**Cyclopropanes in Synthesis**

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**An Brief History of Cyclopropanes-**

1884 First synthesis of a cyclopropane derivative by William Henry Perkin with Adolf von Baeyer's.
1896 Vinyliccyclopropane synthesized by Gustavson.
1922 Existence of vinylcyclopropane secured, yet faces despite residual disbelief.
1931 Pauling describes the banana bonding model of cyclopropane.
1942 Cyclopropanol synthesized by Cottle.
1947 Walsh describes cyclopropane as a coordinate bond between ethylene and \( \cdot \text{CH}_2 \).
1952 Hexafluorocyclopropane generated by TFE photolysis.
1954 Doering et al. find dichlorocarbene adds into alkenes to generate gem-dichlorocyclopropane.
1957 Triphenyl/cyclopropenium perchlorate synthesized by Breslow, constituting the smallest aromatic species possible.
1958 Simmons and Smith determine that iodoalkylzinc species are capable of cyclopropanation.
1964 Wittig elaborates diazoalkanes as an alternative to iodoalkane precursors of organozinc species.

**Physical Descriptions of Cyclopropane-**

-Pauling's \( \text{sp}^3 \), "banana" bonded cyclopropane: This model suggests that \( \text{sp}^3 \) hybridized carbons give rise to a stable, trigonal planar arrangement. Further instability is inferred as all hydrogens are eclipsed.

-Walsh cyclopropane description: In an analogy to epoxides, A.D. Walsh proposed that cyclopropanes be considered as an insertion of methylene into ethylene, ultimately giving rise to the \( D_{3h} \) symmetric product.

Thus, Walsh cyclopropane has significant \( \text{sp}^2 \) character and should react in analogy to olefins; further, as reactivity is generally governed by HOMO-LUMO chemistry, one can also see why Walsh cyclopropane has a propensity to open, yet while it is also a stable compound. The dative bond suggestion was immediately hated by the British chemical community, with Sir. R. Robinson leading the criticism. Walsh's suggestions had been picked apart due to his suggestion of subtle similarities between ethylene oxide/cyclopropane and N-oxide species, ethylene, and the relationship between chemical character and depiction. Experimental support, however, was presented a year later for cyclopropane's olefinic character, strengthening Walsh's hypothesis.

**Walsh Orbital Energies**

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**Outline of Cyclopropanes in Synthesis:**

- **Stereocontrol via cyclopropanation:**
  - Corey's syntheses of (\( \alpha \))-Atractylenigmin and (\( \alpha \))-Cafestol
  - Smith's synthesis of (\( \alpha \))-MycorrhizinA and (\( \alpha \))-Dechlorormycorrhizin A
- **Cyclopropanes as equivalents or masked groups:**
  - Danishefsky's synthesis of Epothilone A
  - Carreira's synthesis of (+)-Spirotyptostatin and (\( \alpha \))-Horsfilin
- **Synthesis of unusual cyclopropanated natural products:**
  - Barrett's synthesis of FR-900846
  - Falck's synthesis of FR-900846
Cyclopropanes in Synthesis

Epothilone A: Danishefsky et al., JACS, 1997, 10073

1. TMS-Li, BF$_3$-Et$_2$O, THF, -78°C, 76%
2. MOMCl, Py, NEt$_3$, (CH$_2$)$_2$, 55°C, 85%
3. PPTS, MeOH, 95%

Epoxide: 1) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, -78°C; Et$_3$N, -78°C-r.t.
2) MeMgBr, Et$_2$O, 0°C-r.t. 85% for 2 steps
3) TPAP, NMO, 4 Å M.S., CH$_2$Cl$_2$, 0°C-r.t.

A: R=MOM 1) PhSH, BF$_3$-Et$_2$O, CH$_2$Cl$_2$, r.t.
B: S=Ac 2) Ac$_2$O, pyr., 4-DMAP, CH$_2$Cl$_2$, r.t.
86%; 99%

BnO CHO + OTMS
1) TiCl$_4$, CH$_2$Cl$_2$, -78°C 87%
2) CSA, PhH

FR-900848

1) 1,3-propane diol, TiCl$_4$
CH$_2$Cl$_2$, -78°C--40°C 78%

2) TBSOTf, 2,6-Lutidine, CH$_2$Cl$_2$, 98%

TPSCI, imid., DMF, r.t., 97%

Bu$_3$SnH, AIBN(cat), PhH, Δ 80% for 2 steps

NIS, MeOH, r.t.
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(-)-Spirotryptostatin B, Carriera et al., ACIEE, 2003, 42, 694

1) DDQ, CH$_2$Cl$_2$/H$_2$O, 89%
2) (COCI)$_2$, DMSO, CH$_2$Cl$_2$
   -78 °C; Et$_3$N, -78-0 °C, 90%

1) pTsOH, Diox./H$_2$O, 50 °C, 99%
2) CH$_3$PPh$_3$Br, NaHMDS, PhCH$_3$, 0 °C-r.t., 76%

1) 9-BBN, THF, r.t.
2) "B", PdCl$_2$(dpff)$_2$

1) Dess Martin Periodinane (DMP), CH$_2$Cl$_2$, r.t.
2) NaBH$_4$

1) HF-Pyr., THF, Pyr., r.t, 99%
2) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, -30 °C, 93%

1) DMP, CH$_2$Cl$_2$, r.t., 84%
2) HF-Pyr., THF, r.t., 99%
3) 3,3 DMDO, CH$_2$Cl$_2$, 35 °C, 49%

Epithilone A

H$_2$, Pd' BaSO$_4$, quinoline, EtO, r.t., 90%
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FR-900848, Falck et al, JACS 1996, 6096

FR-900848, Barrett et al, CC, 1997, 1693

FR-900848, Nagao et al, JACS 1998, 12012