
A Brief Synopsis

-Mike DeMartino
-Group Meeting: 10-29-2003
Overview

• Some general observations

• The “prime-time-players”…what were they doing in JOC? (Thanks Dick Vitale, baby!)

• Some selected total syntheses
General Observations from Title Perusing

- Heterocyclic chemistry prevalent
- Surprisingly little Tin/Palladium chemistry
- Lots of Rearrangements:
  - Thermal
  - Photolytic
  - Acid Catalyzed
- $^{13}$C spectroscopy a new thing in organic chemistry?!?
- Not many total syntheses, mostly steroids
- Sulfur chemistry very prevalent
- A lot of degradation chemistry
E.J. Corey (Harvard)

- Preparation of an optically active intermediate for the prostaglandins (p. 356)
  - A racemic route had previously been developed from (+/-) 1 to (+/-)-11-deoxyprostaglandins

\[
\begin{align*}
\text{LiOH} & \quad \text{(-)-1-(1naphthyl)ethylamine} \\
\text{1} & \quad \text{3 recrystallizations} \\
\text{1} & \quad \text{1. Removal of salt} \\
\text{1} & \quad \text{2. 10 N HCl}
\end{align*}
\]

- Condensation of an allylic Phosphonium Ylide (p. 821)
  - Generally, allylic phosphorous ylides condense on the \( \text{I} \) carbon
  - Many geometric isomers usually obtained
E. J. Corey (p. 256)

Scheme I

Generally, E/Z > 1
Samuel Danishefsky (Univ. of Pitt)

-A route to functionalized heterocycles by homoconjugate addition (p. 1979)
  -The use of a highly substituted cyclopropane as an electrophile (generated by reacting the olefin with dimethyl diazomalonate in the presence of copper bronze)

-Showed in earlier work that mechanism goes through "Spiro-mode"
Samuel Danishefsky (Univ. of Pitt)

-Furanoid systems by intramolecular homoconjugate addition (p. 2658)

-O-Alkylation was dominant pathway in all systems they tried in this paper
Gilbert Stork (Columbia)

-Regiospecific Aldol condensations of the kinetic lithium enolates of methyl ketones (p. 3459)

-It had previously been difficult to trap the kinetic enolate with alkyl halides
-So, used a more reactive electrophile to trap the enolate

$$\text{O} \xrightarrow{\text{LDA, THF, } -78^\circ} \text{CH}_3\text{CH} = \text{CH}\text{CH}_2\text{O}^\text{Li}$$ 
$$\text{O}^\text{Li} \xrightarrow{\text{Butyraldehyde}} \text{CH}_3\text{CH} = \text{CH}\text{CH}_2\text{CH} = \text{CH}_{\text{O}}\text{OH}$$ 
65% (90% Kinetic enolate)

$$\text{O} \xrightarrow{\text{LDA, THF, } -78^\circ} \text{CH}_3\text{CH} = \text{CH}\text{CH}_2\text{O}^\text{Li}$$ 
$$\text{O}^\text{Li} \xrightarrow{\text{Benzaldehyde}} \text{CH}_3\text{CH} = \text{CH}\text{CH}_2\text{OC} = \text{C(Ph)}\text{OH}$$ 
75-80%

$$\text{O} \xrightarrow{\text{LDA, THF, } -78^\circ} \text{CH}_3\text{CH} = \text{CH}\text{CH}_2\text{O}^\text{Li}$$ 
$$\text{O}^\text{Li} \xrightarrow{\text{Crotonaldehyde}} \text{CH}_2\text{C} = \text{C(Ph)CH}=\text{CH}_{\text{O}}\text{OH}$$ 
70%
Barry M. Trost (Wisconsin, Madison)

- Chemospecificity of allylic alkylations (p. 737)
  - Use of cis and trans geranylacetone

![Chemical Structures with Reactions](image)

Conditions: PdCl$_2$, NaCl, CuCl, NaOAc in AcOH

- [4]-allyl complexes are remarkably stable

![Chemical Structure with Reaction](image)
Alkylations

1, 2, or 3

1. HOCH₂CH₂OH,
   TsOH, PhH, Reflux
2. Li, C₂H₅NH₂, 0°C
3. H₂O, HCl

NaH

CH₃SO₂CH₂CO₂CH₃

H₃CO₂S-CH₂-CO₂CH₃

Lil, NaCN, DMF

130°C

H₃CO₂S-CH₂-CO₂CH₃
Barry M. Trost (Wisconsin, Madison)

- Alkylation of Lactam Derivatives (p. 2475)

- Both of the above examples proceeded with C-alkylation exclusively with alkyl halides, chlorosilanes.
- For 1 (Stronger enolate), reaction with methyl vinyl ketone proceeds with 1,2 addition; for 2, (weaker reagent), reaction to MVK proceeded with conjugate addition

This selectivity is due to the less reactive reagent having its charge more delocalized in the transition state. To test this hypothesis, a control experiment:

- Exclusively 1,4 addition, 29%
Barry M. Trost (Wisconsin, Madison)

- A convenient approach to Methyl 3-oxo-4-pentenoate (p. 2648)
  - Not easily synthesized
    - The two main previous methods either ended with a final step of 7-12% (acid catalyzed elimination), or was based on a retro-Diels-Alder step (great yield, but requires special high-temp pyrolysis apparatus).
  - Utility seen as an "annelating agent" in the synthesis of terpenes and alkaloids

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O
PhSH

\[
\begin{align*}
\text{O} & \quad \text{PhSH} \\
\text{Ph-S-CH(OH)CO} & \quad \text{1. SOCl}_2 \\
\text{Ph-S-CH(OH)CO} & \quad \text{2. LiO} \\
\text{Ph-S-CH(OH)CO} & \quad \text{MeO} \\
\text{H^+} & \quad \text{PhSCH}_2! \\
\text{Ph-S-CH(OH)CO} & \quad \text{MeO} \\
\end{align*}
\]
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Summary: 3-step route, 60-76% overall; 5-step route, 60-72% overall
R. F. Heck (Univ. of Delaware :-) )

-Palladium caralyzed Amidation of aryl, heterocyclic, and vinylic halides (p. 3327)

Possible Mechanism:

\[
\begin{align*}
PdX_4[P(C_6H_5)_3]_2 + 2\text{CO} + R'NH_2 & \rightarrow [Pd(CO)[P(C_6H_5)_3]_2] + R'NHCONHR' + 2HX \\
[Pd(CO)[P(C_6H_5)_3]_2] + RX & \xrightleftharpoons[-\text{CO}]{\text{CO}} R'NHCONHR' + 2HX \\
RPd(X)[P(C_6H_5)_3]_2 & \xrightleftharpoons{\text{CO}}{\text{CO}} RCPd(X)[P(C_6H_5)_3]_2 \xrightarrow{R'NH_2} R'NHCONHR' + HPd(X)[P(C_6H_5)_3]_2 \\
HPd(X)[P(C_6H_5)_3]_2 & \xrightarrow{\text{CO}} HX + Pd(CO)[P(C_6H_5)_3]_2 \\
HX + R_3''N & \rightarrow R_3''NH^+X^-
\end{align*}
\]
R. F. Heck (Univ. of Delaware :-))

-Palladium caralyzed carboalkoylation of aryl, benzyl, and vinylic halides (p. 3318)

\[
\text{RX} + \text{Pd(CO)(PPh}_3\text{)}_2 \rightarrow \left[ \begin{array}{c} \text{CO} \\ \text{R-Pd-X} \\ \text{PPh}_3 \end{array} \right] + \text{PPh}_3
\]

\[
\left[ \begin{array}{c} \text{CO} \\ \text{R-Pd-X} \\ \text{PPh}_3 \end{array} \right] + \text{R'}\text{OH} + \text{Bu}_3\text{N} + \text{PPh}_3 \rightarrow
\]

\[
\left[ \begin{array}{c} \text{COOR'} \\ \text{R-Pd-PPh}_3 \\ \text{PPh}_3 \end{array} \right] + \text{Bu}_3\text{NH}^+\text{X}^- \]

\[
\left[ \begin{array}{c} \text{COOR'} \\ \text{R-Pd-PPh}_3 \\ \text{PPh}_3 \end{array} \right] + \text{CO} \rightarrow \text{R-COO}R' + \text{Pd(CO)(PPh}_3\text{)}_2
\]

Possible Mechanism:
• The following people did wonderful chemistry in JOC, ‘74, but time constraints cause their omission:
  – David Evans (UCLA)
    • Useful Prostaglandin Intermediate (p. 3176)
    • Applications of trimethylsilyl cyanide (p. 914)
  – Herbert C. Brown
    • New organoborane structures via alpha-bromination of borapolycyclanes (p. 861)
    • Synthesis of olefins: alpha-elimination of alpha-chloroboronic esters (p. 2817)
    • Synthesis of terminal acetylenes via treatment of lithium ethynyltrialkylborates with Iodine (p. 731)
  – Herbert House
    • Chemistry of Carbanions (p. 3102)
    • Electron transfer reactions: reduction of enones with Cr(II) compounds (p. 1173), and of nonconjugated acetylenes (p. 747)
  – Robert E. Ireland
    • Claisen rearrangement of N-Allylketene O,N-Acetals (p. 421)
  – And of course, many others…
(S)-Carlosic Acid

Blommer and Kappler, p. 113

Temple University

Note: all yields in the synthesis were 70-80%, except the "key step," the cyclization
Cassamedine

Cava and Libsch, p. 577

UPenn

-An alkaloid isolated from Cassytha americana
The Sex Pheromone of the Pink Bollworm

Phillip E. Sonnet, p. 3793

U.S. Dept. of Agriculture, Maryland

-Isolated from the *Pectinophora gossypiella*, the pink bollworm moth
-Isolated as 1:1 mixture of geometric isomers
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\[
\text{H}_2, \text{Pd/BaSO}_4 \quad \text{Pentane, 84%}
\]

\[
\text{NaNO}_2(aq) \quad \text{HNO}_3(aq) \quad 74\%
\]

\[
\text{H}_2, \text{Pd/BaSO}_4 \quad \text{Pentane, 80%}
\]

The Sex Pheromone of the Pink Bollworm
A Trail Pheromone of the Pharaoh Ant

Sonnet, Oliver, p. 2663

U.S. Dept. of Agriculture, Maryland

- Isolated from the *Monomorium pharaonis*, the Pharaoh Ant
- It was known that the pheromone had the general structure of 3-butyl-5-methoctahydroindolizine, but absolute stereochemistry of active pheromone was not elucidated
- Synthesized all four stereoisomers because they were interested in the pheromone's utility as a pest control agent

![Chemical structures A, B, C, D](attachment:image.png)

A Trail Pheromone of the Pink Bollworm
Fagaronine Chloride

Stermitz, p. 3239

Colorado St. Univ., Fort Collins

- Extremely active antileukemic alkaloid
- Isolated from *Faraga zanthoxyloides*
- Note: synthesis also proved structure
Fagaronine Chloride

Stermitz, p. 3239

Colorado St. Univ., Fort Collins

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![Reaction Scheme]

1. Na, NH₃(liq)
2. 1
3. NH₄Cl, 24%

Dimethyl Sulfate, PhNO₂/Xylene 180°C
\((+/−) 11\text{-deoxyprostaglandin E}_2\)

John Petterson, John Fried, p. 2506

Syntex, California
3-Arylcephalosporins

Firestone, Maciejewicz, Christensen, p. 3384

Merck Sharp and Dohme Research, New Jersey

-Semisynthetic Lactam Antibiotics
-High potency, acid stable, high degree of tolerance by man
-Many modifications prior to this work

**Chemical Structures:**

1. 
   
   ![Chemical Structure 1]

   Reported in 1973 by same the group

   Ar = C₆H₅
   p-C₆H₄-CO₂Me
   4-thiazolyl

2. 
   
   ![Chemical Structure 2]

   ![Chemical Structure 3]

   ![Chemical Structure 4]

   ![Chemical Structure 5]

   ![Chemical Structure 6]
3-Arylcephalosporins

Firestone, Maciejewicz, Christensen, p. 3384

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\[
\text{2,4-DNPH} \quad \xrightarrow{\text{Et}_3\text{N}} \quad \text{Anisole} \quad \xrightarrow{TFA} \quad \text{3-Arylcephalosporins}
\]