A spirocycle is a bicyclic organic compound with rings connected through just one atom. The rings can be different in nature or identical. The connecting atom is also called the spiroatome. For this lecture, we will only discuss spirocarbons, which are by definition quaternary.

**What we WILL be discussing:**
- Methods to make all-carbon spirocycles
- Natural products containing all-carbon spirocycles
- Natural products containing complex quaternary centers constructed via all-carbon spirocycles
- Only key transformations will be covered

**What we WILL NOT be discussing:**
- spiroketals, spiroethers, spiroamines, spiroaminals, spirohemiaminals, and MOST all-carbon quaternary centers containing spiro-cyclopropanes

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**Part 1 - Methods**

**Alkylations**


$$
\text{NaOMe, THF, rt to 50 °C}
$$

**Part 2 - Syntheses**

**Indole Alkaloids**

**Other Alkaloids**

**Non-Nitrogen [5.5]Spirocycles**

**Non-Nitrogen [5.4]Spirocycles**

**Non-Nitrogen[4.4]Spirocycles**

**Miscellaneous**

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**Group Meetings that relate to this topic:**
- Burns "Vetinanes" 2004
- Guerrero "Quadrane" 2004
- Guerrero "Prenylated Indole Alkaloids" 2004
- Khoroski "Aphidicolin" 2005
- Richter "Indolizidine Alkaloids" 2006
- Krawczuk "Discorhabdin Alkaloids" 2006
- Seiple "Ingenol" 2007

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**Excellent Review:** Tetrahedron(1999) v. 55, pp 9007-9071
Spirocycles Containing All-Carbon Quaternary Centers

**Alkylation Continued**


\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Ph} \quad \text{N} \equiv \text{H} \\
\text{MgBr}, \text{ACN}, 70^\circ \text{C} \rightarrow 60-70\%
\]

**Suresh - Synthesis (2008)** v. 7, 1065-1068

\[
\begin{align*}
\text{Ph} \quad \text{N} \quad \text{Me} \\
\text{Ph} \quad \text{N} \quad \text{Me}
\end{align*}
\]

**Gravel - Org. Lett. (2010)** v. 12, 5772-5775

"Domino Stetter-Aldol-Aldol reaction"

\[
\begin{align*}
\text{H} \\
\text{Me}
\end{align*}
\]

**Tanner - Tetrahedron (1989)** v 45, 4309-4316

\[
\begin{align*}
\text{Ts} \quad \text{HNN} \\
\text{Ts} \quad \text{HNN}
\end{align*}
\]

\[
\begin{align*}
\text{Ts} \quad \text{HNN} \\
\text{Ts} \quad \text{HNN}
\end{align*}
\]


\[
\begin{align*}
\text{Ts} \quad \text{HNN} \\
\text{Ts} \quad \text{HNN}
\end{align*}
\]

**Sum it up! Common Alkylation Strategies:**

1. double alkylation of bis-halide or other bis-electrophile α- to ketone, malonate, etc.
2. intramolecular cyclizations onto epoxides, halides, or other electrophiles
3. intramolecular Michael or Aldol reactions to form quaternary centers
4. intramolecular Sakurai allylations to form quaternary centers
5. use of chiral amines to form chiral enamines for diastereoselective Aldol and Michael reactions
6. I didn’t cover oxidative dearom/intramolecular Prins-type closure. This is included later!
**Spirocycles Containing All-Carbon Quaternary Centers**

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**Transition Metal-Based Methods**

Moreto- JACS (1992) v. 114, 10449-10461

Mori- JACS (1997) v. 119, 7615-7616


Buchwald- JACS (2011) v. 133, 9282-9285

Rainey- JACS (2012) v. 134, 3615-3618


Overman- JACS (1998) v. 120, 6477-6487

Busacca developed new phosphine ligands to improve ee for this reaction. See: Org. Lett. (2003) v.5, 595-598

Mikami- JACS (2003) v. 125, 4704-4705

Toste- JACS (2007) v. 129, 2764-2765

* Preliminary assymetric results were obtained with chiral phosphine ligands providing up to 74% yield, 81% ee on the substrate shown.

* Authors propose a PdIII catalytic cycle

**Note:** The first assymetric Heck reactions were described in 1989 by Shibasaki and Overman. We will see many more examples demonstrating the power of the assymetric Heck in Part 2.
Spirocycles Containing All-Carbon Quaternary Centers

Rearrangement Methods


\[ \text{OCONH} + BF_3\cdot OEt_2 \rightarrow \text{OCONH} \] (95%)

Burnell- JOC (1998) v. 63, 5708-5710 Acyloin Condensation/Ring Expansion

\[ \text{TMSO} \rightarrow \text{TMSO} \] (85%)


\[ \text{ZnBr}_2 (4 \text{ mol}%) \rightarrow \text{OH} \] (91%)

For enantioselective version of semipinacol shift onto enone instead of epoxide with chiral iminium catalysis see: Tu- JACS (2009) v. 131, 14626-14627


\[ \text{hv}, \text{dioxiane} \rightarrow \text{AcOH, Ac}_2\text{O, H}_2\text{SO}_4 \] (66%)

Trost- JACS (1996) v. 118, 12541-12554 Vinylicyclobutane Rearrangement

\[ \text{TMSOTf (1 eq.) pyridine (0.7 eq.) DCM} \rightarrow \text{OMe} \] (64%)

Vinylicyclopropane Rearrangement

\[ \text{OMe} \rightarrow \text{OMe} \] (64%)

\[ \text{Me}^{\ddagger} \rightarrow \text{OMe} \] (64%)

- Free OH can be used for the vinylcyclobutane rearrangements

Hwu- JOC (1992) v. 57, 922-928 Silicon-Facilitated Ring Contraction

\[ \text{FeBr}_3, \text{DCM,} -60^\circ \text{C} \rightarrow \text{Me} \] (54%)

\[ \beta\text{-silicon effect stabilizes positive charge build up during ring contraction rearrangement} \]


\[ \text{Rh}_2(\text{OAc})_4, \text{PhH, reflux} \rightarrow \text{EtO}_2\text{C} \] (72%)


\[ \text{TMSO} \rightarrow \text{FeCl}_3, \text{DCM,} -60^\circ \text{C} \] (67%)

\[ \text{Nazarov/ Wagner Meerwein Shifts} \]

\[ \text{[Cu(II)(box)](SbF}_3)_2 \rightarrow \text{Me}_2\text{Ar} \] (79%)

\[ \text{Ar=2,4,6-triMeO-Ph} \]

\[ \text{Conversion of Bridged Systems} \]


\[ \text{OMs} \rightarrow \text{tBuOK} \] (60%)

\[ \text{Grob Fragmentation} \]
Spirocycles Containing All-Carbon Quaternary Centers

Conversion of Bridged Systems-Continued


\[
\text{O} + \text{H} \quad \text{BF}_3 \cdot \text{OEt}_2 \quad \text{DCM} \quad \text{Me} \quad \text{Me} \\
\text{Me} \quad \text{Me} \quad \text{H} \quad \text{OH} \quad \text{Me} \quad \text{Me}
\]

80% Grob on Bicycle


\[
\text{O} + \text{OH} \quad \text{Me} \quad \text{Me} \\
\text{Me}
\]

hydroquinone, nBu₅N, 190 °C 78% Husson- ACIE (1998) v. 37 104-105 Reduction of Hemiaminal

\[
\text{CHO} + \text{NaSO₄} + \text{PhH} \quad \text{ZnBr₂} \quad \text{Ph} \quad \text{Ph} \\
\text{Ph} \quad \text{Ph} \quad \text{NH₃} \quad \text{CHO}
\]

51% 82% Ring Closure of Geminaly Disubstituted Cyclic Systems

Your functional group handle can be many things--anything that you can form a quaternary center from. Some popular choices in the literature are:

1: Start with a Ring that has a handle!

2: Don’t be a Whimp-Make that Quat. Center! If you have set yourself up with proper functionality on your ring, this should be a piece of cake. You have many reaction to choose from--here are the most popular:

- **Alkylation** with an Electrophile: deprotonate at the future spirocarbon (or go through an enamine) usually works (unless you are dealing with maoecrystal V)
- **Allylation:** asymmetric or not, there are methodologies devoted to doing just this. It is sort of under the category of alkylation, but so much work has been done in this area, it get’s its own line.
- **Addition** of a Nucleophile: if you are adding to a Michael acceptor you are all set, if you are adding to a ketone you still have work to do
- **Claisen Rearrangement:** works in tough situations to make sterically hindered quaternary centers

3. Follow through and Close the Second Ring!

- **Dieckmann Condensation**
- **Acyloin Condensation**
- **Wittig olefination, etc.**
  - **RCM**
  - **Aldol Condensation**
  - **Lactonization**

All you have to do is make one last bond--it doesn’t even necessarily have to be a C-C bond. Did I mention that everything is intramolecular? As they say, "it’s like falling off a log." Common reactions are listed along with the following "bold" disconnection:

**Cycloaddition Methods**

Norman- JOC (1975) v. 40, 1602-1606 Diels-Alder on Exocyclic Olefins

\[
\begin{align*}
\text{Me} \quad \text{Me} \\
\text{SnCl₄} \cdot 5\text{H₂O} \quad \text{rt} \quad \text{Me} \quad \text{Me} \\
\end{align*}
\]


issue with this approach: always have to cleave the cyclobutane to get to the spirocycle. The same is true for intramolecular cyclopropanations. For examples see:

**Spirocycles Containing All-Carbon Quaternary Centers**

**Cycloaddition Methods Continued**


Greene- JACS (1996) v. 118, 9992-9992

**Ene Reaction**


**Conia Ene Reaction**

**Radical Cyclization Methods**


Greene- JACS (1996) v. 118, 9992-9992

**Ene Reaction**

Back- JOC (1996) v. 61, 3806-3814

**Motherwell- Tet. (1992) 8031-8052**

*substrates with C(CO₂Bn)₂ instead of NTs require only 3 eq

Cossy- JOC (1997) v. 62, 7106-7113 Ene Reaction

*90% 99% ee"
**Spirocycles Containing All-Carbon Quaternary Centers**

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**Part 2-Total Synthesis**

Quaternary centers derived from spirocycles and all-carbon spirocycles are highlighted in red.

**Indole Alkaloids**

**Strychnine:** Woodward- JACS (1954) v. 76, 4749 (total synthesis)

1. Pd2dba3, Et3N, DMA
2. 1 N HCl
3. Boc2O, Et3N, DMAP
4. SeO2, AcOH, BuOH
5. Boc2O, Et3N, DMAP

**Strychnofoline:** Carreira- JACS (2002) v. 124, 14826 (total synthesis)

**Horsetoline:**

Trost- Org. Lett. (2006) v. 8, 2707-2730

**White- JOC (2010) v. 75, 3569-3577**

**Perophoramidine:** Qin- JACS (2010) v. 132, 14051-14054

**Funk- JACS (2004) v. 126, 5068-5069**
**Indole Alkaloids Continued**


\[
\text{Pd}_{2}(\text{dba})_{3} (10 \text{ mol\%}) \quad \text{Trost Ligand}
\]

Gong- Org. Lett. (2011) v. 13, 2418-2421

H₂N
CO₂Et
\[ \text{OHC} \quad \text{CO₂Et} \quad \text{Me} \quad \text{Me} \quad \text{MeO} \quad \text{NO}_2 \]

\[
\text{EtO}_2\text{C} \quad \text{Me} \quad \text{Me} \quad \text{MeO} \quad \text{NO}_2
\]

Marcfortine B: Trost- JACS (2007) v. 129, 3086-3087

CHIMONANTHRINE AND CALYCANTHINE:

Overman- JACS (1999) v. 121, 7702-7703

Gelsemin: Cliffnotes on the Spirooxindole Strategies:

1) Intramolecular Heck (Overman and Speckamp)
2) Radical Cyclization (Hart)
5) Divinylcyclopropene rearrangement (Fukuyama)

Note: Fukuyama recently used a similar transformation in the synthesis of Gelsemonimine:

JACS (2011) v. 133, 17634-17637

**Alkaloids (Other)**

Nakadomarin A: Nishida- JACS (2003) v. 125, 7484-7485

1) PhSO₂Cl, NaHCO₃
2) allyl-Bn, K₂CO₃
3) ethylene glycol, TsOH

77% - 3 steps
4) resolve

Williams- Org. Lett. (2004) v. 6, 4539-4541

35% single diast.

3) Photo Induced Radical Cyclization (Johnson)
4) Eschenmoser Claisen Rearrangement (Danishefsky)
Spirocycles Containing All-Carbon Quaternary Centers

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Emily Cherney

Alkaloids (Other) Continued

MeO -OBn
HN-OH
TBDPSO
Br
87%
4A MS
(Yb(OTf)₃ (15 mol%)
MeO -OBn
C₂Me
C₂Me
PMB
N
CO₂Me
CO₂Me
DiXon- JACS (2009) v. 131, 16632-16633

Chiral Urea (15 mol%)
cat. controlled
condensation/nitro-Mannich/68% lactamization
MeO₂C
MeO₂C
H₂N
48%
85%

Gymnodimine:
Romo- ACIE (2009) v. 48, 7402-7405

TsN
CuCl₂ (20 mol%)
85%
dr > 19:1
Chiral Box Ligand (22 mol%)
95% ee
AgSbF₆ (40 mol%)

TIPSO
HO
KHMD, THF, 0°C; KHMD, 0°C to rt
72%

Kishi- JACS (1998) v. 120, 7647-7648
NOTE: Kishi made ent-pinnatxin, but I didn’t have time to draw the other enantiomer. Sorry.

Inoue- ACIE (2004) v. 43, 6505-6510

TesO
TIPSO
KHMD, THF, 0°C; KHMD, 0°C to rt
72%

Zakarian- JACS (2008) v. 120, 3774-3776

TIPSO
Me
Me
Me
Me
84%

Ireland-
Clausen

MOMO
Me
Me
Me
Me
94%
**Spirocycles Containing All-Carbon Quaternary Centers**

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**Spirocycles Containing [5.5]Spirocycles**

**Non-Nitrogen Containing [5.5]Spirocycles**

**Cyathiwiginin AC**

**Siculine**

**Stephaninone**

**Pinnatoxins**: Hashimoto- ACIE (2008) v. 47, 7091-7094

**Alkaloids (Other) Continued**

**Futoenone**: Angle- JOC (1993) v. 58, 5360-5369

**Elatol**: Stoltz- JACS (2008) v.130, 810-811

**Salvileucalin B**: Chen- Org. Lett. (2011) v. 13, 4410-4413 (Studies Toward)

**To see many other examples: Discorhabdin GM**
**Spirocycles Containing All-Carbon Quaternary Centers**

*Baran Group Meeting*  
*Emily Cherney*

### Non-Nitrogen Containing [5.5]Spirocycles Continued

**Maocystal Z:** Reisman- JACS (2011) v. 133, 14964-14967

- **Acutimine:** Castle- JACS (2009) v. 131, 6674-6675

- **Vannusals A and B:** Nicolaou- JACS (2010) v. 132, 7153-7176

### Non-Nitrogen Containing [5.4]Spirocycles

**Platensimycin:** Nicolaou- ACIE (2006) v. 45, 7096-7090/ JACS (2009) 16905

**Fredericamycin:** Kelly- JACS (1988) v. 110, 6471

---

There are over a dozen total synthesis and studies toward papers on this molecule. To the best of my knowledge, the Nicolaou approach is the only one that goes through a spirocycle. Most go through a fused 6.6- or 5.5-system en route to the cage structure.

---

**Non-Nitrogen Containing [4.4]Spirocycles**

**Dimethyl Gloiosiphone A:** Takahashi- JOC (2007) v. 72, 3667-3671 (Formal)
**Spirocycles Containing All-Carbon Quaternary Centers**

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**Non-Nitrogen Containing [4.4]Spirocycles Continued**

**Fredericamycin**: Clive - JACS (1994) v. 116, 11275-11286


**Fredericamycin**: Bach - JACS (1994) v. 116, 9921-9926

**Fredericamycin**: Boger - JACS (1995) v. 117, 11839-11849

**Fredericamycin**: Kita - JACS (2001) v. 123, 3214-3222

**Miscellaneous**

**SNF4435 C and D**: Parker - JACS (2004) v. 126, 15968-15969

**SNF4435 C and D**: Parker - JACS (2004) v. 126, 15968-15969

**Lideraspirone A and Bi-linderone**: Wang - Org. Lett. (2011) v. 13, 2192-2195

**Lideraspirone A and Bi-linderone**: Wang - Org. Lett. (2011) v. 13, 2192-2195

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**Non-Nitrogen Containing [4.4]Spirocycles Continued**

**Fredericamycin**: Clive - JACS (1994) v. 116, 11275-11286

**Fredericamycin**: Clive - JACS (1994) v. 116, 11275-11286

**Fredericamycin**: Bach - JACS (1994) v. 116, 9921-9926

**Fredericamycin**: Bach - JACS (1994) v. 116, 9921-9926

**Fredericamycin**: Boger - JACS (1995) v. 117, 11839-11849

**Fredericamycin**: Boger - JACS (1995) v. 117, 11839-11849

**Fredericamycin**: Kita - JACS (2001) v. 123, 3214-3222

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**Miscellaneous**

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**Lideraspirone A and Bi-linderone**: Wang - Org. Lett. (2011) v. 13, 2192-2195