>99</td>
<td>98:2</td>
</tr>
<tr>
<td>4</td>
<td>Ph (2a)</td>
<td>2-MeC\text{6}H\text{4} (12d)</td>
<td>13d</td>
<td>82</td>
<td>88:12</td>
</tr>
<tr>
<td>5</td>
<td>Ph (2a)</td>
<td>Ph (12e)</td>
<td>13e\text{d}</td>
<td>99</td>
<td>98:2</td>
</tr>
<tr>
<td>6</td>
<td>4-OMeC\text{6}H\text{4} (2b)</td>
<td>Ph (12e)</td>
<td>13f</td>
<td>99</td>
<td>97:3</td>
</tr>
<tr>
<td>7</td>
<td>4-NO\text{2}C\text{6}H\text{4} (2l)</td>
<td>Ph (12e)</td>
<td>13g</td>
<td>90</td>
<td>95:5</td>
</tr>
<tr>
<td>8</td>
<td>3-ClC\text{6}H\text{4} (2d)</td>
<td>4-ClC\text{6}H\text{4} (12a)</td>
<td>13h</td>
<td>99</td>
<td>98:2</td>
</tr>
<tr>
<td>9</td>
<td>2-CF\text{3}C\text{6}H\text{4} (2h)</td>
<td>4-ClC\text{6}H\text{4} (12a)</td>
<td>13i</td>
<td>80</td>
<td>90:10</td>
</tr>
<tr>
<td>10</td>
<td>2-ClC\text{6}H\text{4} (2e)</td>
<td>3-OMeC\text{6}H\text{4} (12c)</td>
<td>13j</td>
<td>96</td>
<td>83:17</td>
</tr>
<tr>
<td>11</td>
<td>4-MeC\text{6}H\text{4} (2c)</td>
<td>3-OMeC\text{6}H\text{4} (12c)</td>
<td>13k</td>
<td>99</td>
<td>98:2</td>
</tr>
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</table>

---

# Asymmetric 4+2 Reaction

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>phosphine</th>
<th>ee (%)</th>
<th>cis:trans</th>
<th>isolated yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>Me-BPE</td>
<td>-72</td>
<td>72:28</td>
<td>94</td>
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<tr>
<td>2</td>
<td>Et-BPE</td>
<td>-87</td>
<td>66:34</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>TANGPHOS</td>
<td>-44</td>
<td>34:66</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>-21</td>
<td>74:26</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>-7</td>
<td>75:25</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>-62</td>
<td>72:28</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>0</td>
<td>70:30</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>51</td>
<td>69:31</td>
<td>99</td>
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<tr>
<td>9</td>
<td>1</td>
<td>98</td>
<td>91:9</td>
<td>93</td>
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<tr>
<td>10</td>
<td>BINAPINE</td>
<td>-</td>
<td>-</td>
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</table>

Allene Scope

![Chemical structure]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>cis:trans</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>98</td>
<td>91:9</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>87</td>
<td>99:1</td>
<td>78</td>
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<tr>
<td>3</td>
<td>4-(CF&lt;sub&gt;3&lt;/sub&gt;)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>88</td>
<td>99:1</td>
<td>81</td>
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<tr>
<td>4</td>
<td>H</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>68</td>
<td>—</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>COPh</td>
<td>76</td>
<td>—</td>
<td>97</td>
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</table>

# Imine Scope

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>cis:trans</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>98</td>
<td>91:9</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>3-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>98</td>
<td>93:7</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>3,4,5-(MeO)&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>96</td>
<td>96:4</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>4-(MeO)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>98</td>
<td>93:7</td>
<td>42</td>
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<tr>
<td>5</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>96</td>
<td>91:9</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>3-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>99</td>
<td>89:11</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>2-(NO&lt;sub&gt;2&lt;/sub&gt;)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>68</td>
<td>96:4</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>2-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>60</td>
<td>79:21</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>2-naphthyl</td>
<td>99</td>
<td>93:7</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>2-furyl</td>
<td>97</td>
<td>87:13</td>
<td>98</td>
</tr>
<tr>
<td>11</td>
<td>3-pyridyl</td>
<td>97</td>
<td>91:9</td>
<td>76</td>
</tr>
</tbody>
</table>

Use in Synthesis

Why Not…

OR