Recent Advances in the Chemistry of Alleneamides

Denmark Group Meeting
Nate Duncan-Gould
9-25-07
The Structure

allene

allenamine

Cummulenes

\[
\begin{align*}
&\text{C=C=C} \\
&\text{X} \\
&\text{N} \\
&\text{X}
\end{align*}
\]

\[
\begin{align*}
&\text{C=C-C} \\
&\text{X} \\
&\text{N} \\
&\text{X}
\end{align*}
\]

\[
\begin{align*}
&\text{C-C=C} \\
&\text{X} \\
&\text{N} \\
&\text{X}
\end{align*}
\]

\[
\begin{align*}
&\text{C=C=C} \\
&\text{X} \\
&\text{N} \\
&\text{X}
\end{align*}
\]
Comparison of MO’s

FMO at PM3 level

<table>
<thead>
<tr>
<th></th>
<th>HOMO</th>
<th>LUMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cummulene</td>
<td>-10.18</td>
<td>1.11</td>
</tr>
<tr>
<td>H</td>
<td>-9.46</td>
<td>0.37</td>
</tr>
<tr>
<td>O</td>
<td>-8.41</td>
<td>1.10</td>
</tr>
<tr>
<td>FMO</td>
<td>-9.29</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Stability of the Parent Allenamine

H₂N

flash thermolysis

700 °C, 10⁻⁵ torr

→

H₂N

NMR and IR (-195 to -80 °C)
isolable as
HCl salt

-65 °C
t₁/₂ minutes

HN

polymer

Molar
to
mMolar conc.

Representative Known, Isolable allenamides

Representative Reactions


Craig and Ekwuribe, TL 1980, 21, 533.
Representative Cycloaddition

\[ \text{EtOH, reflux} \]

Mechanistic Rationale

Scheme 2. Ts = p-MeC₆H₄SO₂.
Stability: Substitution and Thermal

Often “undistillable oils”

Kurtz, *JOC*. 1966, 31, 2955
Proposed Mechanism

1,4-proton shift → 1,7-electrocyclization

1,5-hydride shift → 1,7-electrocyclization
Outline

- Recent Advances in Preparation
  - Lithiation and Subsequent 1,2-addition reactions
- Exploring their stability / reactivity
  - Hetero [4+2] (Tamaru & Hsung)
  - [2+1] and subsequent reactions… (Seebach & Hsung)
  - [2+2] and subsequent reactions… (Tamaru & Hsung)
1,2-Addition: a chiral homoenoate

- Seebach

In this arrangement, the larger substituent R1 on the COC-atom adopts an equatorial position.

<table>
<thead>
<tr>
<th>9</th>
<th>R</th>
<th>Yield [%]</th>
<th>dp [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>i-Pr</td>
<td>67</td>
<td>97</td>
</tr>
<tr>
<td>b</td>
<td>Pr</td>
<td>66</td>
<td>97</td>
</tr>
<tr>
<td>c</td>
<td>Methacryl</td>
<td>60</td>
<td>98</td>
</tr>
<tr>
<td>d</td>
<td>Ph</td>
<td>64</td>
<td>97</td>
</tr>
</tbody>
</table>
1,2-Additions and Subsequent Rxns

- Hegedus

1. nBuLi, THF, TMEDA, -78 °C
2. B-MeO-9-BBN, -45 °C
3. BF$_2$OEt$_2$, -45 °C
4. RCHO, -45 °C, 2 h

0.3 M

~80%, (>95:5)
Aliphatic, aromatic

Able to CC with Boronic acids
1,2-Addition: a chiral homo-enolate

- Hsung

\[ \text{Hsung} \]

![Chemical structures and reactions](image)

**J. Org. Chem. 2005, 70, 4038.**
Probing Reactivity/Stability with Hetero Diels-Alder reaction

\[
\begin{align*}
\text{Hsung, et al. } & \text{TL, 1999, 40, 6903.}
\end{align*}
\]
Comparison of Allenamide reactivity

Performance in hetero-Diels-Alder

Diastereoselective Hetero-DA

Solvent Effect: CH$_3$CN = 5 h
ClCH$_2$CH$_2$Cl = 15h
Implying stepwise mechanism
Lower dr with oxazolidinones

<table>
<thead>
<tr>
<th>R</th>
<th>yield</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>65</td>
<td>87:13</td>
</tr>
<tr>
<td>Me</td>
<td>57</td>
<td>94:6</td>
</tr>
<tr>
<td>Ph</td>
<td>63</td>
<td>95:5</td>
</tr>
<tr>
<td>1-nap</td>
<td>74</td>
<td>94:6</td>
</tr>
<tr>
<td>Cy</td>
<td>19</td>
<td>95:5</td>
</tr>
<tr>
<td>N-hex</td>
<td>50</td>
<td>95:5</td>
</tr>
</tbody>
</table>

>60% >12:1 dr

Hsung et al., OL, 1999, 1, 2145.
Hsung et al., Synlett, 2003, 1241.
Hetero Diels-Alder Stereochemical Model
A new class of allenamide (Tamaru)

Representative Preparations

\[ \text{TsHN} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{NHTs} \]
\[ \text{1q} \]
\[ [\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3 \]
\[ (0.005 \text{ equiv}) \]
\[ \text{Et}_3\text{N} (0.1 \text{ equiv}) \]
\[ \text{THF}, 25^\circ \text{C}, 16 \text{ h} \]
\[ \text{O} \]
\[ \text{NTs} \]
\[ \text{2q} (59\%) \]

\[ \text{Cl}_3\text{C}_2\text{CO}_3\text{SNH} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{NHSO}_3\text{CH}_2\text{CCl}_3 \]
\[ \text{1r} \]
\[ [\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3 \]
\[ (0.005 \text{ equiv}) \]
\[ \text{Et}_3\text{N} (0.1 \text{ equiv}) \]
\[ \text{THF}, 25^\circ \text{C}, 16 \text{ h} \]
\[ \text{O} \]
\[ \text{NCl}_3\text{CH}_2\text{CCl}_3 \]
\[ \text{2r} \]
(28% overall based on 1,1-dimethyl-2-butyn-1,4-diol)

See:
Tamaru et al. ACIE, 1999, 38, 121.
Tamaru et al. JACS, 1997, 119, 10867.
Structural Analysis

2a

2b

2n

2q

R R

O

N

S

O

Me

O

C4

C5

C

172.5°

174.5°

2.854 Å

2.829 Å

2.834 Å

2.817 Å

a: H
b: o-Ts
n: Et
q: Me
Mechanistic Continuum observed with aldehydes and ketones

![Mechanistic Continuum diagram](image)

<table>
<thead>
<tr>
<th>Run</th>
<th>Enone</th>
<th>$t^{[a]}$ [h]</th>
<th>Yield [%] of <strong>10</strong> and <strong>8</strong>[^b]</th>
<th>$E_{act}^{[c]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>10</strong></td>
<td><strong>8</strong></td>
</tr>
<tr>
<td>1</td>
<td>$\text{CH}_2=\text{CHCH}_2\text{CO}_2\text{H}$</td>
<td>2</td>
<td>[<strong>10a</strong> (80)]</td>
<td>[<strong>8i</strong> (18)]</td>
</tr>
<tr>
<td>2</td>
<td>$\text{CH}_2=\text{CHCH}_2\text{CHO}$</td>
<td>6</td>
<td>[<strong>10b</strong> (52)]</td>
<td>[<strong>8j</strong> (44)]</td>
</tr>
<tr>
<td>3</td>
<td>$\text{CH}_2=\text{CHCH}_2\text{CO}_2\text{H}$</td>
<td>14</td>
<td>[<strong>10c</strong> (40)]</td>
<td>[<strong>8k</strong> (57)]</td>
</tr>
<tr>
<td>4</td>
<td>$\text{CH}_2=\text{CHCH}_2\text{CHO}$</td>
<td>10</td>
<td>[<strong>10d</strong> (11)]</td>
<td>[<strong>8l</strong> (83)]</td>
</tr>
</tbody>
</table>

Pdt distribution rationalized qualitatively by donating ability of substituents
Tamaru’s allenamide as $2\pi$ component

Substrates | T/t | products
--- | --- | ---
1. ONTs | $\equiv\text{CO}_2\text{Me}$ | 80/4 | (Z)-6b (51)
13. 2m | 80/120 | 7f (55)$^{[c]}$
15. 2m | OTIPS | 100/8 | 8g (98)$^{[d]}$

Concerted??

2a + $\equiv\text{Ph}$ | $100 ^\circ C, 4$ h | (Z)-6a (61%)
2m + $\equiv\text{Ph}$ | $100 ^\circ C, 28$ h | [D$_1$]-(Z,E)-7h (90%)
The unique reactivity associated with 2 might be primarily attributed to a strong $\sigma^*(\text{N-SO}_2) - \pi^*(\text{C}_{\alpha\beta}=\text{C}_{\beta\beta})$ interaction... (or $\sigma^*(\text{N-CO})-\pi^*(\text{C}_{\alpha\beta}=\text{C}_{\beta\beta})$ interaction...which causes

1) the lowering of the $\pi^*(\text{C}_{\alpha\beta}=\text{C}_{\beta\beta})$ energy level (and hence, lowering of the activation energy for the [2+2] addition) and

2) the rehybridization of the $\pi^*(\text{C}_{\alpha\beta}=\text{C}_{\beta\beta})$ orbitals (sp3-like, and hence, better overlap between the p orbitals of alkene C1 and allene C in the opposite face to N-Ts).
Allenamide as Latent allyl cation: entry into [4+3]

- Exothermic (~40 kcal/mol)
- Ea typical of rt reaction (~10-15 kcal/mol)
**[4+3] Proof of Principle**

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{C} & \quad \text{C} \quad \text{C} \\
\text{N} & \quad \text{C} \quad \text{C} \quad \text{C} \\
\text{O} & \quad \text{C} \quad \text{C} \quad \text{C} \\
\end{align*}
\]

60% Only endo observed

\[\text{2 - 3 equiv DMD} \quad \text{THF, } -45^\circ \text{C, } 8-10 \text{ h}\]

TL 1980, 36, 2296.
Tet 2002, 58, 7027.
JACS 1982, 104, 1119.
Optimization of [4+3] Protocol

Exploratory Studies

<table>
<thead>
<tr>
<th>additive</th>
<th>T (°C)</th>
<th>facial selectivity (oxallyl cation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiClO₄</td>
<td>-40</td>
<td>75:25</td>
</tr>
<tr>
<td>MgB₄₂</td>
<td>-40</td>
<td>not reported</td>
</tr>
<tr>
<td>ZnCl₂</td>
<td>-40</td>
<td>94:6</td>
</tr>
<tr>
<td>ZnCl₂</td>
<td>-78</td>
<td>&gt;96:4</td>
</tr>
</tbody>
</table>

Scope:
Substitution not Tollerated (slow)

Major pdt

rotate counterclockwise
[4+3] Stereochemical Rationale

major
Approach from bottom face of oxallyl cation

minor
Approach from top face of oxallyl cation
NMR studies: epoxidation with $m$-CPBA
NMR studies: epoxidation with DMDO

11

2-5 equiv DMDO
acetone, -40 °C, 2 h

no additive

15: R = H [None]
16: R = OH [86%]

additive: 0.5 equiv PPTS

15: R = H [ratio a/b: 5 : 1]
16: R = OH [ratio a/b: 3.5 : 1]
96% combined yield
cratio of 15 : 16 = 1 : 3

Not observed

Observed
Catalytic, Enantioselective via Lewis Acid

![Chemical structures and reactions](image)

<table>
<thead>
<tr>
<th>Lewis acids</th>
<th>equiv</th>
<th>ligands&lt;sup&gt;a&lt;/sup&gt;</th>
<th>[equiv]</th>
<th>temp</th>
<th>yield (%)</th>
<th>ee (%)</th>
<th>R</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZnOTf&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1.1</td>
<td>9a</td>
<td>1.3</td>
<td>−55 °C</td>
<td>48</td>
<td>8[R]</td>
<td>54</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>1.1</td>
<td>9b</td>
<td>1.3</td>
<td>−55</td>
<td>58</td>
<td>2[R]</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>1.1</td>
<td>10</td>
<td>1.3</td>
<td>−55</td>
<td>70</td>
<td>21[R]</td>
<td>61</td>
<td>39.5</td>
</tr>
<tr>
<td>no metal</td>
<td>12</td>
<td>0.25</td>
<td>−78&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>40</td>
<td>3[R]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SnOTf&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1.1</td>
<td>13a</td>
<td>1.3</td>
<td>−55</td>
<td>48</td>
<td>5[R]</td>
<td>53</td>
<td>47.5</td>
</tr>
<tr>
<td>MgI&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.25</td>
<td>13a</td>
<td>0.32</td>
<td>−78</td>
<td>46</td>
<td>3[R]</td>
<td>52</td>
<td>48.5</td>
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<tr>
<td>CuOTf&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.85</td>
<td>13a</td>
<td>1.1</td>
<td>−55 °C</td>
<td>62</td>
<td>78[S]</td>
<td>11</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>13a</td>
<td>0.32</td>
<td>−78&lt;sup&gt;d,f&lt;/sup&gt;</td>
<td>46</td>
<td>74[S]</td>
<td>13</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>1.1</td>
<td>13b</td>
<td>1.2</td>
<td>−55</td>
<td>53</td>
<td>22[S]</td>
<td>61</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>13c</td>
<td>0.32</td>
<td>−78&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>46</td>
<td>10[R]</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>14</td>
<td>0.32</td>
<td>−78&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>54</td>
<td>61[S]</td>
<td>19</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>15a</td>
<td>0.32</td>
<td>−78&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>46</td>
<td>82[S]</td>
<td>9</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>15b</td>
<td>0.32</td>
<td>−78&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>46</td>
<td>90[S]</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>15b</td>
<td>0.12</td>
<td>−78&lt;sup&gt;d,f&lt;/sup&gt;</td>
<td>76</td>
<td>59[S]</td>
<td>21</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>16</td>
<td>0.32</td>
<td>−78&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>84</td>
<td>2[R]</td>
<td>51</td>
<td>49</td>
</tr>
</tbody>
</table>
Scope of Diene

<table>
<thead>
<tr>
<th>entry</th>
<th>dienes</th>
<th>allenes X</th>
<th>W</th>
<th>R =</th>
<th>additive</th>
<th>product</th>
<th>yield</th>
<th>ee</th>
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<tbody>
<tr>
<td>1</td>
<td>7 O</td>
<td>O</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8-S</td>
<td>90%</td>
<td>92%</td>
</tr>
<tr>
<td>2</td>
<td>7 O</td>
<td>O</td>
<td>-</td>
<td>-</td>
<td>AgSbF₆</td>
<td>8-S</td>
<td>91%</td>
<td>99%</td>
</tr>
<tr>
<td>3</td>
<td>7 O</td>
<td>O</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8-R</td>
<td>87%</td>
<td>82%</td>
</tr>
<tr>
<td>4</td>
<td>7 O</td>
<td>CH₂</td>
<td>-</td>
<td>-</td>
<td>AgSbF₆</td>
<td>18-S</td>
<td>90%</td>
<td>43%</td>
</tr>
<tr>
<td>5</td>
<td>17 CH₂</td>
<td>O</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>19-S</td>
<td>60%</td>
<td>58%</td>
</tr>
<tr>
<td>6</td>
<td>20 (CH₂)₂ O</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>21-S</td>
<td>47%</td>
<td>14%</td>
</tr>
<tr>
<td>7</td>
<td>7 O</td>
<td>-</td>
<td>Me</td>
<td>-</td>
<td>-</td>
<td>22-S [4 : 1]</td>
<td>37% f</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>7 O</td>
<td>-</td>
<td>Me</td>
<td>-</td>
<td>AgSbF₆</td>
<td>22-S [20 : 1]</td>
<td>88%</td>
<td>71%</td>
</tr>
<tr>
<td>9</td>
<td>7 O</td>
<td>-</td>
<td>CO₂Me</td>
<td>-</td>
<td>-</td>
<td>23-S [syn only]</td>
<td>33 f</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>7 O</td>
<td>-</td>
<td>CO₂Me</td>
<td>-</td>
<td>AgSbF₆</td>
<td>23-S [syn only]</td>
<td>61%</td>
<td>67%</td>
</tr>
<tr>
<td>11</td>
<td>7 O</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24-S</td>
<td>81%</td>
<td>36%</td>
</tr>
<tr>
<td>12</td>
<td>7 O</td>
<td>-</td>
<td>Me</td>
<td>-</td>
<td>AgSbF₆</td>
<td>25-S [anti only]</td>
<td>91%</td>
<td>99%</td>
</tr>
<tr>
<td>13</td>
<td>7 O</td>
<td>-</td>
<td>Br</td>
<td>-</td>
<td>AgSbF₆</td>
<td>26-S [1 : 14]</td>
<td>58%</td>
<td>84%</td>
</tr>
<tr>
<td>14</td>
<td>7 O</td>
<td>-</td>
<td>CH₂OTPS</td>
<td>-</td>
<td>AgSbF₆</td>
<td>27-S [1 : 2.3]</td>
<td>66%</td>
<td>92%</td>
</tr>
</tbody>
</table>
Enantioselective [4+3]: Stereochemical Model

Scheme 2
Summary

- **Synthesis of Allenamides**
  - Highly diastereomerically enriched syntheses available
  - Can function as Homoenoenate (or Acyl anion)
- **Reactivity**
  - Many interesting modes of reactivity available
    - Hetero-Diels-Alder
    - [4+3] of oxallyl cation (after [2+1])
    - [2+2] (all carbon)

**Not Covered:**
- Pauson-Khand
- Intramolecular Pd catalyzed cyclizations
- Radical cyclizations