Chemistry of Propargyldicobalt Cations: The Nicholas Reaction

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Group Meeting, September 28th 2004
Why do we care?

- The problem with substitution at propargylic positions:
  - Alkynes, unlike alkenes, have a poor stabilizing ability for adjacent positive charge.

- The electronic ground state of the propargylic cation

- Other problems:

Definition of Anchimeric Assistance

• “When neighboring-group participation leads to an enhanced reaction rate, the group is said to provide anchimeric assistance.” -McManus, S. P.

100,000-fold rate increase in hydrolysis. attributed to stabilization of intermediate cation

The thermodynamic stabilities of α-ferrocenyl carbocations are similar to cyclopropenium ions.

Application to Propargylic Alkylation:

- Model:

- Metal clusters with highly polarizable electron clouds can alleviate the positive charge on proximally attached atoms.

- 1956, Sternberg and coworkers found that dicobalt octacarbonyl reacts readily with high selectivity for alkynes to form the dicobalt hexacarbonyl cluster:

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Co$_2$(CO)$_8$ as a Protecting Group:

- **Proposed Mech:**

  Reactive species is proposed to be the dicobalt heptacarbonyl species.

- **Methods of removal:**
  - **Oxidative methods to give decomplexed alkynes**
    - Ferric nitrate, ceric ammonium nitrate, N-methylmorpholine N-oxide, DMSO
  - **Reductive methods to give decomplexed alkenes**
    - Lithium in liq. Ammonia, hydrogenation over Rh-charcoal, hydrogenation over Wilkinson’s cat., tributyltin hydride, tributyltin hydride and N-bromosuccinimide in 1,4-cyclohexadiene, triethylsilane (to give vinylsilane)

Application to Propargylic Alkylation:

- Nicholas and coworkers studied complexation with ene-yynes:

Dehydration of Propargyl Alcohol Complexes:

- Nicholas and coworkers began to evaluate the stability of $\alpha$-(alkynyl)dicobalt hexacarbonyl cations:

<table>
<thead>
<tr>
<th>Alcohol complex</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Alcohol complex 1]</td>
<td>![Product 1]</td>
<td>81</td>
</tr>
<tr>
<td>![Alcohol complex 2]</td>
<td>![Product 2]</td>
<td>76</td>
</tr>
<tr>
<td>![Alcohol complex 3]</td>
<td>![Product 3]</td>
<td>65</td>
</tr>
<tr>
<td>![Alcohol complex 4]</td>
<td>![Product 4]</td>
<td>79</td>
</tr>
</tbody>
</table>

Isolation of $\alpha$-[(ethynyl)dicobalt hexacarbonyl] salts

Carbonyl Absorptions:

<table>
<thead>
<tr>
<th>IR DATA:</th>
<th>Alcohol (cm-1)</th>
<th>Cation (cm-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^1 = R^2 = CH_3$</td>
<td>2025</td>
<td>2085</td>
</tr>
<tr>
<td>$R^1 = R^2 = Ph$</td>
<td>2050</td>
<td>2105</td>
</tr>
<tr>
<td>$R^1 = R^2 = H$</td>
<td>2090</td>
<td>2130</td>
</tr>
</tbody>
</table>

Shift ($\Delta \nu$ +40-60 cm$^{-1}$) indicates increased C-O bonding from decreased d(Co)-$\pi^*$ (CO) donation in electron deficient cations.

NMR DATA:

<table>
<thead>
<tr>
<th>NMR DATA:</th>
<th>Alcohol (ppm)</th>
<th>Cation (ppm)</th>
<th>$\Delta \delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^1 = R^2 = CH_3$</td>
<td>1.5</td>
<td>2.2</td>
<td>-0.7</td>
</tr>
<tr>
<td>H</td>
<td>6.2</td>
<td>7.6</td>
<td>-1.4</td>
</tr>
<tr>
<td>$R^1 = R^2 = Ph$</td>
<td>7.4</td>
<td>7.6</td>
<td>-0.2</td>
</tr>
<tr>
<td>H</td>
<td>6.7</td>
<td>8.2</td>
<td>-1.5</td>
</tr>
<tr>
<td>$R^1 = CH_3$; $R^2 = H$</td>
<td>1.5</td>
<td>2.2</td>
<td>-0.7</td>
</tr>
<tr>
<td>H</td>
<td>5.0</td>
<td>6.6</td>
<td>-1.6</td>
</tr>
<tr>
<td>$R^1 = R^2 = H$</td>
<td>4.7</td>
<td>5.3</td>
<td>-0.7</td>
</tr>
<tr>
<td>H</td>
<td>6.2</td>
<td>7.9</td>
<td>-1.7</td>
</tr>
</tbody>
</table>

X-Ray Structure of \([\text{Co}_2(\text{CO})_6]\)-Propargyl Cation:

- Thermal lability and low crystallinity of organometallic cations makes X-ray characterization very difficult.

- 1998, Melikyan and coworkers:

- Central carbon (C13) nearly flat (out of plane <0.5°) with almost ideal trigonal planar arrangement (119-121°).

- C13-C14 bond is more sensitive to rehybridization (1.43 Å to 1.34 Å) than to the complexed alkynes (C13-C20 1.49 Å vs. 1.45 Å; C13-C26 1.53 Å vs. 1.51 Å).

- Geometry of the alkyne complex (C27-C26-C13, C21-C20-C13) proved indifferent to charge/rehybridization (134-135° vs. 136°).

- Metal clusters are non-equivalent (angle between C26-C27 and Co1-Co2 is 82.3°, C20-C21 and Co3-Co4 is 89.7°) with one adopting a skew from perpendicular by 7.7°.

How Electrophilic are the Complexed Cations?

- Mayr’s nucleophilicity / electrophilicity scale:

Hydride as a Nucleophile:

- Due to competitive elimination reactions for standard acetylene coupling methods, Nicholas and Siegel developed the reduction method for the formation of 2° alkylacetylenes.

- In their synthesis of (+)-bengamide E, Hanaoka et. al. described the deoxygenation of the tertiary propargyl alcohol to the isopropyl derivative A.

Enol Derivatives as a Nucleophile:

- Problem with direct substitution with enols:

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 & \quad \text{R}^3 & \quad \text{Yield (\%)} \\
H & \quad H & \quad \text{CH}_3 & \quad 95 \\
H & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad 65 \\
H & \quad \text{Ph} & \quad \text{CH}_3 & \quad 91 \\
H & \quad H & \quad \text{Ph} & \quad 90 \\
H & \quad \text{CH}_3 & \quad \text{Ph} & \quad 65 \\
H & \quad \text{Ph} & \quad \text{Ph} & \quad 95 
\end{align*}
\]

- Cationic complexes can react with ketones/enolates:

Lewis Acid Mediated Nicholas Reaction

- Schreiber and coworkers found that cobalt-complexed propargylic ethers can undergo the same reaction as Nicholas but with Lewis acids instead of bronsted.

- The results of stereochemical studies that employed both E and Z trimethylsilyl enol ethers of propiophenone:

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>Lewis acid</th>
<th>syn/anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₃Si</td>
<td>Me</td>
<td>H</td>
<td>BF₃-OEt₂</td>
<td>15:1</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>EtAlCl₂</td>
<td>18:1</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>EtAlCl₂</td>
<td>9:1</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>BF₃-OEt₂</td>
<td>6.8:1</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>BF₃-OEt₂</td>
<td>3.5:1</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>EtAlCl₂</td>
<td>1.6:1</td>
</tr>
</tbody>
</table>

Stereochemical Model for Nicholas Rxn:

- Model must take into account the fact that the cobalt complex to the alkyne is **dynamic not static**!
- Hoffman has predicted that bending of the cationic carbon toward one of the cobalt atoms would result in hyperconjugative stabilization, and that the upright structure A is 17.5 kcal / mol higher in energy than B.

![Chemical Structures]

- Schreiber’s variable temp. NMR experiments

Fluxional process of enantiomerization had $\Delta G^\ddagger = 10.1$ kcal/mol

2nd fluxional process that results in syn/anti isomerization was detected at higher temps ($\Delta G^\ddagger = 12.6$ kcal /mol)

Stereochemical Model for Nicholas Rxn:

- The dynamic behavior can be depicted as follows:

- Antarafacial migration and rotation processes result in exposure of the opposite enantiotopic face for attack by a nucleophile.
- Only suprafacial migration preserves exposure of the kinetically formed face.

Racemization occurs at a rate that is fast relative to alkylation!

Stereochemical Model for Nicholas Rxn:

\[
\text{\textsection} + \text{\textsection} \rightarrow \text{\textsection} \quad + \text{\textsection}
\]

Stereochemical Model for Nicholas Rxn:

\[
\begin{align*}
\text{C} + & \quad \text{C} \quad \longrightarrow \quad \text{C} + \text{C}
\end{align*}
\]

Stereochemical Model for Nicholas Rxn:

- The model most successful in providing a rationale for the observed stereochemistry is a synclinal relationship of the donar and acceptor Π systems.

The relative face selectivity of this rxn as compared to Seebach’s model is a result of “unusual topographical features of the cobalt cation”.

Kinetic Resolution of Racemizing Cobalt Cation

- The ability of the cobalt cation to enantiomerize during the alkylation reaction, combined with the intrinsic relative facial selectivity of the reaction “suggests that a double stereodifferentiating process may be achieved with kinetic resolution of a racemizing cation if a suitable chiral, nonracemic nucleophile can be found” (5754).

Kinetic Resolution of Racemizing Cobalt Cation

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Kinetic Resolution of Racemizing Cobalt Cation

Because the two enantiomeric cations undergo interconversion under the reaction conditions and react at different rates, the racemic pair of ethers can be converted to 12:1 mix of diastereomers.

Chiral Enolate Additions to Cobalt Complexes:

• Matched:

• Mis-matched:

Enolates as Nucleophiles:

- Caddick’s kedarcidin synthesis:

- Magnus’ dynemicin synthesis:

\( \forall \beta\text{-alkynl ketones:} \)

Carbon as a Nucleophile: Allylations

- Nicholas and coworkers pioneered the first coupling of allylsilanes and propargyl cobalt complexes:

- Schreiber and coworkers developed an intramolecular variant of the allylation reaction

- Green and coworker’s double Nicholas allylation:

Carbon as a Nucleophile: Allylations

- Isobe and coworker’s synthesis of a taxoid diterpenoid skeleton:

- Asymmetric allylations:

Without complexation, allylation mainly produces polymerization product.

<table>
<thead>
<tr>
<th>aldehyde</th>
<th>borane</th>
<th>yield(%)</th>
<th>de (%)</th>
<th>ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = Ph</td>
<td>R¹ = Me</td>
<td>75</td>
<td>&gt;95</td>
<td>&gt;98</td>
</tr>
<tr>
<td>R = Ph</td>
<td>R¹ = CH₂OMe</td>
<td>62</td>
<td>&gt;95</td>
<td>&gt;96</td>
</tr>
<tr>
<td>R = Me</td>
<td>R¹ = Me</td>
<td>73</td>
<td>&gt;95</td>
<td>&gt;96</td>
</tr>
<tr>
<td>R = Me</td>
<td>R¹ = CH₂OMe</td>
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<td>&gt;95</td>
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<td>R = H</td>
<td>R¹ = Me</td>
<td>76</td>
<td>88</td>
<td>&gt;96</td>
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Carbon as a Nucleophile: Allylations

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<tr>
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<td>50</td>
<td>&gt;95</td>
<td>&gt;95</td>
</tr>
<tr>
<td>R = Me</td>
<td>44</td>
<td>&gt;95</td>
<td>&gt;95</td>
</tr>
<tr>
<td>R = H</td>
<td>20</td>
<td>&gt;95</td>
<td>&gt;95</td>
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</table>
Carbon as a Nucleophile: Allylations

\[
\begin{array}{c}
\text{C} = \text{O} + \text{Ph} \rightarrow \text{C} = \text{O} \\
\text{Ph} \rightarrow \text{Me}
\end{array}
\]

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<td>&gt;95</td>
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Carbon as a Nucleophile: Allylations

Diastereoselectivity:

Enantioselectivity:

Oxygen as a Nucleophile

∀ α-epoxides:

Highly stereoselective endo-mode ring closure (cobalt assisted double inversion process). The intermolecular oxygen addition to α-epoxides has little to no stereoselectivity.

Oxygen as a Nucleophile:

- Mukai and Hanaoka’s synthesis of (+)-secosyrins:

- Medium sized rings and fused bicyclic rings:

Pyranose Ring Opening:

- During Isobe and coworkers' study, whether $\alpha$-substituted pyranoses could undergo a cobalt-assisted ring opening, and whether the intermediates could be manipulated and re-cycled to form another oxepane.

Oxepane Formation:

Exclusive formation of syn stereoisomer:

Oxepane Formation:

- Isobe and coworkers’ synthesis of ciguatoxin (ABC):

Conclusions:

• Through cobalt directed anchimeric assistance a wide variety of nucleophiles can undergo Sn1 – type reactions at the propargylic position.
• Using chiral auxillaries a moderate degree of stereocontrol can be achieved.
• A catalytic enantioselective variant of the Nicholas reaction has not been discovered.

  – Topics not discussed in this talk:
    • Alkenes as nucleophiles
    • Aromatic as nucleophiles
    • Glycosylation chemistry
    • Nitrogen as a nucleophile (azides, amines)
    • Sulphur as a nucleophile
    • Nicholas promoted carbonyl-ene reactions
    • Nicholas promoted rearrangements
    • Radical reactions
    • Nicholas promoted ene-yne additions