Strain driven reactivity of carbocycles

- After proposal that carbons can form rings (Kekulé, 1865) and have tetrahedral geometry (van’t Hoff and LeBel, 1874) many think it impossible to form rings smaller than 5 or 6
- August Freund achieves first synthesis of cyclopropane (1882)
- Adolf von Baeyer proposes a strain theory (1885) for which he wins a Nobel prize (1905)

“Trimethylene” (Freund, 1882)
“Bicyclo[1.1.0]butane” (Wiberg, 1965)
“Cyclobutane” (Willstätter, 1905)
“[1.1.1]Propellane” (Wiberg, 1982)

“[G]enerally, the greater the difference in strain energy between a substrate and a product, the greater the driving force for a reaction” Chem. Commun. 2020, 5718

Contributions to the total strain in a molecule:
- Bondlength distortion
- Bond angle distortion
- Torsional strain
- Nonbonded interactions
- Energy changes due to rehybridization


- Many strained σ bonds have π-like reactivity, responsible for many of their interesting transformations

Group meeting progress

- Focus of this presentation is on synthetic applications of strain (carbocycles only)

Cyclopropanes
The many π-like reactions of cyclopropanes

Hydrogenation

En route to (±)-Δ^9(12)-capnellene
JACS 2009, 7214

En route to (–)-spirochensilide A
JACS 2020, 8116

En route to (±)-steviol
Angew. Chem. Int. Ed. 2013, 9019

Electrophilic fission

Reductive fission

Radical fragmentation

Chem. Ber. 1984, 3004
Chem. Lett. 1993, 545

SE 28 kcal/mol

Homologous Michael addition

Cyclopropane Dauben oxidation

PCC
DCM, rt

EtO_2C\_CO_2Et + NaH

THF, rt

60%
27%
80%
60%
Strain driven reactivity of carbocycles

**Donor acceptor cyclopropanes**

![Chemical structure of donor acceptor cyclopropanes]

Homo-Nazarov cyclization

Aspidospermidine

Angew. Chem. Int. Ed. 2011, 5767

**Vinyl cyclopropanes**

![Chemical structure of vinyl cyclopropanes]

JACS 2003, 13624

Strain release Wolff/Cope

Tetrahedron 1981, 4445

meta arene alkene photocycloaddition then homo-1,5-sigmatropic H-shift

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![Chemical structure of reductive fragmentation]


Isocomene: an exercise in strain

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**Reductive fragmentation**

![Chemical structure of reductive fragmentation]


Isocomene: an exercise in strain
Strain driven reactivity of carbocycles

Carl Mansson

**Burns Group Meeting**

**Overview**

- **E** = CN, CO₂Me, CO₂CH₂CF₃, SO₂Ph
- **NuH** = CN, MeO₂C-Ph, PhCN

**Chemical Reactions**

1. **Rhodocyclization**
   - Reaction of alkenes with alkynes
   - Insertion of CO + alkyne + CO
   - Red. elim. + taut.
   - 6π-electrocyclization
   - Four component [5+1+2+1] cycloaddition
   - 12 examples 42-92%

2. **Alkyldiene cyclopropanes**
   - SE 37 kcal/mol
   - Isomerization

3. **All carbon 1,4 dipole**
   - 8 examples 47-91%
   - 8 examples 67-88%

**Notes**

- JACS 2005, 2836
- JACS 2008, 7178
- JACS 2008, 1814
Burns Group Meeting

Strain driven reactivity of carbocycles

Carl Mansson

\[ \text{Pd} \text{dba}_2 \text{ (10 mol\%)} \]
\[ \text{P(O-2,4-tBu-Ph)}_3 \text{ (26 mol\%)} \]
dioxane, 90°C

10 examples
16-84%

Chem. Commun. 2010, 270

\[ \text{Pd} \text{dba}_2 \text{ (6 mol\%)} \]
L2 or L3 (24 mol%)
dioxane, reflux

7 examples
59-74%
45-64% ee

Angew. Chem. Int. Ed. 2010, 1830

Alkylidene cyclopropanes are common cyclobutene precursors

\[ \text{Alkylidene cyclopropanes are common cyclobutene precursors} \]

JACS 2006, 7430

\[ \text{Pd(OAc)}_2 \text{ (3 mol\%)} \]
CuBr2 (10 mol%)
DCE, rt, 1-3h

52-93%

R = p-tol, p-OMe-Ph, m-OMe-Ph, 2,4-OMe-Ph, o-OBn-Ph

JACS 20007, 11026

Unaffected by radical traps, unusual Cope rearrangement

JOC 2010, 902
Strain driven reactivity of carbocycles

Bu$_2$SnH, Et$_3$B (10 mol%) THF, rt
then
PhI, Pd$_2$(dba)$_3$ (1.5 mol%)
PPh$_3$ (8 mol%), TBAF
80°C

JACS 2008, 2912

Me$_2$O

1. TPAP
2. MeNH$_2$

Tetrahedron Lett. 1995, 1343

Radical fragmentation
cyclization


JACS 2013, 632

JACS 2002, 6312

acceptor methylene cyclopropane
divergent cycloaddition pathway
Strain driven reactivity of carbocycles

**Cyclopropenes**

\[ \text{SR} + \text{R}^1 \text{R}^2 \xrightarrow{[\text{Rh(CO)}_2\text{Cl}]_2 (1 \text{ mol} \%) \text{ PhMe } 80^\circ\text{C}} \\text{R}^1 \text{R}^2 \]

\( n = 1, 2, 3 \)
\( R^1, R^2 = \text{H, Me, Et, Ph} \)
\( R = \text{Me, Et} \)

SE 54 kcal/mol

\[ 65-85\% \]

*Tetrahedron Lett. 2008, 6316*

\[ \text{R}^1 = \text{Ph} \]
\( R^2 = \text{Ph, Me} \)
\( R^3 = \text{Alkyl, Ar, OAlkyl, COMe} \)
\( R^4 = \text{Ar, HetAr, Alkyl, Alkenyl} \)

\[ 13 \text{ examples} \quad 44-96\% \]

*JACS 2006, 14814*

\[ \text{Cyclopropenes as masked vinyl carbenes} \]

\[ \text{Org. Lett. 2000, 2093} \]


\[ \text{Chem. Eur. J. 2008, 10219} \]

\[ \text{SE 54 kcal/mol} \]

\[ \text{Cyclopropenes as masked vinyl carbenes} \]

\[ \text{Org. Lett. 2000, 2093} \]


\[ \text{Chem. Eur. J. 2008, 10219} \]
Strain driven reactivity of carbocycles

Cyclobutanes

SE 27 kcal/mol

\[ \begin{align*}
\text{catalyst} & \xrightarrow{\text{catalyst (20 mol\%)} \text{ oxone}} \text{Et}_2\text{AlCl, PhMe or LiI, DCM} \\
& \text{oxone} \\
& \text{Et}_2\text{AlCl, PhMe or LiI, DCM} \\
& \text{9 examples} \ 89-99\% \\
& \text{80-96\% ee} \\
\end{align*} \]

Angew. Chem. Int. Ed. 2006, 1429

Nitrile generating fragmentation

Chem. Commun. 2017, 11544

JACS 2020, 8585

SE 57 kcal/mol

(-)-Scabrolide A

\[ \begin{align*}
\text{Cyclobutanes} & \xrightarrow{\text{PG} = p-\text{CF}_3-\text{Bz}} \text{Ir(III)} \\
& \text{Ir(III)} \\
& \text{PG} = p-\text{CF}_3-\text{Bz} \\
& \text{Ir(IV)} + \text{MeOH} \\
& \text{Ir(IV)} + \text{MeOH} \\
& \text{8 examples} \ 60-94\% \\
& \text{60-94\% ee} \\
\end{align*} \]


Synlett 2008, 765

JACS 1996, 8285

\[ \begin{align*}
\text{R} & = \text{Bu, Et, Bn} \\
\text{79-98\%} \\
\text{97-99\% ee} \\
\text{89:11 to 93:7 dr} \\
\end{align*} \]
Strain driven reactivity of carbocycles

**Polycyclic compounds**

- **ΔSE = 32 kcal/mol**
  - SE 99 kcal/mol
  - SE 67 kcal/mol

- **ΔSE = 40 kcal/mol**
  - SE 67 kcal/mol
  - SE 27 kcal/mol

**Cascade cyclobutane expansion**

- Ni(cod)$_2$ (10 mol%) + L (12 mol%) → hexane, rt

- β-alkyl elimination

- Rhodium stabilized anti-Bredt olefin

- (R)-DTBM-segphos

- Ar = 3,5-ditBu-4-OMe-C$_6$H$_2$

- 16 examples: 30-83% 80-98% ee

**Angew. Chem. Int. Ed. 2020, 13180**

**Angew. Chem. Int. Ed. 2012, 2485**

**Science 2016, 241**

**JACS 2020, 13180**
Strain driven reactivity of carbocycles

**Radical Precursors**

- R-CO$_2$(IMes)$_{0.5}$
- R-Br
- F$_3$C-I

**Ir(III)**

- Ir(ppy)$_3$ (2 mol%)
- Cu(acac)$_2$ (60 mol%)
- Nu-H

**Cu(I)**

- Cu(I)X

**Nu-Cu(I)**

- Me$_2$CN

**Nu-Cu(II)X**

- Me$_2$CN
- X

**XCu(III)**

- Me$_2$CN

**33-81%**

- 51 examples

**Electrophile**

- X

**[1,2] Metallate Rearrangement**

- 9 examples

- 40-95%

- Ar = o-tol

**JACS 2020, 16766**

**Nat. Chem. 2019, 117**

**JACS 2019, 9511**

**Angew. Chem. Int. Ed. 2020, 3917**
Strain driven reactivity of carbocycles

Carl Mansson

Burns Group Meeting

\[ \text{[1.1.1]propellanes as masked methylene cyclobutane carbenes} \]

JACS 2019, 20325

Extended Grob fragmentation - geometric constraints “stretched considerably”

Tetrahedron Lett. 1982, 7

\[ \text{water soluble \(\beta\)-amino acid polymer from dewar pyridone} \]

ACS Macro Lett. 2020, 731
Strain driven reactivity of carbocycles

Strain driven cyclobutane cope rearrangement

-UV light isomerization to strained olefins
-Cycloheptenones and cyclooctenones react with nitrogen heterocycles
-Tolerates broad solvent scope

Strained medium rings

-First enantioselective trapping of 1,2 cyclohexadiene

-Brown and Wood collaborative synthesis after meeting at the National Organic Symposium
-Quadricyclane (94 kcal/mol SE) to norbornadiene (29 kcal/mol SE) investigated for energy storage
Strain driven reactivity of carbocycles

- Strain provides a strong thermodynamic driving force for reactions
- Many strained σ-bonds have π-like reactivity
- Strain release can promote irreversibility of a reaction
- Strained motifs can often act as masked functional groups (vinyl carbenes, 1,3 dipoles etc.)
- Strain release can be an efficient method for ring expansion
- The cleaving of strained motifs can effectively promote domino reactivity
- Strain release can be an artistic way to quickly access complex scaffolds