N-Heterocyclic(NHC) Carbenes as Organocatalysts

General type of N-Heterocyclic(NHC) carbenes


Introduction

Feature of NHC carbene

Resonance form

Ylide structure

Preparative method of NHC carbene

Utility

(1) As nucleophilic carbene

Topic in this literature seminar

(2) As ligand for metal-based catalyst

Contents

1. First isolation of carbene
2. Classical application: Umpolung reaction
to Expanded application: Conjugate Umpolung reaction
3. Examples of Expanded application: Conjugate Umpolung reaction
   3.1 Homoenolate addition to aldehyde or imine
   3.2 Catalytic generation of activated carboxylates
   3.3 C-C bond formation via enol or enolate
   3.4 Cyclopentene-forming reaction (Benzoin oxi-Cope reaction)
4. Summary
1. First isolation of carbene

History of discovering stable singlet carbenes

1) Bertrand work

Analogous α,α'-Bis-Carbene Triply Bonded Species: Synthesis of a Stable
λ1-Phosphinocarbene-λ1-Phosphaacetylene

A. Phosphinocarbene
B. Phosphorus vinyl ylide
C. Phosphaacetylene

/Stable for several weeks at r.t
/Bp 75-80 °C(0.01 mmHg)
/Distillable
/Reactivity of carbene and multiple bond was observed.

Reason of stability. Electron donation from the heteroatom lone pair into the formally empty p-orbital of the carbene center

The interaction of the carbene lone pair with the α* orbitals of silyl groups

This is the first report of bottle stable carbene.
But Bertrand didn't insist that point because his focus was "chemistry of C-P triple-bond".

2) Arduengo work

A Stable Crystalline Carbene

Anthony J. Arduengo, III,* Richard L. Harlow, and
Michael Kline


First characterization of the crystalline carbene
They insisted until now there have not been any "bottle-able" carbenes

<Structural features of NHC carbene>

Table 1. Selected Bond Lengths (pm) and Angles (deg) in 1

<table>
<thead>
<tr>
<th>Bond</th>
<th>C=N</th>
<th>C-N</th>
<th>N=C-N</th>
<th>C=C-N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>136.7 (3)</td>
<td>137.3 (2)</td>
<td>102.2 (2)</td>
<td>112.1 (3)</td>
</tr>
<tr>
<td>2</td>
<td>133.8 (3)</td>
<td>138.2 (2)</td>
<td>112.3 (2)</td>
<td>107.2 (2)</td>
</tr>
<tr>
<td>3</td>
<td>138.6 (2)</td>
<td>138.6 (2)</td>
<td>106.2 (2)</td>
<td>123.4 (2)</td>
</tr>
<tr>
<td>4</td>
<td>148.2 (2)</td>
<td>148.5 (1M)</td>
<td>123.4 (2)</td>
<td>122.1 (3)</td>
</tr>
</tbody>
</table>

Pickup
imidazolium salts(2) carbene 1
N1-C2 132.8 pm N1-C2 136.7 pm
N3-C2 132.8 pm N3-C2 137.3 pm
N1-C2-N3 109.7° N1-C2-N3 102.2°

(from X-ray analysis)

Difference between imidazolium ion 2 and carbene 1
1) a diminished γ-delocalization in 1
   as compared to imidazolium salts
2) hybridization at the carbene center that influence bond distances
   more s-orbital character is used to stabilize
   the in-plane lone pair of electrons at the carbene center,
   the N-C α-bonds take on more p-character at the carbene center.

Typical angle of carbene(calculated)

triplet

singlet

repulsion

130°-150°

100°-110°
2 Classical application: Umpolung reaction to Expanded application: Conjugate Umpolung reaction

In 1943, Ugai et al. recognized that thiazolium salts could also be used as catalysts in the benzoin condensation.

<Mechanistic proposal of benzoin condensation>

On the Mechanism of Thiamine Action, IV: Evidence from Studies on Model Systems

J. Am. Chem. Soc. 1958, 80, 3719

Catalytic Cycle of the Benzoin Condensation as Proposed by Breslow:

\[
\begin{align*}
\text{R} & \xrightarrow{\text{cat. base}} \text{R} = \text{Aryl} \\
\text{R} & \xrightarrow{\text{cat. base}} \text{R} = \text{Aryl}
\end{align*}
\]

+Thiazol-2-ylidene and triazol-5-ylidene are used as cat.
+Asymmetric version also is developed by using chiral NHC catalyst.

Expanded application

Conceptually new approach the generation of homoenolate

Control the reaction pathways
1) Substrate control
2) Catalyst control
/Ligand structure
/Imidazole, triazole, thiazole
/Steric hinderance
/Base selection
/Additive

Various reactions has been developed by using this system.
3.1 Homoenoate addition to aldehyde or imine

![Chemical structure diagram]

3.1.1 Homoenoate addition to aldehyde
Organocatalyzed Conjugate Umpolung of α,β-Unsaturated Aldehydes for the Synthesis of γ-Butyrolactones

Christian Burstein and Frank Glorius
N-Heterocyclic Carbene-Catalyzed Generation of Homoenoates: γ-Butyrolactones by Direct Annulations of Enals and Aldehydes
Stephanie S. Sohn, Evelyn L. Rosen, and Jeffrey W. Bode
J. Am. Chem. Soc. 2004, 126, 14370

Reaction
Scheme 55. Generation of γ-Butyrolactones by Burstein and Glorius and Bode and Co-workers

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>53</td>
<td>81:19</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph</td>
<td>49</td>
<td>80:20</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Ph</td>
<td>70</td>
<td>79:21</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>44</td>
<td>77:23</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Ph</td>
<td>57</td>
<td>78:22</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>Ph</td>
<td>61</td>
<td>79:21</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>Ph</td>
<td>60</td>
<td>79:21</td>
</tr>
</tbody>
</table>

Table 16. Results of Burstein and Glorius: 5 mol % 19d, 10 mol % KOr-Bu, THF, 16 h

Entry | R¹ | R² | Yield (%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Ph</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Ph</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>Ph</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>Ph</td>
<td>67</td>
</tr>
</tbody>
</table>

Bode: 2 eq of aldehyde was used.
(Benzoin product of the excess aldehyde was obtained)
Glorius: 1 eq of aldehyde was used.

Postulated mechanism
Scheme 54. Postulated Catalytic Cycle for the Carbene-Catalyzed Formation of γ-Butyrolactones

Desired γ-butyrolactones was obtained.
3.1.1 Homoenolate addition to imine

Catalytic Synthesis of \(\gamma\)-Lactams via Direct Annulations of Enals and 
\(N\)-Sulfonylimines

Ming He and Jeffrey W. Bode* 
*Org. Lett. 2005, 7, 3131

About protecting group of imine

+ N-alkyl or N-aryl imine was unreactive. (Only dimers of enal)
+ N-phosphinanyl and N-tosyl was so reactive. (Reacted directly with catalyst)
+ Moderate electrophilicity is needed about imine. They screened electron-rich N-sulfonyl imines.

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Substrate scope

**Conditions**
1 equiv of enal, 1 equiv of imine, 15 mol % IMes-Cl, and 10 mol % DBU at 0.1 M in tert-BuOH at 60 °C for 14 h.
Ar = 4-MeOC6H4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Cmp (%)</th>
<th>Yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>15</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>91</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>20</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>38</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>14</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>93</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>96</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>73</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>12</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

Electronegative aldehydes and Electron-rich imines gave better result

To suppress the other pathways

His unpublished data (from SSOCJ Lectureship Award presentation)

Highly enantioselective reaction is now difficult.

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\[\text{\textsuperscript{4}All reactions were performed with 1 equiv of 2, 1 equiv of imine, 15 mol % IMes-Cl, and 10 mol % DBU at 0.1 M in tert-BuOH at 60 °C.}\]

\[\text{\textsuperscript{5}Ratio of remaining enal to lactona and/or lactone products as measured by \(\text{H NMR}^\text{a} \text{of unspired reaction mixtures.}\}\]

\[\text{\textsuperscript{6}Isolated yield following silica gel chromatography.}\]

\[\text{\textsuperscript{7}Lactone homodimer.}\]

\[\text{\textsuperscript{7}Performed with 10 equiv of NEt3.}\]
3.2 Catalytic generation of activated carboxylates

**background**

Esterification and amidation by using activation reagent (reliable method)

![Chemical Reaction](image)

**Problem**

Stoichiometric use

**Activation reagent** = DCC, Cl, S, Cl, etc.

Breslow indicated 2-Acetyltiazolium salts work as active acetate
(In the Thiamine chemistry)

Breslow et al. J. Am. Chem. Soc. 1960, 82, 2394-2395

**Concepts:** Catalytic generation of activated carboxylates by NHC catalyst.

**Scheme 1:** Catalytic Generation of Activated Carboxylates via Internal Redox Reactions

![Scheme 1](image)

**Scheme 2:** Reaction Pathways of Catalytically Generated Activated Carboxylates

![Scheme 2](image)

Olefine is used as reducible FG

**Suppression of producing compound 17**

*By increasing the size of the substituents, production of phenyl ester can be suppressed completely.*
3.2.2 α, β-Unsaturated Aldehydes into Saturated Esters

~Importance of base selection~

Catalytic Generation of Activated Carboxylates from Enals: A Product-Determining Role for the Base

Stephanie S. Sohn and Jeffrey W. Bode* Org. Lett., 2005, 7, 3873

NHC catalyst selection

Scheme 3. Heterocyclic Precatalyst for the Catalytic Generation of Activated Carboxylates from Cinnamaldehyde

Table 1. Catalysts and Conditions for Redox Esterifications

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>temp (°C)</th>
<th>conversion (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[M]Cl</td>
<td>40</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>[M]Cl</td>
<td>40</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>[M]Cl</td>
<td>40</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>[M]Cl</td>
<td>40</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>[M]Cl</td>
<td>40</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>[M]Cl</td>
<td>40</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>[M]Cl</td>
<td>40</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>[M]Cl</td>
<td>40</td>
<td>99</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>[M]Cl</td>
<td>40</td>
<td>95</td>
<td></td>
</tr>
</tbody>
</table>

+ Thiazolium salt is not effective.

+ \[\text{Ph} \text{N}^+ \text{N}^-\text{Ph} \]
+ \[\text{Mes} \text{N}^+ \text{Mes} \]

Not effective best catalyst entry 6

Other example

Reductive FG : epoxide conversion β-hydroxyester from α, β-epoxyaldehyde

Scheme 1

Reductive FG : α-halogen conversion ester from α-haloaldehyde


Table 3. Effect of the Anionic Base of Catalytic Esterifications

| entry | X (mol %) | base | pKa of conjugate acid in THF | relative yield (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>NEt3</td>
<td>12.6</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>DIPEA</td>
<td>~11</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>DBU</td>
<td>16.8</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>P2C-Bu</td>
<td>20.9</td>
<td>&gt;5</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>KO-Bu</td>
<td>29.4</td>
<td>&gt;5</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>KO-Bu</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>DIPEA</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

+ A clear correlation between the success of the reaction and the pKa of the conjugate acid emerged + Excess triazolium salt gave good result. Triazolium salt itself may serve as the catalytic proton shuttle

Effect of catalytic base to resulting product

Mechanism

Scheme 5. Proposed Catalytic Cycle for Catalytic Redox Esterifications of Enals

3.3 C-C bond formation via enol or enolate

Scheme 1. Proposed NHC-Mediated Enolate Generation

3.3.1 β-lactone forming reaction


Scheme 55. Condition for the Generation of γ-Butyrolactones from Ketones by Glorius and Co-workers

Scheme 56. Synthesis of β-Lactones by Glorius and Co-workers

Table 17. Generation of γ-Butyrolactones from Ketones by Glorius and Co-workers

<table>
<thead>
<tr>
<th>entry</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>product yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>CF3</td>
<td>19d</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>H</td>
<td>CF3</td>
<td>19a</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>H</td>
<td>CH3</td>
<td>19b</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>19c</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>H</td>
<td>COOEt</td>
<td>19d</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>H</td>
<td>COOMe</td>
<td>19d</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>H</td>
<td>COOMe</td>
<td>19d</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>H</td>
<td>COOMe</td>
<td>19d</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>H</td>
<td>CF3</td>
<td>19d</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>Pr</td>
<td>H</td>
<td>CF3</td>
<td>19d</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>iPr</td>
<td>H</td>
<td>CF3</td>
<td>19d</td>
<td>66</td>
</tr>
<tr>
<td>12</td>
<td>Me</td>
<td>H</td>
<td>COOMe</td>
<td>19d</td>
<td>87</td>
</tr>
<tr>
<td>13</td>
<td>Pr</td>
<td>H</td>
<td>COOMe</td>
<td>19d</td>
<td>71</td>
</tr>
</tbody>
</table>

Table 18. Substrate Scope for the Synthesis of β-Lactones by Glorius and Co-workers

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>CF3</td>
<td>34</td>
<td>69:40</td>
</tr>
<tr>
<td>Pr</td>
<td>CF3</td>
<td>45</td>
<td>55:45</td>
</tr>
<tr>
<td>iPr</td>
<td>CF3</td>
<td>48</td>
<td>62:38</td>
</tr>
<tr>
<td>Ph</td>
<td>CF3</td>
<td>30</td>
<td>70:30</td>
</tr>
<tr>
<td>i-Pr</td>
<td>COOMe</td>
<td>22a</td>
<td>71:29</td>
</tr>
</tbody>
</table>

*Reaction was performed with 10 mol % 19d and 10 mol % DBU.

Mechanism

NHC catalyst

<table>
<thead>
<tr>
<th>Difference</th>
<th>γ-lactones</th>
<th>β-lactones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>KOTBu or DBU</td>
<td>NEt3 (less basic)</td>
</tr>
<tr>
<td>solvent</td>
<td>THF</td>
<td>toluene</td>
</tr>
<tr>
<td>temperature</td>
<td>rt</td>
<td>60°C</td>
</tr>
</tbody>
</table>

+ Weak base promote proton transfer
⇒ β-lactones

+ Addition to ketone of homoenolate
⇒ γ-lactones
3.3.2 Highly Enantioselective Azadiene Diels-Alder Reactions

Highly Enantioselective Azadiene Diels–Alder Reactions Catalyzed by Chiral N-Heterocyclic Carbenes

Ming He, Justin R. Doub, and Jeffrey W. Bode*

J. AM. CHEM. SOC. 2006, 128, 8418

Investigation of conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (%)</th>
<th>Conditions</th>
<th>% Conv.</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 (15)</td>
<td>10 mol % of DBU, 0.1 M THF</td>
<td>&gt;10.1</td>
<td>36 (7.3%)</td>
</tr>
<tr>
<td>2</td>
<td>5 (15)</td>
<td>10 mol % of DIPEA, 0.1 M THF</td>
<td>&gt;10.1</td>
<td>13 (2.1%)</td>
</tr>
<tr>
<td>3</td>
<td>0 (10)</td>
<td>10 mol % of DBU, 0.1 M THF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5 (15)</td>
<td>10 mol % of DBU, 0.1 M THF</td>
<td>1.8</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>7 (15)</td>
<td>10 mol % of DBU, 0.1 M EtOAc</td>
<td>1.5</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>7 (15)</td>
<td>10 mol % of DBU, 0.1 M toluene</td>
<td>1.10</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>7 (15)</td>
<td>10 mol % of DIPEA, 0.1 M toluene</td>
<td>1.129</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>7 (10)</td>
<td>10 mol % of DIPEA, 25 h</td>
<td>1.20</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>7 (10)</td>
<td>10 mol % of DIPEA, 25 h</td>
<td>0.03 M 1:1 toluene:THF</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>9 (10)</td>
<td>10 mol % of DIPEA, 25 h</td>
<td>0.03 M 1:1 toluene:THF</td>
<td></td>
</tr>
</tbody>
</table>

*Product ratios and diastereoselectivities determined by 'H NMR analysis of unpurified reaction mixtures. 
* Ratio of lactam product relative to starting imine. 
* Lactam 3 was not detected. 
* Yield of isolated product. DIPEA = N,N-diisopropylethylamine.

Figure 1. Stereochemical model for endo-Diels–Alder cycloaddition

Electrowithdrawing group is essential (from substrate scope)
+ supposable reason 1
[tautomeric form shown below is essential]

<Test reaction>

reaction proceeded
+ supposable reason 1 is not so important
+ supposable reason 2
[Only increase electrophilicity of enal]
When less electrophilic enals are employed, the NHC catalyst reacts preferentially with the electrophilic imine.

<Related work>

Chiral N-Heterocyclic Carbene Catalyzed, Enantioselective Oxadiene Diels–Alder Reactions with Low Catalyst Loadings Ming He, Gerson J. Ur, and Jeffrey W. Bode*

J. AM. CHEM. SOC. 2006, 128, 15088

Similar reaction system.
(To trap HCl, 1.5 eq of Et3N is used)
3.4 Cyclopentene-forming reaction (Benzoin oxi-Cope reaction)

**N-Heterocyclic Carbene-Catalyzed Reaction of Chalcones and Enals via Homoenoate: an Efficient Synthesis of 1,3,4-Trisubstituted Cyclopentenes**

*Vigyan Nair*, R. Sreekumar Veetesh*, Manjumol Poonith and Eriqvaldo Store*  
**J. AM. CHEM. SOC. 2006, 128, 8736-8737**

Nair’s work (racemic)  
Substrate  
Cinnamaldehyde and chalcone

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-phenyl</td>
<td>2-thienyl</td>
<td>4-chlorophenyl</td>
<td>4b 88</td>
</tr>
<tr>
<td>2</td>
<td>2-phenyl</td>
<td>1-naphthyl</td>
<td>4-chlorophenyl</td>
<td>4c 76</td>
</tr>
<tr>
<td>3</td>
<td>4-MP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2-thienyl</td>
<td>4-methylphenyl</td>
<td>4d 87</td>
</tr>
<tr>
<td>4</td>
<td>4-MP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4-cyanophenyl</td>
<td>4-chlorophenyl</td>
<td>4e 76</td>
</tr>
<tr>
<td>5</td>
<td>4-MP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>phenyl</td>
<td>phenyl</td>
<td>4f 88</td>
</tr>
<tr>
<td>6</td>
<td>phenyl</td>
<td>phenyl</td>
<td>phenyl</td>
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<td>4-chlorophenyl</td>
<td>4i 76</td>
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<tr>
<td>9</td>
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<td>phenyl</td>
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<td>4-chlorophenyl</td>
<td>4l 55</td>
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<tr>
<td>12</td>
<td>methyl</td>
<td>2-thienyl</td>
<td>4-chlorophenyl</td>
<td>4m 73</td>
</tr>
</tbody>
</table>

* Isolated yield  
<sup>a</sup> MP = metaoxy phenyl.

Scheme 3. Postulated Catalytic Cycle Involving NHC

**Enantioselective, Cyclopentene-Forming Annulations via NHC-Catalyzed Benzoin-Oxy-Cope Reactions**

*Pei-Chen Chang, Aojiangai Kaobamthun, and Jeffrey W. Bode*  
**J. AM. CHEM. SOC. 2007, 129, 3520-3521**

Bode’s work (asymmetric)  
Substrate  
Cinnamaldehyde and 4-oxoene

![Diagram](image)

Proposed mechanism

**Nair**  
Conjugate addition of homoenoate to enone  
tautomerization and intramolecular aldol  
lactonization and decarboxylation  
cyclopentenes

**Bode**  
Benzoin-Oxy Cope reactions  
tagomerization and intramolecular aldol  
acyl addition and decarboxylation
Control experiments to explain Oxy-Cope reaction

(a) Benzoin type reaction can take place reversibly.

(b) 12 can be obtained.

(c) (+ EtOH standard conditions) 12 was not detected. >> Tautomerization and aldol reaction is fast compared to nucleophilic addition of EtOH.

About result of (b)
If oxy-Cope reaction doesn't take place, retro benzoin followed by catalytic homoenolate addition is mechanism.
But from (c), 12 was not detected. So, oxy-Cope reaction should take place.


Conclusion

Bode

Nair

Two catalysts show different reaction pathways

Enantioselective, NHC-Catalyzed Bicyclo-a-Lactam Formation via Direct Annulations of Enals and Unsaturated N-Sulfonyl Ketimines

Ming He and Jeffrey W. Bode

J. AM. CHEM. SOC. 2008, 130, 418
4. Summary

Weak base is efficient (Et₃N, DIPEA)

Proton transfer

activated carboxylate

3.2 → R'OH

Esterification

2005

enantioselective reaction

Utility as organocatalyst

<table>
<thead>
<tr>
<th>Homoenolate Chemistry (Conjugate umpolung)</th>
<th>Best catalyst of homoenolate additions</th>
<th>Widely used</th>
<th>Not Effective</th>
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</thead>
<tbody>
<tr>
<td>Benzoin and Stetter (Umpolung)</td>
<td>scarcely used</td>
<td>Widely used</td>
<td>Widely used</td>
</tr>
</tbody>
</table>

Asymmetric Version

Almost is C-2 symmetric catalyst. Now another type of asymmetric catalyst is needed and developed.