Intramolecular Cyclobutadiene
Cycloaddition/Cyclopropanation/Thermal Rearrangement:
An Effective Strategy for the Asymmetric Syntheses of Pleocarpenene and Pleocarpenone

Michael J. Williams, Holly L. Deak and Mark L. Snapper

Outline

• Cyclobutadiene introduction
• Cyclobutadiene in synthesis
• Snapper work with cyclobutadiene
• Pleocarpenene and pleocarpenone
• Total syntheses of pleocarpenene and pleocarpenone
• Conclusions
Cyclobutadiene

- Anti-aromatic species that rapidly dimerizes
- Observed at 8 K (JACS, 1973, 95, 614)
- First synthesized in 1965 by Rowland Pettit (JACS, 1965, 87, 131)
- Reactivity modulated with stabilizing groups
  - Bulky groups
  - Electron withdrawing, donating groups
- Stabilized when complexed to metal
  - As tricarbonylcyclobutadiene iron complex:
    - Stable to Friedel-Crafts conditions, NaBH₄, Grignard Reagents, HCl, mild oxidants, etc. (JACS, 1965, 87, 3254)
    - Iron complex can be readily removed with CAN, FeCl₃, Pb(OAc)₄ or trimethyl ammonium N-oxide
Cyclobutadiene Synthesis

- Synthetic methods:
  - Cyclobutane, (JACS, 1965, 87, 131)
    \[
    \text{BrBr} \xrightarrow{\text{Fe}_2(\text{CO})_2} \text{(CO)}_3\text{Fe}
    \]
  - Pyranone, (JACS, 1967, 89, 5074)
    \[
    \text{MeO} \xrightarrow{hv, \text{toluene}} \text{(CO)}_3\text{Fe}
    \]
  - Alkyne (JACS, 2005, 127, 3473)
    \[
    \text{CO}_2\text{Et} \xrightarrow{\text{CpCo(CO)}_2, \text{toluene, reflux}} \text{CoCp}
    \]
Cyclobutadiene Reactions


\[
\begin{array}{c}
\text{(CO)}_3\text{Fe} \\
\text{O} \\
\text{O} \\
\text{CHO} \\
\text{[O]} \\
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{CHO} \\
\text{[O]} \\
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{CHO} \\
\text{[O]} \\
\end{array}
\quad \rightarrow \quad \text{O} \\
\text{O} \\
\text{O} \\
\text{CHO}
\]

Typically run at 1 mM

• 2+2 (Pettit, *JACS*, **1966**, 1328)

\[
\begin{array}{c}
\text{(CO)}_3\text{Fe} \\
\text{O} \\
\text{O} \\
\text{CHO} \\
\text{CAN} \\
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{CHO} \\
\text{CAN} \\
\end{array}
\quad \rightarrow \quad \text{O} \\
\text{O} \\
\text{O} \\
\text{CHO}
\]
Early Snapper Work

• (2+2) (*JACS*, **1996**, **118**, 9196)

\[
\text{(CO)}_3\text{Fe} \quad \xrightarrow{\text{CAN}} \quad \text{cycloadduct} \quad \text{thermal product}
\]

• (4+2) (*JOC*, **1998**, **63**, 6440)

\[
\text{(CO)}_3\text{Fe} \quad \xrightarrow{\text{CAN}} \quad \text{cycloadduct} + \text{thermal product}
\]


\[
\text{(CO)}_3\text{Fe} \quad \xrightarrow{\text{CAN, CO}} \quad \text{Huisgen Notation}
\]
Snapper Work (cont.)

- Asteriscanolide (*JACS*, **2000**, 122, 8071)

Rearrangement Stereochemistry

Thermal Rearrangement

Acid-Mediated Rearrangement

Org. Lett, 2005, 7, 5785
Trends

• The activation energy for intramolecular cyclization must be less than 13.5 kcal/mol or dimerization becomes the major competitive pathway (*JACS*, 2003, 125, 16310)

• 3 atom heteroatom containing tethers with electronically unactivated olefins yield the best results

• When there is the possibility of either a 2+2 or 4+2 cyclization, the 2+2 product can be thermally converted to the 4+2 product
Pleocarpenene and Pleocarpenone

- *Pleocarphus revolutus* is a small shrub found in Chile. Powdered extracts showed anti-cancer activity in the Cancer Chemotherapy National Service Center Screen (Phytochemistry, 1977, 16, 379)
- Also isolated from *Chenopodium botrys*, C. A medicinal plant found in Southern Europe (Tetrahedron, 1980, 36, 371)

![Pleocarpenone and Pleocarpenene](image)
Retrosynthesis
Cyclobutene Synthesis

\[
\text{CO}_2\text{Me} (\text{CO})_3\text{Fe}h v, \text{PhH Fe}_2(\text{CO})_9 \rightarrow (\text{CO})_3\text{Fe} \rightarrow \text{CO}_2\text{Me}
\]

1. DIBALH (95%)
2. MnO\(_2\) (83%)
3. 3-butenylMgBr (96%)

\[
(\text{CO})_3\text{Fe} \rightarrow \text{HO} \rightarrow \text{CO}_2\text{Me} + \text{HO} + \text{HO} + \text{CO}_2\text{Me}
\]

1. MnO\(_2\) (90%)
2. 11 (96%)
3. Grubb's methyl acrylate (94%)

\[
\text{CAN} (80%) \rightarrow \text{CAN} (91%)
\]

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2/25/2007
Cyclopropanation

1. LAH
2. TIPSCI, Ac₂O (87-89%)

1. EDA, Cu(acac)₂, then NaOEt

1. Swern then MeMgCl (79-82%)

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End Game

1. benzene, 200 °C
   DBU (76%)

RaNi, H₂
(63%)

1. TBAF (99%)
2. TsCl, Et₃N, DMAP (99%)
3. NaI, DBU (83%)

O₃, MeOH, NaOMe
(85%)
Conclusions

• Iron tricarbonyl is a robust protecting group that modifies the reactivity of cyclobutadiene so that it can be synthetically useful

• Iron tricarbonylcyclobutadiene is stable to acid, base, mild oxidative and reductive conditions. Treatment with CAN unmasks a highly reactive species that can provide access to structurally interesting intermediates.

• The total syntheses of pleocarpenene and pleocarpenone were accomplished in 16 steps and 8.1% overall yield, and 17 steps and 6.9% overall yield respectively