A Survey of Recent Advances In Non-Lewis Acid Catalyzed Catalytic, Enantioselective Cycloadditions

**Scope:**

[4+2]

\[ B \equiv A \quad Y \quad C \equiv D \quad X \rightarrow B \quad A \quad Y \quad C \quad D \quad X \]

[3+2]

\[ B \equiv A \quad Y \quad C \quad X \rightarrow B \quad A \quad Y \quad C \quad X \]

[2+2]

\[ A \quad Y \quad B \quad X \rightarrow A \quad C \quad B \quad D \]

**The Limitations Imposed:**
1. No Lewis Acid
2. No Transition metals
3. Published within last 10-15 years (not included in “Comprehensive Asymmetric Catalysis”)
4. Trivial derivitization of known work is excluded (eg. Take a cross-section of the literature)

**Motivation:**
1. Identify current directions of the field
2. Identify potential advantages (if any) to a non-Lewis Acid promoted pericyclic process
3. Identify modes of activation DIFFERENT than the LUMO-lowering function of LA’s
4. Pay special attention to methods that DO NOT activate the 2π component

**Purposefully Excluded:**
1. Chiral Bronsted Acids: see motivation 3 and we just had a group meeting on it
2. Antibodies (entire group meeting)
Non-LA Catalyzed Pericyclic Reaction: Where to Start?

```
... successful application of chiral Lewis acids to the Diels-Alder reaction if frequently a reliable indicator of the potential utility to other classes of reactions. Notably, facile extension to aldol, ene, Michael, dipolar cycloaddition, and hetero-Diels-Alder reactions are a common outgrowth of studies in the enantioselective catalysis of the carbocyclic Diels-Alder reaction.” (Evans and Johnson)
```

Motivating Questions

- What do you do when your Substrate (4π or 2π) is not Stable to LA’s?
- In the situation where LA’s simply Fail, what methods are available?

Corollaries:

- Are any of these other methods general?
- In what areas is there a dire need for New Methodology?

Yates, P., and Eaton, P., JACS, 1960, 82, 4436;

A superabreviated summary of the “Standard Method” (1992 review)

<table>
<thead>
<tr>
<th>chiral catalyst (mol equiv)</th>
<th>reactants</th>
<th>ee max (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>methylaluminum binaphtholate A (eq 2)</td>
<td>hetero Diels–Alder reaction</td>
<td>97</td>
</tr>
<tr>
<td>dichlorotitanium diolate + MS 4 A (eq 8)</td>
<td>3-Acyl-1,3-oxazolidin-2-ones + Cp or isoprene</td>
<td>94</td>
</tr>
<tr>
<td>diborate from binaphthol (eq 16)</td>
<td>Cp + acrylate or methacrolein</td>
<td>90</td>
</tr>
<tr>
<td>acyloxy-borane (eq 18)</td>
<td>dienes + acrylic acid or α,β-unsaturated aldehydes</td>
<td>96</td>
</tr>
<tr>
<td>alkyldichloroborane (Figure 11)</td>
<td>dienes + α,β-unsaturated esters</td>
<td>97</td>
</tr>
<tr>
<td>oxazaborolidinone (Figure 12)</td>
<td>dienes + 2-bromoacrolein</td>
<td>95</td>
</tr>
<tr>
<td>BBr₃ + N-methylprolinol (eq 23)</td>
<td>Cp + α,β-unsaturated aldehydes</td>
<td>97</td>
</tr>
<tr>
<td>Co complex with chiral diphosphines</td>
<td>homo Diels–Alder reaction</td>
<td>98</td>
</tr>
</tbody>
</table>

Some Useful [4+2]Reviews: (including Non-LAPromoted processes)

Material Will be Covered in the order of “FG Complexity”

Aldehyde Ketone Carboxylic Acid Derivative 1,2 inclusive FG’s (eg. Dimethylethlenedicarboxylate) etc…

2\pi

4\pi

Aldehyde Ketone Carboxylic Acid Derivative 1,2 inclusive FG’s (eg. Dimethylethlenedicarboxylate) 1,1-exclusive FG’s (eg. Ketoester) etc…

Carbocyclic only

Acyclic

O-substituted (danishefsky’s diene)

Heterocyclic (imine, special aldehydes)

More complex Inverse electron demand (polycyclic, Heterocyclic, etc)

Increasing FG complexity (more difficult to implement in a long synthesis)
MacMillan: Extension from Imminium ion catalysis

\[
\begin{align*}
\text{R} & \xrightarrow{5 \text{ mol}\% \text{cat.}} \text{MeOH-H}_2\text{O,} \\
& \quad 23^\circ \text{C} \rightarrow \text{(2S)-endo} \quad \text{R} \quad \text{(2S)-exo} \\
\end{align*}
\]

**Catalyst survey**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>\text{ex}:\text{endo}</th>
<th>\text{exo ee} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>27</td>
<td>81</td>
<td>2.7:1</td>
<td>48 (2R)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>10</td>
<td>80</td>
<td>2.3:1</td>
<td>59 (2S)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>23</td>
<td>92</td>
<td>2.6:1</td>
<td>57 (2R)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>84</td>
<td>82</td>
<td>3.6:1</td>
<td>74 (2R)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>8</td>
<td>99</td>
<td>1.3:1</td>
<td>93 (2S)</td>
</tr>
</tbody>
</table>

**Aldehyde scope**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>\text{ex}:\text{endo}</th>
<th>\text{exo ee} (%)</th>
<th>\text{endo ee} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>16</td>
<td>75</td>
<td>1:1</td>
<td>86 (2S)</td>
<td>90 (2S)</td>
</tr>
<tr>
<td>2</td>
<td>Pr</td>
<td>14</td>
<td>92</td>
<td>1:1</td>
<td>86 (2S)</td>
<td>90 (2S)</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>14</td>
<td>81</td>
<td>1:1</td>
<td>84 (2S)</td>
<td>93 (2S)</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>21</td>
<td>99</td>
<td>1.3:1</td>
<td>93 (2S)</td>
<td>93 (2S)</td>
</tr>
<tr>
<td>5</td>
<td>Furyl</td>
<td>24</td>
<td>89</td>
<td>1:1</td>
<td>91 (2S)</td>
<td>93 (2S)</td>
</tr>
</tbody>
</table>

Imine Lumo-lowering capability of imines extended to pericyclic process

MacMillan, et al., *JACS*, 2000, 122, 4243
Imine activation of acetylene: *JOC*, 1976, 41, 183
MacMillan: [4+2] diene scope

### Diene Scope

\[
\text{entry} \quad \text{diene} \quad R \quad \text{product} \quad \text{yield} \quad \text{exo:endo} \quad \% \text{ee}^{a,b}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>diene</th>
<th>R</th>
<th>product</th>
<th>yield</th>
<th>exo:endo</th>
<th>% ee$^{a,b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="diene" /></td>
<td>Me</td>
<td><img src="image2" alt="product" /></td>
<td>75</td>
<td>35:1</td>
<td>96$^c$</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="diene" /></td>
<td>H</td>
<td><img src="image4" alt="product" /></td>
<td>82</td>
<td>1:14</td>
<td>94$^d$</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="diene" /></td>
<td>H</td>
<td><img src="image6" alt="product" /></td>
<td>84</td>
<td>--</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="diene" /></td>
<td>H</td>
<td><img src="image8" alt="product" /></td>
<td>90</td>
<td>--</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="diene" /></td>
<td>Me</td>
<td><img src="image10" alt="product" /></td>
<td>75</td>
<td>--</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="diene" /></td>
<td>H</td>
<td><img src="image12" alt="product" /></td>
<td>75</td>
<td>1:5</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="diene" /></td>
<td>H</td>
<td><img src="image14" alt="product" /></td>
<td>72</td>
<td>1:11</td>
<td>85</td>
</tr>
</tbody>
</table>

**Gem-dimethyl group enforces E-enamine**

Typically difficult substrates
Enal dienophile: Broaden Scope and Increase Utility

- **1,2 Diamine**  

![Reaction Scheme]

- **Hydrazide Derived**

Use of HClO₄ and F₃CSO₃H as cocatalyst increases rates and selectivity

### Optimized

Substrate, crotonaldehyde,  
Yield 97%, endo:exo (7.8:1),  
er (96:4)

### Goal: Increase rate via a-effect

don’t provide reaction times  
do show that imminium ion formation if faster than imidazolidinone

<table>
<thead>
<tr>
<th>entry</th>
<th>diene</th>
<th>yield (%)</th>
<th>exo:endo</th>
<th>exo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CP</td>
<td>96</td>
<td>1.9:1</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>CP</td>
<td>93</td>
<td>2.2:1</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>CP</td>
<td>92</td>
<td>2:1</td>
<td>90⁺</td>
</tr>
<tr>
<td>4</td>
<td>CP</td>
<td>84</td>
<td>1.7:1</td>
<td>90⁺</td>
</tr>
<tr>
<td>5</td>
<td>PBD</td>
<td>86</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>MPD</td>
<td>71</td>
<td>1.9:1</td>
<td>69⁺</td>
</tr>
<tr>
<td>7</td>
<td>CP</td>
<td>90</td>
<td>1.2:1</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>CP</td>
<td>88</td>
<td>2.1:1</td>
<td>94⁺</td>
</tr>
<tr>
<td>9</td>
<td>CP</td>
<td>83</td>
<td>1.6:1</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>CP</td>
<td>84</td>
<td>2.6:1</td>
<td>85</td>
</tr>
</tbody>
</table>

**A highly Exo Selective Catalyst**

- **Binam Derived**

\[
\begin{align*}
\text{CHO} & \quad + \quad \text{CHO} \\
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array} & \quad \xrightarrow{\text{CF}_3\text{C}_6\text{H}_5} \quad \begin{array}{c}
\text{CHO} \\
\text{Ph}
\end{array}
\end{align*}
\]

RT, 20h, 87%
Exo:endo (6.5:1),
er (86:14)

Need -20, 160h
To get higher Exo or Exo selectivity

**For Comparison**

\[
\begin{align*}
\text{CHO} & \quad + \quad \text{CHO} \\
\begin{array}{c}
\text{R}_1 \\
\text{R}_2
\end{array} & \quad \xrightarrow{\text{cat.} \quad \text{-78}^\circ\text{C, CH}_2\text{Cl}_2} \quad 4\text{h}
\end{align*}
\]

cat B
endo/exo: 99/1
99% ee
Extension to $\alpha$-Acetoxy Substituted Aldehydes

Standard Catalysts (a-j) gave low yields, and poor selectivity, $X = \text{Halide (Br)}$

Work well with LA’s. Is the point moot?

Enamine intermediates: Hetero-Diels-Alder Screening and Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Eno[ equiv]</th>
<th>Solvent</th>
<th>T[°C]</th>
<th>Yield[%]</th>
<th>ee[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a (20)</td>
<td>1.1</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>69</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>1b (20)</td>
<td>1.1</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>1c (20)</td>
<td>1.1</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>6</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>1d (20)</td>
<td>1.1</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>46</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>1e (10)</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>71</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>1e (10)</td>
<td>1.5</td>
<td>CH₂Cl₂</td>
<td>−15°C→RT</td>
<td>70</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>1e (10)</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>−15°C→RT</td>
<td>93</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>1e (10)</td>
<td>2</td>
<td>toluene</td>
<td>−15°C→RT</td>
<td>77</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>1e (10)</td>
<td>2</td>
<td>CDCl₃</td>
<td>−15°C→RT</td>
<td>69</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>1e (10)</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>−15°C→RT</td>
<td>74</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>1e (10)</td>
<td>2</td>
<td>MeCN</td>
<td>−15°C→RT</td>
<td>59</td>
<td>90</td>
</tr>
</tbody>
</table>

[a] Solvent (0.5 mL). [b] RT = room temperature. [c] Combined yield of 6ba and 7ba. [d] The ee values were determined by HPLC.

Note two step procedure
Reaction time ~15-40h

<table>
<thead>
<tr>
<th>Carboxylic Acid Derivative</th>
<th>1,2 inclusive FG’s (eg. Dimethylethlenedicarboxylate)</th>
<th>1,1-exclusive FG’s (eg. Ketoester)</th>
<th>etc…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldehyde</td>
<td>Ktone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Increasing FG complexity**

(1) *Increasing FG complexity* (more difficult to implement in a long synthesis)

- **2π**
  - Carbocyclic only
  - Acyclic
    - O-substituted (danishefsky’s diene)
    - Heterocyclic (imine, special aldehydes)

- **4π**
  - More complex
  - Inverse electron demand (polycyclic, Heterocyclic, etc)
MacMillan: Ketone Substrates

Obstacles to overcome

Table 1. Effect of Amine Architecture on the Diels—Alder Reaction between 4-Hexen-3-one and Cyclopentadiene

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>R₁</th>
<th>R₂ (R₃)</th>
<th>time (h)</th>
<th>% yield</th>
<th>endo:exo</th>
<th>% ee⁺⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Bn</td>
<td>Me (Me)</td>
<td>48</td>
<td>20⁺⁻</td>
<td>7:1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Bn</td>
<td>i-Bu (H)</td>
<td>48</td>
<td>27⁺⁻</td>
<td>9:1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Ph</td>
<td>Ph (H)</td>
<td>22</td>
<td>88⁺⁻</td>
<td>21:1</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Bn</td>
<td>Ph (H)</td>
<td>42</td>
<td>83⁺⁻</td>
<td>23:1</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>Bn</td>
<td>5-Me-furyl (H)</td>
<td>22</td>
<td>89⁺⁻</td>
<td>25:1</td>
<td>90</td>
</tr>
</tbody>
</table>

Note perchlorate counterion

For rate acceleration with perchlorate (5.0 M) see Grieco, JACS, 1990, 112, 4595.
Extension to Inverse Electron Demand: Imine Dienophile: Enaminediene

1. Generate Imine
2. Generate enamine
3. Undergo reaction
4. Release secondary amine catalyst

- TS Model, Implying stepwise mechanism

- Catalysts Surveyed

- Scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Product</th>
<th>t [h]</th>
<th>T [°C]</th>
<th>Yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>24</td>
<td>50</td>
<td>82</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
<td>48</td>
<td>50</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>2b</td>
<td>17</td>
<td>RT</td>
<td>70</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>2c</td>
<td>24</td>
<td>50</td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>2c</td>
<td>24</td>
<td>RT</td>
<td>75</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>2c</td>
<td>24</td>
<td>RT</td>
<td>20</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>1d</td>
<td>2d</td>
<td>24</td>
<td>RT</td>
<td>40</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>1e</td>
<td>2e</td>
<td>24</td>
<td>RT</td>
<td>10</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Imine Dienophile 1,1-disubstituted allene = Diene equivalent

The reaction

\[
\begin{array}{c}
R = \text{Ph} \\
3 = 3\text{-MeC}_6\text{H}_4 \\
4 = 4\text{-MeO}\text{C}_6\text{H}_4 \\
6 = 3\text{-BrC}_6\text{H}_4 \\
7 = 3\text{-(NO}_2)\text{C}_6\text{H}_4 \\
8 = 2\text{-ClC}_6\text{H}_4 \\
9 = 2\text{-naphthyl} \\
10 = 2\text{-furyl} \\
11 = 3\text{-pyridyl}
\end{array}
\]

For the initial racemic report see:

Catalysts: Bis-phosphines and phosphepines

Mechanism?

Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>ee (%)</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(_6)H(_4)</td>
<td>98</td>
<td>93:7</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>3,4,5-(MeO)(_3)C(_6)H(_2)</td>
<td>96</td>
<td>96:4</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>4-(MeO)(_2)C(_6)H(_4)</td>
<td>98</td>
<td>93:7</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>4-ClC(_6)H(_4)</td>
<td>96</td>
<td>91:9</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>3-BrC(_6)H(_4)</td>
<td>99</td>
<td>89:11</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>2-(NO(_2))C(_6)H(_4)</td>
<td>68</td>
<td>96:4</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>2-ClC(_6)H(_4)</td>
<td>60</td>
<td>79:21</td>
<td>75</td>
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<tr>
<td>9</td>
<td>2-naphthyl</td>
<td>99</td>
<td>93:7</td>
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<td>10</td>
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<tr>
<td>11</td>
<td>3-pyridyl</td>
<td>97</td>
<td>91:9</td>
<td>76</td>
</tr>
</tbody>
</table>

The reaction moderate with electron poor substrates

dr with bisphosphines variable in Benzaldehyde imine test substrate
Outline

Increasing FG complexity
(more difficult to implement
In a long synthesis)

More complex
Inverse electron demand
(polycyclic,
Heterocyclic, etc)
Chiral Base Activation of Diene (1,2-inclusive)

Halogenated solvents are best (\(\text{MeOH}, \text{THF}\) and \(\text{Toluene}\) screened too). Up to 89:11 er at -78 ºC

Rigid, tertiary, cyclic amines perform better (er) than primary or secondary.


Catalyst survey

<table>
<thead>
<tr>
<th>entry</th>
<th>catalysts (eq)</th>
<th>time/h</th>
<th>yield/%</th>
<th>3a:3b</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 (1.0)</td>
<td>0.5</td>
<td>91</td>
<td>7.8:1</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>5 (1.0)</td>
<td>0.5</td>
<td>100</td>
<td>8.2:1</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>6a (0.1)</td>
<td>0.5</td>
<td>95</td>
<td>7.1:1</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>7 (1.0)</td>
<td>0.5</td>
<td>100</td>
<td>7.2:1</td>
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<tr>
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<td>8 (1.0)</td>
<td>0.5</td>
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<td>9.6:1</td>
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<td>9 (1.0)</td>
<td>0.5</td>
<td>98</td>
<td>8.5:1</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>6b (1.0)</td>
<td>1.0</td>
<td>93</td>
<td>5.9:1</td>
<td>17</td>
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<tr>
<td>8</td>
<td>6c (1.0)</td>
<td>1.5</td>
<td>93</td>
<td>6.6:1</td>
<td>0</td>
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</table>

Solvent and Temperature

<table>
<thead>
<tr>
<th>entry</th>
<th>catalysts</th>
<th>solvent</th>
<th>tempºC</th>
<th>yield/%</th>
<th>3a:3b</th>
<th>% ee</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>4 (1.0)</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>-78/-20</td>
<td>98</td>
<td>11:1</td>
<td>77</td>
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<tr>
<td>2</td>
<td>4 (1.0)</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>0</td>
<td>91</td>
<td>7.8:1</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>4 (0.1)</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>0</td>
<td>100</td>
<td>6.9:1</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>4 (&lt;0.1)d</td>
<td>toluene</td>
<td>0</td>
<td>89</td>
<td>2.6:1</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>4 (1.0)</td>
<td>THF</td>
<td>0</td>
<td>96</td>
<td>2.1:1</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>4 (1.0)</td>
<td>(\text{MeOH})</td>
<td>0</td>
<td>98</td>
<td>7.7:1</td>
<td>0</td>
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<tr>
<td>7</td>
<td>6a (&lt;0.1)d</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>-78/-20</td>
<td>95</td>
<td>12:1</td>
<td>51</td>
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<tr>
<td>8</td>
<td>6a (0.1)d</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>0</td>
<td>95</td>
<td>7.1:1</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>6a (&lt;0.1)d</td>
<td>toluene</td>
<td>0</td>
<td>93</td>
<td>3.7:1</td>
<td>44</td>
</tr>
<tr>
<td>10</td>
<td>6a (0.5)d</td>
<td>THF</td>
<td>0</td>
<td>95</td>
<td>4.6:1</td>
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</tr>
<tr>
<td>11</td>
<td>6a (1.0)</td>
<td>(\text{MeOH})</td>
<td>0</td>
<td>100</td>
<td>10:1</td>
<td>0</td>
</tr>
</tbody>
</table>
Chiral Base: Recent Application to Anthrone

Catalysts

1d : Ar = Ph
1f : Ar = \( \text{N} \)
1h : Ar = \( \text{Ph} \)

Proposed Model

<table>
<thead>
<tr>
<th>Product</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>Catalyst</th>
<th>( t/h )</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5e</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2</td>
<td>1</td>
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<td></td>
<td></td>
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<td>24</td>
<td>91</td>
<td>61</td>
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<td>5d</td>
<td>H</td>
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<td>H</td>
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<td></td>
<td></td>
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<td>H</td>
<td>F</td>
<td>H</td>
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<td>30</td>
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<td>73</td>
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<td></td>
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<td>1h</td>
<td>96</td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>5i</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>2</td>
<td>10</td>
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<td></td>
<td></td>
<td></td>
<td>1h</td>
<td>72</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>5j</td>
<td>Bu(^\d)</td>
<td>H</td>
<td>H</td>
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<td>0.25</td>
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<td></td>
<td>1h</td>
<td>3</td>
<td>97</td>
<td>87</td>
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</tbody>
</table>

C2 Symmetric Guanidine as Chiral Base

**Solvent effect**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>temp/°C</th>
<th>time/h</th>
<th>yield/%</th>
<th>ee/%</th>
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<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>rt</td>
<td>1</td>
<td>92</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>rt</td>
<td>1</td>
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<td>52</td>
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<tr>
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<td>CHCl₃</td>
<td>rt</td>
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<td>95</td>
<td>52</td>
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<td>1.5</td>
<td>90</td>
<td>68</td>
</tr>
<tr>
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<td>CH₂Cl₂</td>
<td>−20</td>
<td>3</td>
<td>90</td>
<td>81c</td>
</tr>
<tr>
<td>8</td>
<td>CH₂Cl₂</td>
<td>−40</td>
<td>6</td>
<td>91</td>
<td>75</td>
</tr>
</tbody>
</table>

Only halogenated
Gives good er

Halogenated anthrones can be used. If hydroxylated, then michael addition pdts are isolated (in excellent er) (maleate and fumaratederivatives do not work)

<table>
<thead>
<tr>
<th>Carbocyclic only</th>
<th>Acyclic</th>
<th>O-substituted (danishefsky’s diene)</th>
<th>Heterocyclic (imine, special aldehydes)</th>
<th>Increasing FG complexity (more difficult to implement in a long synthesis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldehyde</td>
<td>Ketone</td>
<td>Carboxylic Acid Derivative</td>
<td>1,2 inclusive FG’s (eg. Dimethylethlenedicarboxylate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,1-exclusive FG’s (eg. Ketoester)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>etc…</td>
</tr>
</tbody>
</table>

More complex Inverse electron demand (polycyclic, Heterocyclic, etc)
Ketenes dienophiles!? (from Enals!)

Ketenes dienophiles!? (from Enals!)

**Scope**

![Chemical reaction diagram]

Ketones too

<table>
<thead>
<tr>
<th>entry</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>product</th>
<th>% yield$^b$</th>
<th>% ee$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OEt</td>
<td>Ph</td>
<td>[Product image]</td>
<td>90</td>
<td>99 (S,S)</td>
</tr>
<tr>
<td>3</td>
<td>OEt</td>
<td>[Substituted ring]</td>
<td>81</td>
<td>99 (S,S)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>OEt</td>
<td>Me</td>
<td>[Product image]</td>
<td>55</td>
<td>99 (S,S)</td>
</tr>
<tr>
<td>5</td>
<td>OEt</td>
<td>[Furan ring]</td>
<td>71</td>
<td>99 (S,S)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>OEt</td>
<td>$n$-Pr</td>
<td>[Product image]</td>
<td>58</td>
<td>99 (S,S)</td>
</tr>
</tbody>
</table>

Ketones show slightly depressed Yields (still excellent er’s!)
Bode ketene [4+2] model

- Intermediate geometry from stoichiometric experiments and by analogy to other reactions with same intermediate (maybe)

Similar transformations

Extension to synthesis of δ-lactones

**Reaction**

\[ \text{HCl} + \text{R}^1 + \text{R}^2 \text{CO}_2\text{Me} \rightarrow \text{products} \]

**Scope**

| entry | R\(^1\) | R\(^2\) | product | % yield | % ee 

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>p-Tol</td>
<td>74</td>
<td>97 (S,S)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>n-Pr</td>
<td>84</td>
<td>98 (S,S)</td>
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<td>3</td>
<td>Ph</td>
<td>c-Hex</td>
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<td>95 (S,S)</td>
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</tr>
<tr>
<td>4</td>
<td>n-C(_3)H(_9)</td>
<td>p-Tol</td>
<td>70</td>
<td>99 (S,S)</td>
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<tr>
<td>5</td>
<td>OTBS</td>
<td>p-Tol</td>
<td>83</td>
<td>95 (R,S)</td>
<td></td>
</tr>
</tbody>
</table>

Dr's typically >10:1
OTBs substate 3:1

<table>
<thead>
<tr>
<th>Carbo cyclic only</th>
<th>Aldehyde</th>
<th>Ketone</th>
<th>Carboxylic Acid Derivative</th>
<th>1,2 inclusive FG’s (eg. Dimethylethlenedicarboxylate)</th>
<th>1,1-exclusive FG’s (eg. Ketoester)</th>
<th>etc…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclic</td>
<td></td>
<td></td>
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<tr>
<td>O-substituted (danishefsky’s diene)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Heterocyclic (imine, special aldehydes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

More complex
Inverse electron demand (polycyclic, Heterocyclic, etc)

Increasing FG complexity (more difficult to implement in a long synthesis)
Carboxylic Acid to Ketene + o-quinone: Extension of [2+2]

\[
\text{Hünig's base, THF, -78°C}
\]

Ultimate applicability

Table 1. Synthesis of o-Chloranil-Derived Cycloadducts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid Chloride</th>
<th>Product</th>
<th>% ee</th>
<th>% Yield</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂C-Cl</td>
<td>2a</td>
<td>99</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>H₂C-CH₃</td>
<td>2b</td>
<td>93</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>Pr</td>
<td>2c</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>2d</td>
<td>99</td>
<td>72</td>
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<tr>
<td>5</td>
<td>pOMePhCl</td>
<td>2e</td>
<td>99</td>
<td>58</td>
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<tr>
<td>6</td>
<td>pOMePhCl</td>
<td>2f</td>
<td>93</td>
<td>75</td>
</tr>
</tbody>
</table>

\[ \text{Reactions run with 10 mol% catalyst, 0.55 mmol Hünig's base, 0.55 mmol acid halide, and 0.55 mmol 1a at -78 °C with slow addition of the acid halide over 5 h employed for α-aryl acid halides (2c-e, f). Yields given are for isolated products.} \]

Lecta, T., et al., JACS, 2006, 128, 1810-1811 also with diimides and cat. Zn(OTf)₂
[4+2] Summary: By Catalyst and Reaction Type

**Lewis Acid**

**Imine Activating dienophile**

**Enamine Activating dienophile**

**Enamine Activating diene**

Variable, but Optimizable
Exo/endo Labile dipolarophile

stoichiometric
[4+2] Summary

**Tertiary Phosphines Activating “diene”**

\[
\begin{align*}
&\text{all carbon} \\
&\text{equivalent} \\
&\text{"special cases"}
\end{align*}
\]

**Tertiary Amines Activating “diene”**

Cyclic, Conjugated ketones and esters

\( \square = C, O \)

**Tertiary Amines Activating dienophile**

\( X = Y = \text{Carbon} \)

\( A = D = \text{Oxygen or Nitrogen} \)
[4+2] Summary

NHC’s activating dienophile

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{X} & \quad \text{Y} \\
\text{OR} & \\
\text{Cl} & \\
\end{align*}
\]

\[\text{NHC} \rightarrow \text{TS} \]

\[
\begin{align*}
\text{H} & \quad \text{NTs} \\
\text{R} & \\
\end{align*}
\]

\[\text{R} = \text{Alkyl, Aryl} \]

\[
\begin{align*}
\text{A} & = \text{N} \\
\text{B} & = \text{O} \\
\text{R} & \text{CO}_2 \text{R} \\
\text{Ts} & = \text{O} \\
\text{T} & = \text{A} \\
\end{align*}
\]
[3+2]: Outline:

- A=B=C=X=Y=Carbon
- A, B, or C are heteroatoms
All Carbon [3+2]: Activate the $4\pi$ (3 atom) Method is predominant

- Background literature, Proof of principle and Preliminary reports

Limitations / Trends
Crotonates and methyl methacrylate
Dimerize too fast ---> Need
Activated alkene
Alkynes need more nucleophilic Phosphine,

1995: $X = \text{OMe}$
EWG = Ester, Ketone, Nitrile
0.1 equiv PR$_3$, Benzene, rt
TEA does not work

yield 60-80's (methyl ketone 55)

Other reactions too
For reviews see:
and
Denmark, S. E., Beutner, G. E., Lewis Base Catalysis:
An Emerging Paradigm in Organic Synthesis...
Enantioselective All Carbon [3+2]!

The Reaction

Catalysts

Results

<table>
<thead>
<tr>
<th>entry</th>
<th>phosphine</th>
<th>E</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>solvent</th>
<th>T(°C)</th>
<th>yield (%)</th>
<th>A:B</th>
<th>% ee of A</th>
<th>config</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>COOEt</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>benzene</td>
<td>rt</td>
<td>66</td>
<td>95:5</td>
<td>81</td>
<td>(−) R</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>COOEt</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>benzene</td>
<td>rt</td>
<td>76</td>
<td>97:3</td>
<td>81</td>
<td>(−) R</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>COOEt</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>benzene</td>
<td>rt</td>
<td>80</td>
<td>80:20</td>
<td>56</td>
<td>(+) S</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>COOEt</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>benzene</td>
<td>rt</td>
<td>83</td>
<td>72:29</td>
<td>6</td>
<td>(+) S</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>COOEt</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>benzene</td>
<td>rt</td>
<td>33</td>
<td>73:27</td>
<td>12</td>
<td>(−) R</td>
</tr>
<tr>
<td>11</td>
<td>8</td>
<td>COOEt</td>
<td>Et</td>
<td>H</td>
<td>H</td>
<td>toluene</td>
<td>0</td>
<td>88</td>
<td>100:0</td>
<td>93</td>
<td>(−) R</td>
</tr>
</tbody>
</table>

Proposed TS: concerted [3+2]

Geometry of Acceptor Olefin unchanged
Acrylonitrile, fumarate and maleate give depressed yields and er’s.

Extension to Imine dipolarophiles

The Reaction

![Reaction Diagram]

\[ \text{CO}_2\text{R'} + \text{Ar} \xrightarrow{\text{Ts, PR}_3} \text{R} - \text{Ar} - \text{CO}_2\text{R'} \]

Catalysts

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>ee</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-BINAP</td>
<td>45% (+)</td>
<td>13</td>
</tr>
<tr>
<td>(R)(-)-MOP</td>
<td>11% (+)</td>
<td>45</td>
</tr>
<tr>
<td>(R,R)-Trost ligand</td>
<td>19% (-)</td>
<td>60</td>
</tr>
<tr>
<td>(R)-PHOX</td>
<td>0%</td>
<td>18</td>
</tr>
<tr>
<td>(R,R)-Me-BPE</td>
<td>0%</td>
<td>70</td>
</tr>
<tr>
<td>(R,R)-Me-DuPHOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R,S)-Josiphos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R,R)-Et-FerroTANE</td>
<td>22% (+)</td>
<td>47</td>
</tr>
<tr>
<td>(S,S)-iPr-A</td>
<td>44% (+)</td>
<td>34</td>
</tr>
</tbody>
</table>

Results

Unsubstituted (Ar = Ph, Naph)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>ee&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>ee</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-BINAP</td>
<td>45% (+)</td>
<td>13</td>
<td>18% (+)</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>(R)(-)-MOP</td>
<td>11% (+)</td>
<td>45</td>
<td>15% (+)</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-Trost ligand</td>
<td>19% (-)</td>
<td>60</td>
<td>28% (+)</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>(R)-PHOX</td>
<td>0%</td>
<td>18</td>
<td>29% (+)</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>(R,R)-Me-BPE</td>
<td>0%</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(R,R)-Me-DuPHOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(R,S)-Josiphos</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(R,R)-Et-FerroTANE</td>
<td>22% (+)</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(S,S)-iPr-A</td>
<td>44% (+)</td>
<td>34</td>
<td></td>
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</tr>
</tbody>
</table>

Effect of Ester Substituent

<table>
<thead>
<tr>
<th>Substrate</th>
<th>((R,R))-Et-FerroTANE</th>
<th>(S,S)-iPr-FerroTANE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ee&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Conv.&lt;sup&gt;b&lt;/sup&gt; (%)</td>
<td>ee&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ia, R' = Et</td>
<td>22 (+)</td>
<td>60</td>
</tr>
<tr>
<td>Ib, R' = i-Pr</td>
<td><strong>52</strong> (+)</td>
<td>44</td>
</tr>
<tr>
<td>Ic, R' = Cy</td>
<td>31 (+)</td>
<td>72 (98&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Id, R' = t-Bu</td>
<td><strong>60</strong> (+)</td>
<td>36</td>
</tr>
<tr>
<td>Ie, R' = Ph</td>
<td>2 (+)</td>
<td>63</td>
</tr>
</tbody>
</table>

Phenyl imine

<table>
<thead>
<tr>
<th>R-A</th>
<th>ee&lt;sup&gt;d&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;d&lt;/sup&gt;</th>
<th>R-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S,S)-iPr</td>
<td>44% (+)</td>
<td>48% (+)</td>
<td>28% (-)</td>
</tr>
<tr>
<td>(S,S)-Cy</td>
<td>48% (+)</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

Phosphepines save the day!

The Reaction

Exocyclic Enones as $2\pi$ components: Extension to spirocycles

The Reaction

![Reaction diagram]

Results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Enone</th>
<th>Products</th>
<th>Yield$^b$</th>
<th>PPh$_3$ a : b$^a$</th>
<th>Yield$^c$</th>
<th>DIOP a : b$^a$</th>
<th>ee (a)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5a, 5b</td>
<td>58</td>
<td>70 : 30</td>
<td>73</td>
<td>95 : 5</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>MeO 6</td>
<td>6a, 6b</td>
<td>64</td>
<td>62 : 38</td>
<td>75</td>
<td>91 : 9</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>MeO 7</td>
<td>7a, 7b</td>
<td>73</td>
<td>56 : 44</td>
<td>63</td>
<td>80 : 20</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>8a, 8b</td>
<td>82</td>
<td>54 : 46</td>
<td>80</td>
<td>90 : 10</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>BrO 9</td>
<td>9a, 9b</td>
<td>84</td>
<td>55 : 45</td>
<td>71</td>
<td>95 : 5</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>Ph 10</td>
<td>10a, 10b</td>
<td>72$^d$</td>
<td>2 : 98</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Ar 11</td>
<td>11a, 11b</td>
<td>61$^d$</td>
<td>2 : 98</td>
<td>48$^d$</td>
<td>85 : 15</td>
<td>30$^d$</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 0.5 M in toluene, 15 mol % ligand, 1.3 equiv of allene, room temperature, 12 h. $^b$ Based on HPLC. $^c$ At 0 °C. $^d$ Using 30 mol % phosphine, or slow addition of allene at 0 °C.

Catalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>conversion$^b$</th>
<th>5a:5b$^b$</th>
<th>ee (5a)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh$_3$</td>
<td>75</td>
<td>62 : 38</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Xanphos</td>
<td>31</td>
<td>82 : 18</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Pt(O-Tol)$_3$</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>rac-BINAP</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PC$_{y_3}$</td>
<td>18</td>
<td>95 : 5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>dpff</td>
<td>67</td>
<td>93 : 7</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>PBu$_3$</td>
<td>81</td>
<td>97 : 3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>DIOP</td>
<td>90</td>
<td>90 : 10</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>DIOP$^e$</td>
<td>90</td>
<td>97 : 3</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>Prophos</td>
<td>87</td>
<td>90 : 10</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>DIPAMP</td>
<td>85</td>
<td>87 : 13</td>
<td>34</td>
</tr>
<tr>
<td>12</td>
<td>Trost ligand</td>
<td>20</td>
<td>60 : 40</td>
<td>-</td>
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<tr>
<td>13</td>
<td>Pfaltz ligand</td>
<td>0</td>
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<td>-</td>
</tr>
<tr>
<td>14</td>
<td>DIOP$^{16}$</td>
<td>100</td>
<td>97 : 3</td>
<td>68</td>
</tr>
</tbody>
</table>

Major Side Rxn is Dimerization Of allenic ketone

Wallace, D. J., et al., JOC. 2007, 72, 1051-1054.

Note Quaternary Steogenic Center!!
[3+2]: Outline:

A = B = C = X = Y = Carbon
- A, B, or C are heteroatoms
- X or Y = heteroatoms not covered
Back to “Normal” Dipolar Cycloaddition: Nitrone + Enal

Counterion Effect

<table>
<thead>
<tr>
<th>entry</th>
<th>HX co-catalyst</th>
<th>Time (h)</th>
<th>% yield</th>
<th>endo:exo</th>
<th>% ee (endo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCl (1a)</td>
<td>108</td>
<td>70</td>
<td>88:12</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>TfOH (5)</td>
<td>101</td>
<td>88</td>
<td>89:11</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>TFA (6)</td>
<td>80</td>
<td>65</td>
<td>72:28</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>HBr (7)</td>
<td>80</td>
<td>77</td>
<td>94:6</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>HClO₄ (8)</td>
<td>80</td>
<td>86</td>
<td>94:6</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>HClO₄ (8)</td>
<td>100</td>
<td>98</td>
<td>94:6</td>
<td>94 b</td>
</tr>
</tbody>
</table>

Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>Z</th>
<th>R</th>
<th>R₁</th>
<th>endo:exo</th>
<th>yield</th>
<th>% ee (endo)³ b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>Ph</td>
<td>Me</td>
<td>94:6</td>
<td>98</td>
<td>94</td>
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<td>2</td>
<td>Allyl</td>
<td>Ph</td>
<td>Me</td>
<td>93:7</td>
<td>73</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Ph</td>
<td>Me</td>
<td>95:5</td>
<td>66</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>C₆H₄Cl-4</td>
<td>Me</td>
<td>92:8</td>
<td>78</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>C₆H₄Cl-4</td>
<td>Me</td>
<td>93:7</td>
<td>76</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>C₆H₄OMe-4</td>
<td>Me</td>
<td>98:2</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>C₆H₄Me-4</td>
<td>Me</td>
<td>93:7</td>
<td>82</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>2-naph</td>
<td>Me</td>
<td>95:5</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>c-hex</td>
<td>Me</td>
<td>99:1</td>
<td>70</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>Bn</td>
<td>Ph</td>
<td>H</td>
<td>81:19</td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>Bn</td>
<td>Ph</td>
<td>H</td>
<td>86:14</td>
<td>80</td>
<td>92³</td>
</tr>
<tr>
<td>12</td>
<td>Bn</td>
<td>C₆H₄Me-4</td>
<td>H</td>
<td>85:15</td>
<td>80</td>
<td>90³</td>
</tr>
<tr>
<td>13</td>
<td>Bn</td>
<td>C₆H₄Cl-4</td>
<td>H</td>
<td>80:20</td>
<td>80</td>
<td>91³</td>
</tr>
<tr>
<td>14</td>
<td>Bn</td>
<td>2-naph</td>
<td>H</td>
<td>81:19</td>
<td>82</td>
<td>90³</td>
</tr>
<tr>
<td>15</td>
<td>Bn</td>
<td>C₆H₄OMe-4</td>
<td>H</td>
<td>91:9</td>
<td>83</td>
<td>90³</td>
</tr>
</tbody>
</table>

R = Aryl, Z = Me / Bn
Nitrones + Cycloalkene carboxaldehydes

Catalysts

Favored by analogy

Scope in nitrone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Nitrone</th>
<th>Temp.</th>
<th>Time</th>
<th>exo product</th>
<th>Yield[%]</th>
<th>dr exo/endo[%]</th>
<th>ee exo[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[^a]</td>
<td>1A</td>
<td>1a</td>
<td>+10°C</td>
<td>72 h</td>
<td>3a</td>
<td>49%</td>
<td>97.3</td>
<td>92%</td>
</tr>
<tr>
<td>2[c,e]</td>
<td>1A</td>
<td>2a</td>
<td>+10°C</td>
<td>120 h</td>
<td>3a</td>
<td>63%</td>
<td>89:11</td>
<td>83%</td>
</tr>
<tr>
<td>3[c,e]</td>
<td>1A</td>
<td>2a</td>
<td>-25°C</td>
<td>120 h</td>
<td>3a</td>
<td>17%</td>
<td>28:72</td>
<td>91%</td>
</tr>
<tr>
<td>4</td>
<td>1A</td>
<td>2b</td>
<td>+10°C</td>
<td>120 h</td>
<td>3b</td>
<td>68%</td>
<td>98.2</td>
<td>76%</td>
</tr>
<tr>
<td>5[b]</td>
<td>1A</td>
<td>2b</td>
<td>+10°C</td>
<td>120 h</td>
<td>3b</td>
<td>61%</td>
<td>99:1</td>
<td>84%</td>
</tr>
<tr>
<td>6</td>
<td>1A</td>
<td>2b</td>
<td>-10°C</td>
<td>120 h</td>
<td>3b</td>
<td>50%</td>
<td>97:3</td>
<td>90%</td>
</tr>
<tr>
<td>7</td>
<td>1A</td>
<td>2e</td>
<td>-25°C</td>
<td>144 h</td>
<td>3e</td>
<td>76%</td>
<td>&gt;99:1</td>
<td>57%</td>
</tr>
<tr>
<td>8</td>
<td>1A</td>
<td>2d</td>
<td>+20°C</td>
<td>24 h</td>
<td>3d</td>
<td>58%</td>
<td>&gt;99:1</td>
<td>41%</td>
</tr>
<tr>
<td>9</td>
<td>1A</td>
<td>2d</td>
<td>-20°C</td>
<td>24 h</td>
<td>3d</td>
<td>48%</td>
<td>&gt;99:1</td>
<td>41%</td>
</tr>
<tr>
<td>10</td>
<td>1A</td>
<td>2e</td>
<td>+20°C</td>
<td>144 h</td>
<td>3e</td>
<td>51%</td>
<td>98:2</td>
<td>53%</td>
</tr>
<tr>
<td>11</td>
<td>1A</td>
<td>2f</td>
<td>-20°C</td>
<td>96 h</td>
<td>3f</td>
<td>56%</td>
<td>&gt;99:1</td>
<td>70%[^i]</td>
</tr>
<tr>
<td>12</td>
<td>1A</td>
<td>2g</td>
<td>+5°C</td>
<td>72 h</td>
<td>3g</td>
<td>-</td>
<td>56:44</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>1B</td>
<td>2d</td>
<td>+20°C</td>
<td>24 h</td>
<td>5d</td>
<td>19%</td>
<td>&gt;99:1</td>
<td>48%</td>
</tr>
<tr>
<td>14</td>
<td>1B</td>
<td>2d</td>
<td>+20°C</td>
<td>120 h</td>
<td>5d</td>
<td>38%</td>
<td>&gt;99:1</td>
<td>37%</td>
</tr>
</tbody>
</table>


Increased Scope in Nitrone
[3+2] Summary

Tertiary Phosphines activating all carbon dipoles

Secondary Amines activating dipolarophiles

Can generate acyl chloride in-situ from with

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(27)
Beta-Lactams:

“Background rates are often so high using this process that it was necessary for us to first break the reaction before we could fix it to render it catalytic, not to mention asymmetric.”

How so… By breaking the classical Staudinger pathway (in which the iminenitrogen acts as a nucleophile toward the ketene) and restart it with a reaction of reversed polarity (umpolung) in which the ketene and imine switch roles; namely, the imine becomes an electrophile and the ketene a nucleophile.

Preformed, disubstituted ketenes

Electron donating
And aryl ketenes
EWG or alkene
On imine

83%, er 96:4

Summary and Conclusions

- Inadvertant tribute to LB catalysis
  - Many interesting opportunities
    - Activate diene
      - Phosphene + Allene
      - Chiral Base + diene (O or H acid)
      - Cross-conjugated enamine
    - Ketenes as dienophiles
      - NHC + “special aldehydes”
      - 3º amines + ketenes (limited dienes possible)
  - “Activate Dipole”
    - Phosphine + electron poor allene
  - Activate Diene/polarophile
    - 2º amine

- Pros/Cons
  Most are rt-50 ºC
  Reaction times often long
  Some still require acid
  Often highly optimizable (at least it appears)
  Interesting (new?) reactivity in many cases