Baran Group Meeting

Breaking the Rules: "Anti-Baldwin" Cyclizations

Sarah Wengryniuk

Baldwins Rules of Ring Closure

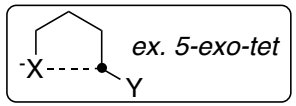
Sir Jack Baldwin
- 1938: Born in London
- 1964: Awarded Ph.D. from Imperial College under Professor Sir Derek Barton. Studied structure elucidation of byssochalmic acid using chemical methods.
- 1965: Assistant lecturer at Imperial College
- 1967: Moved to UPenn
- 1970: Moved to MIT
- 1972: Moved to King's College
- 1972: Back to MIT
- *1976:* ***Published "Baldwin's Rules" and two related articles***
- *1977:* ***Published Rules on Enolates***
- 1978: Moved to Oxford. Elected as Fellow of Royal Society and appointed as Waynflete Professor of Chemistry at Oxford.
- *1982:* ***Published Rules on Aldols***
- 1997: Awarded a Knighthood for his contributions to organic chemistry
- Other areas of Investigation:
  - Biomimetic syntheses of sponge alkaloids and fungal metabolites.
  - Development of synthetic methods
  - Chem. and bio studies on biosynthesis of b-lactam antibiotics
- More than 600 papers. See "Sir Jack Baldwin" GM (Georgiades, 2006)

Seminal Papers:
Tetrahedral Sys: Eschenmoser, A.; *Helv. Chim. Acta,* **1970***, 53*, 2059.
Radicals: Beckwith, A. L. J.; *JACS,* **1974***, 96,* 1613.
Burgi-Dunitz: Burgi, H.B., Dunitz, J.D.; *Tet.* **1974**, *30*, 1563.
Rules: Baldwin, J.; *J.C.S. Chem. Comm.,* **1976**, 734.
5-endo-trig: Baldwin, J.; *J.C.S. Chem. Comm.* **1976**, 736.
Vector Analysis: Baldwin, J.; *J.C.S. Chem. Comm.* **1976**, 738.
Enolates: Baldwin, J.; *J.C.S. Chem. Comm.,* **1977**, 233.
Radical Rules: Beckwith, A. L. J.; *J.C.S. Chem. Comm.*, **1980**, 482.
Aldols: Baldwin, J.; *TL*, **1982**, *38*, 2939.

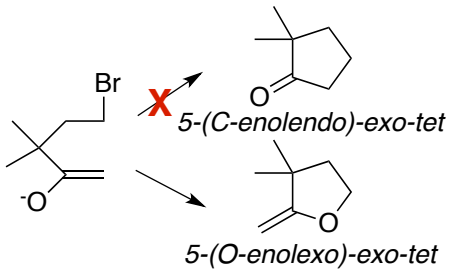
- According to CRC, over 90% of natural products contain a carbo- or hetereocycle
- Seminal paper in 1976: Cited 2,160 times. (plus an extra 685 for papers immediately following.)
- Most cited paper in history of RSC Chemical Communications.
- Baldwin published formal rules but compliation of many people's work
- Beckwith published rules specific to radical cyclizations

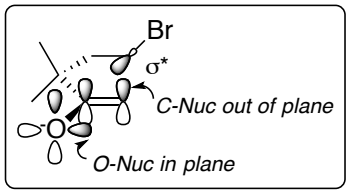
Terminology

#- refers to number of carbons in the forming ring (≥3)
Endo/Exo- refers to position of breaking bond relative to forming ring
Endo bond is inside the newly formed ring
Exo bond is outside of the newly formed ring
Tet/Trig/Dig- Hybridization at the ring closure point.
Tet- sp^3; **Trig**- sp^2; **Dig**- sp



For enolate reactions:
Same terms as above, plus designator for position of enolate.
Enol-endo: Enolate is inside of the newly forming ring.
Enol-exo: Enolate is outside of the newly forming ring.
C vs. O: Whether cyclization occurs via C or O centered nucleophile.

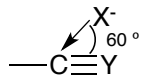




Based on ideal angle of trajectory for maximal orbital overlap

tet: 180 °
Walden Inversion

trig: 107 °
Burgi-Dunitz



dig: acute angle 60 °
Wegner and Baughman

"Caveats" to the Rules:
- *Atoms involved must be in the first row*
  - Larger atomic radii and longer bond lengths allow for more flexibility with second row elements and below

- *Do not apply to concerted electrocyclic processes.*
  - Rules imply inversions at the reacting centers and therefore do not apply to processes where inversion is not required.
  - "I thank Professor R.B. Woodward for pointing this out to me." -JEB

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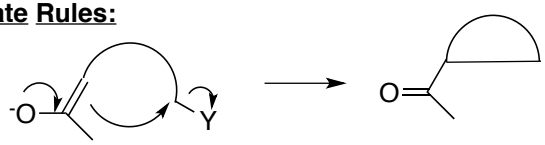
Baldwin's Original Rules: Apply to Nuc⁻, Rad•, Elec⁺

TET	3-exo-tet ***Favored***	4-exo-tet ***Favored***	5-exo-tet ***Favored***	6-exo-tet ***Favored***
	3-endo-tet ***????***	4-endo-tet ***????***	5-endo-tet ***Disfavored***	6-endo-tet ***Disfavored***
TRIG	3-exo-trig ***Favored***	4-exo-trig ***Favored***	5-exo-trig ***Favored***	6-exo-trig ***Favored***
	3-endo-trig ***Disfavored***	4-endo-trig ***Disfavored***	5-endo-trig ***Disfavored***	6-endo-trig ***Favored***
DIG	3-exo-dig ***Disfavored***	4-exo-dig ***Disfavored***	5-exo-dig ***Favored***	6-exo-dig ***Favored***
	3-endo-dig ***Favored***	4-endo-dig ***Favored***	5-endo-dig ***Favored***	6-endo-dig ***Favored***

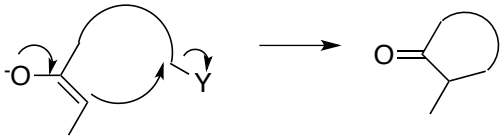
Baldwin's Enolate Rules:

ENOLEXO-EXO-TET



*All 3-7 membered ring closures are **favored**!!!*
Same applies to (enolexo)-exo-trig ALDOLS.

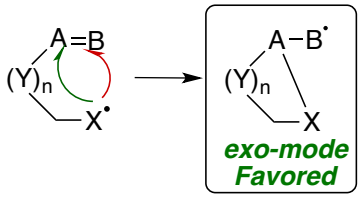
ENOLENDO-EXO-TET



*3-5 membered ring closures are **disfavored***
*6-7 membered ring closures are **favored***
Same rules apply to (enolendo)-exo-trig ALDOLS

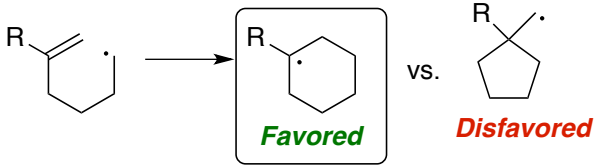
Beckwith's Radical Rules:

1. Intramolecular addition under kinetic control when n≤5, *cyclization occurs preferentially in the exo mode.*



Thermodynamic preference for secondary radical overridden by kinetic pref. based on required orbital alignment for cyclization.

2. Substituents disfavor cyclization at substituted position.



3. Homolytic cleavage is favored when bond concerned lies close to plane of adjacent semi-occupied, filled non-bonding, or π-orbital

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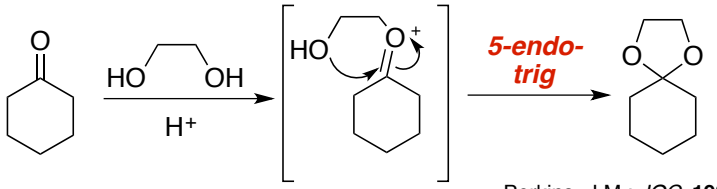
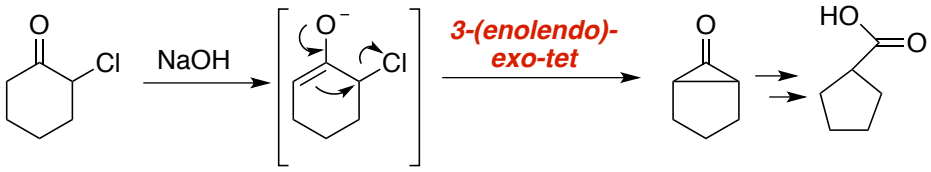
Common Transformations that Break the Rules:

Cyclic Acetal Formation: 5-endo-trig via oxonium



Perkins, J.M.; *JOC*, **1981**, *46*, 2196.

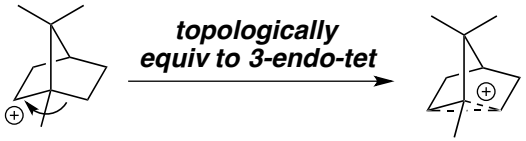
Favorskii Rearrangement: 3-enolendo?

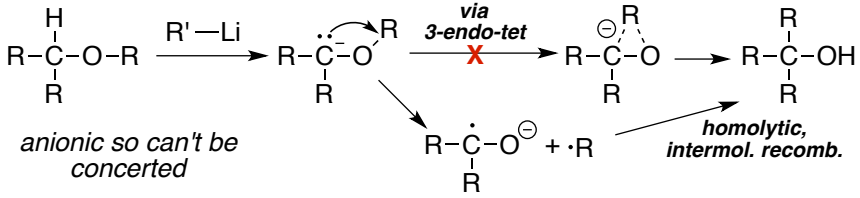


Common Transformations that Make you Question the Rules:

-Baldwin says his rules extend to "nucleophilic, electrophilic, and homolytic" processes but is this true?

Wagner Meerwein vs [1,2]-Wittig RAR



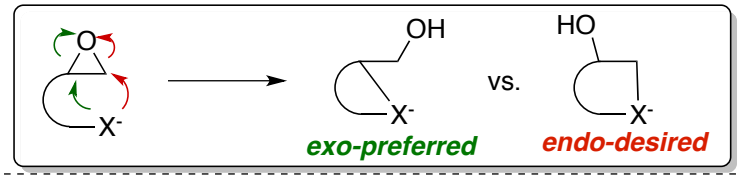


"Tet"-Cyclizations: Overriding exo- to get endo-

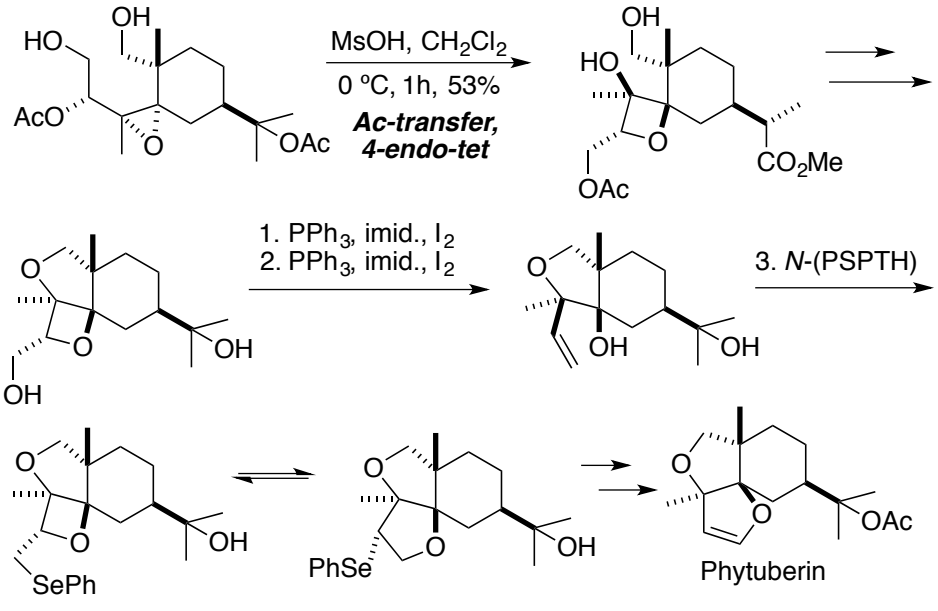
-Since all *exo-tets* are favored this section with discuss how to override that selectivity to get *endo*-selectivity.
-Examples of anionic openings (Cationic and Radical not common)
-This section could also be called: *"Regiochemical control in epoxide opening"*
-Seminal work by Nicolaou during brevotoxin synthesis

Baldwin says:

Nuc, Elec, Rad					
-trig	3	4	5	6	7
endo	n	n	n	y	--
exo	y	y	y	y	y



4-endo-tet: Synthesis of Phytotuberin



Suarez, E.; *JOC*, **2003**, *68*, 4422.

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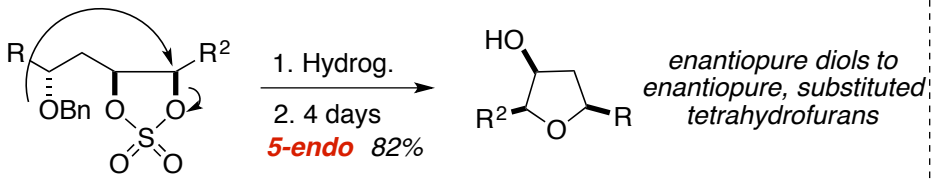
5,6,7-endo-tet over 4,5,6-exo-tet

General comments:
-Exo- mode is always preferred (even in 6-endo case)
-However, control of regiochemistry in these systems is very well understood.
-Few basic strategies are employed, section catagorized by approach:
- Cyclic sulfates (Sharpless)
- Substituent effects (started with Nicolaou vinyl oxiranes)
- Use of "-onium" ions (iodo-, bromo-, seleno-)
- Use of select activating agents (LA, antibodies)

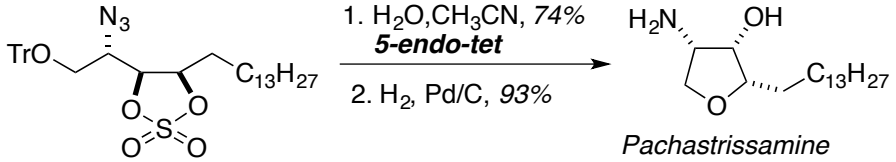
Cyclic Sulfates

Enantiopure Tetrahydrofurans



Sharpless, B.K.; *Acta Chim Scanda*, **1993**, *47,* 307.

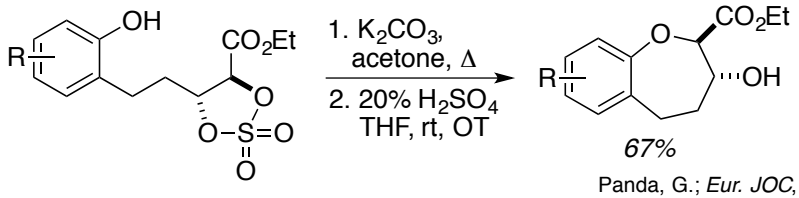
Pachastrissamine



Analogous reaction with epoxide gave only trace product under various cond.

Kim, S.; *OL*, **2007**, *9*, 429.

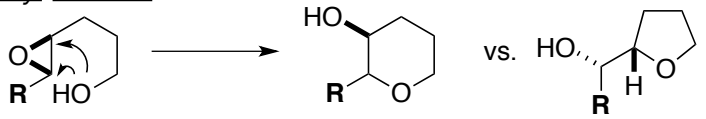
1-Benzoxepines



Panda, G.; *Eur. JOC*, **2009**, 204.

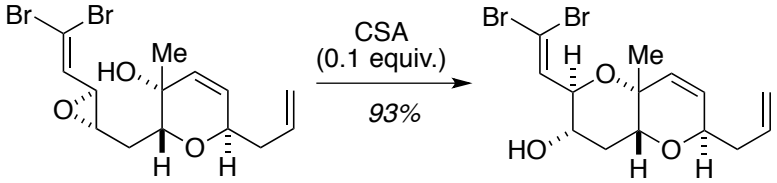
Nicolaou and Brevetoxin: Endo-control via Substituent Effects

Vinyl oxiranes



R	*6-endo*	*5-exo*
$CH_2CH_2CO_2Me$	0	100
E-CH=CHCO$_2$Me	60	40
$CH=CH_2$	100	0
$CH=CBr_2$	100	0

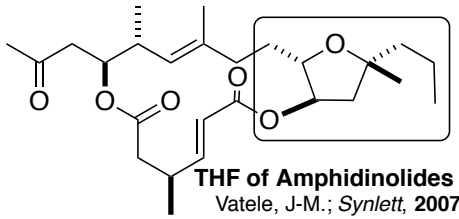
A,B,C Rings of Brevetoxin B



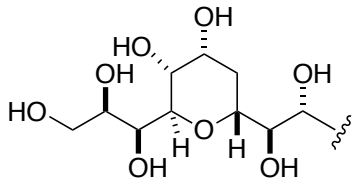
Nicolaou, K.C.; *JCS Chem. Commun.*, **1985**, 1359.
Nicolaou, K.C.; *JACS*, **1989**, 5330.

Similar strategy used in approaches to numerous natural products

5-endo over 4-exo

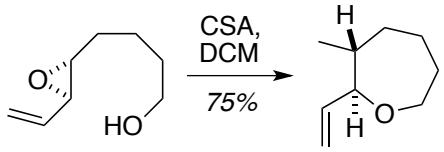


THF of Amphidinolides X and Y
Vatele, J-M.; *Synlett*, **2007**, *6*, 983



THP Unit of Amphidinol 3
Oishi, T.; *JOC*, **2009**, *74*, 8810.

7-endo over 6-exo



R	*6-endo*	*5-exo*
$CH_2CH_2CO_2Me$	0	100
E-CH=CHCO$_2$Me	22	78
$CH=CH_2$	82	18
Z-CH=CHCl	60	40
E-CH=CHCl	92	8

Nicolaou, K.C.; *JACS*, **1989**, *111*, 5335.

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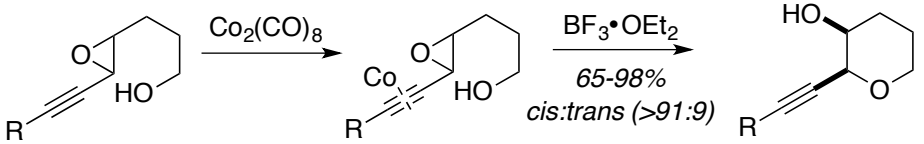
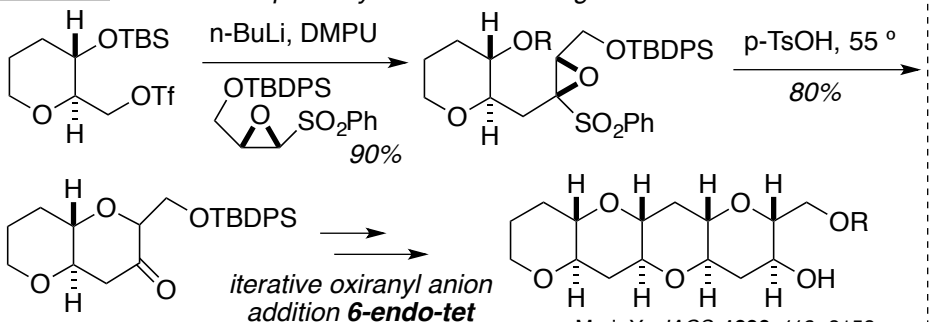
Propargyl Oxiranes

Cobalt Complexed Propargyl Epoxides: *6-endo-tet*



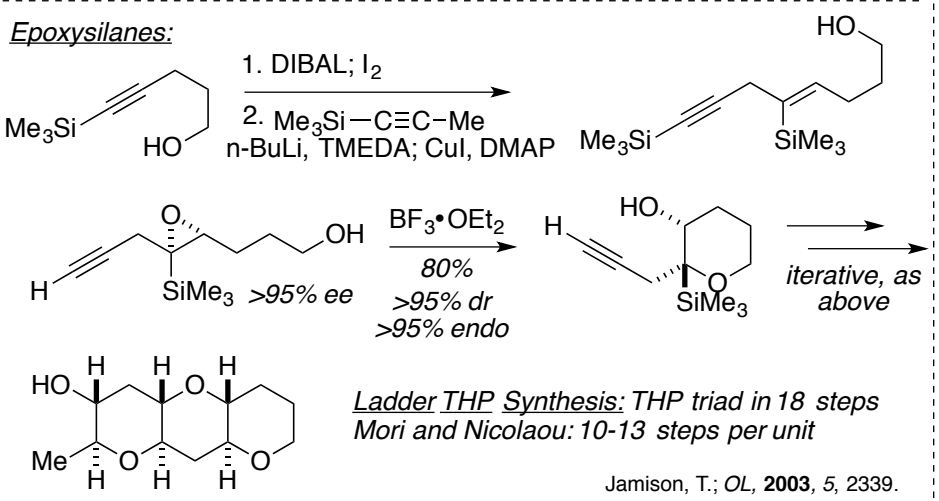
Hanaoka, M.; *TL*, **1994**, *35*, 2179.
w/o Co: Hanaoka, M.; *TL*, **1994**, *35*, 2183.

Sulfones: Disfavor exo-pathway via e⁻-withdrawing



Mori, Y.; *JACS*, **1996**, *118*, 8158.
Other ex: Mori, Y.; *Chem. Eur. J.*; **1997**, *3*, 849.
Mori, Y.; *TL*, **1995**, *40*, 8019.

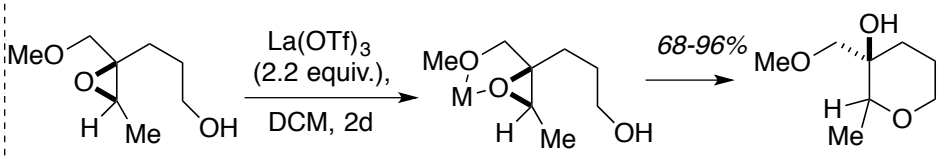
Epoxysilanes:



Ladder THP Synthesis: THP triad in 18 steps
Mori and Nicolaou: 10-13 steps per unit

Jamison, T.; *OL*, **2003**, *5*, 2339.
Mech on regio: Schumann; *TL*, **1995**, *36*, 8771.

Methoxy-Methyl Ethers: Use Lanthanide Metal

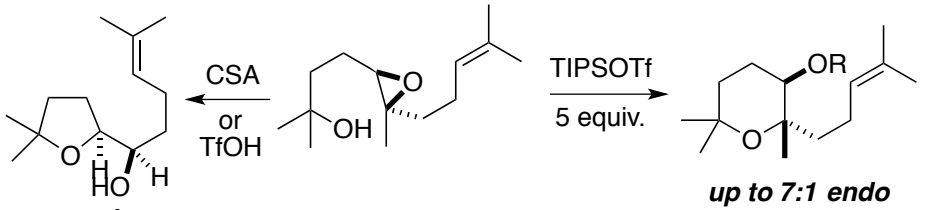


68-96% yield; 82:18 – 90:10 endo:exo
No metal: Exclusive exo-cyclization

Murai, A.; *TL*, **1995**, *36*, 8063.

Reagent Control: Selection of Activator

Exclusive reagent control: Approach to Oxasqualenoids



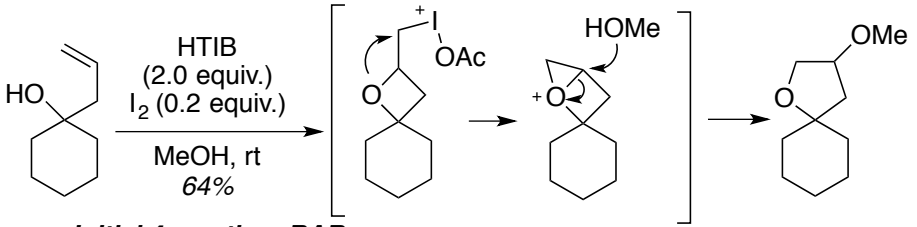
Morimoto, Y.; *ACIE*, **2006**, *45*, 810.

6-endo Cyclizations onto Activated Alkenes

Se: Noto R.; *Tet.*, **2001**, *57*, 1819.
S: Noto, R.; *J. Het. Chem.*, **2001**, 765.

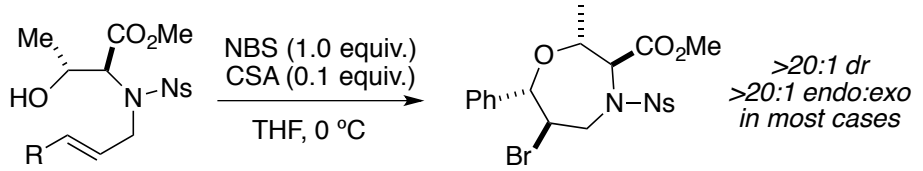
"-Onium Ions"

Iodonium Ions: 4-exo then RAR



Giannis, A.; *JOC*, **2011**, *76*, 1499.
Another ex of 5-endo with I_2: Elliott, M. C.; *OL*, **2007**, *9*, 3635.

Bromonium Ion: 7-endo by desymm. of bromonium give oxazepanes



Moitessier, N.; *JOC*, **2013**, *78*, 872.

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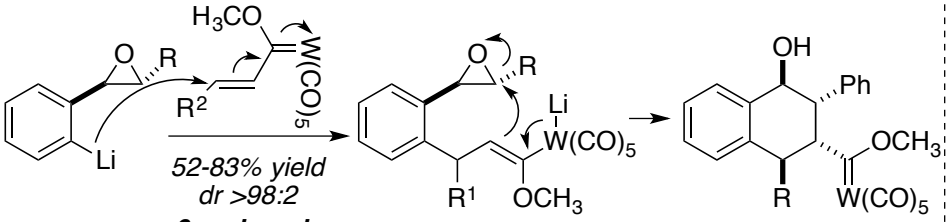
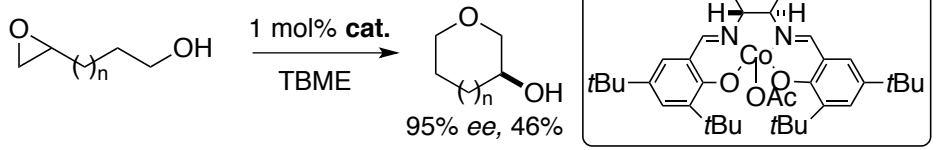
Random Other Methods

Fischer Carbene: Example of a carbon nucleophile: Tetrahydronapthols



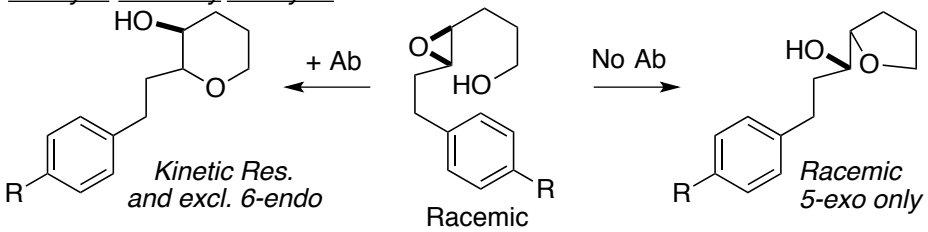
Gasparrini, F.; *OL*, **2005**, *7*, 4895.

[Co^{III}(salen)] Complex: Regio- and Kinetic Res.

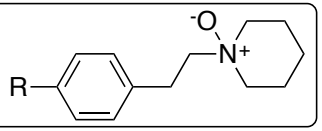


Jacobsen, E. N.; *ACIE*, **1999**, *38*, 2012.

Catalytic Antibody Catalysis



Antibodies produced by immunization of mice with compound to mimic *t.s.*:



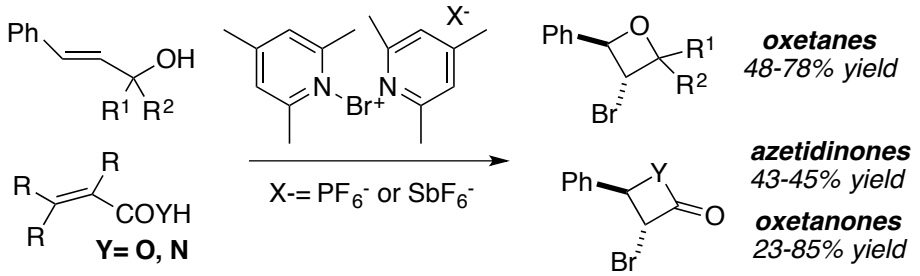
Lerner, R.; *Science*, **1993**, *259*, 490.

"Trig" Cyclizations

-Many examples of overcoming Baldwin's rules here
-Primarily rely on heteroatoms (O, N, S...)
-Nucleophilic, electrophilic and radical methods
-Primary focus will be on **5-endo-trig**
  -Will be broken down by method of activation

3-endo-trig: As you might imagine, no examples in the literature

4-endo-trig: Examples using heteroatom nucleophiles



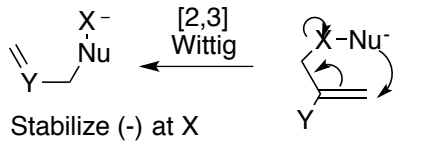
Rousseau, G.; *TL*, **2001**, *42*, 2477.
Rousseau, G.l *JOC*, **1999**, *64*, 81.

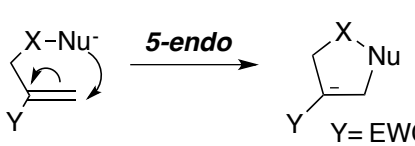
5-endo-trig

Alabugin suggests aromatic character to 5-endo t.s.: lone pair, π-bond, σ-bond

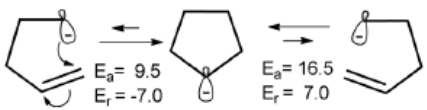
"Anionic 5-endo closures are "aborted" sigmatropic shifts"

Think of 5-endo closures are competition between pericyclic and ring closure:





tions: "Aborted" sigmatropic shift



EWGs at the Y-position promote 5-endo cyclizations by further lowering energy of "intermediate".

Alabugin, I.; *JACS*, **2012**, *134*, 10584.

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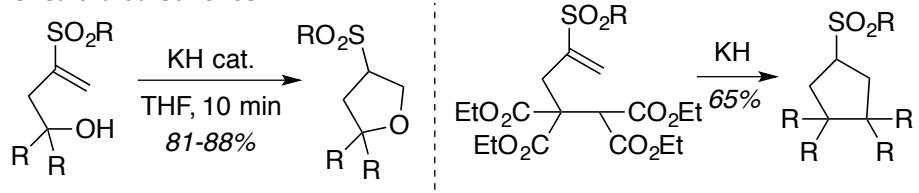
Breaking the Rules: "Anti-Baldwin" Cyclizations

Sarah Wengryniuk

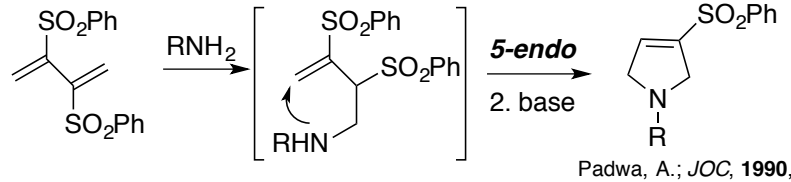
Nucleophilic Cyclizations: EWGs at 4-position

Unsaturated Sulfones:



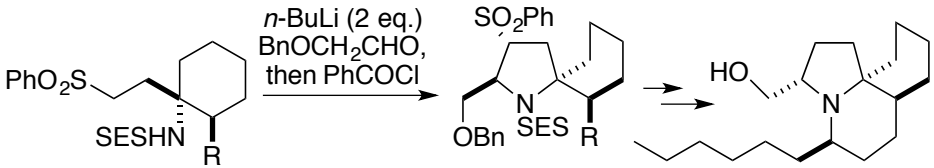
Knochel, P.; *TL*, **1985**, *26*, 4455.

Tandem Intermol-Michael then 5-endo-trig to pyrrolidines



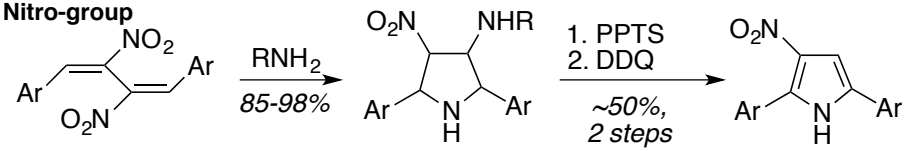
Padwa, A.; *JOC*, **1990**, *55*, 4801.

Total Synthesis of (±)-Lepadiformine



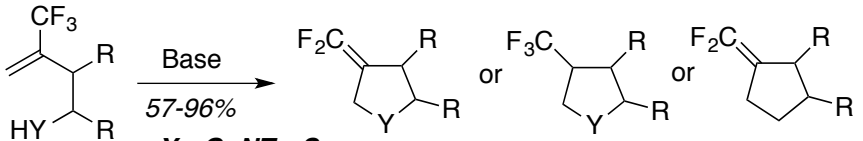
Craig, D.; *ACIE*, **2007**, *46*, 2631.

Nitro-group



Tavani, C.; *Eur. JOC,* **2000**, 903.

-CF_3 group: Fluorinated hetereocycles

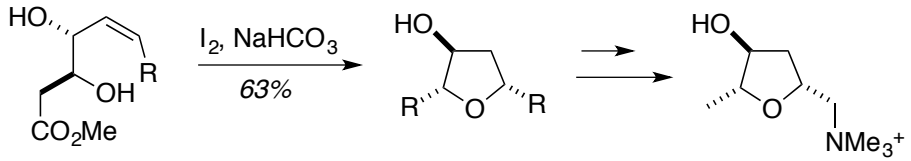


Ichikawa, J.; *Chem. Asian J.*, **2008**, *3*, 393.

Activating Alkene: "-Onium Cyclizations

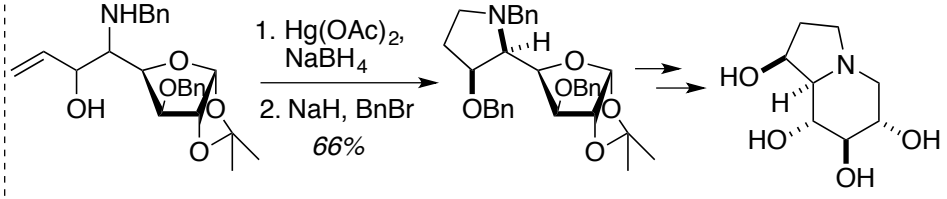
-Put them here because these the authors called *5-endo-trig,* but similar approach to -onium ions in 5-endo-tet section

More iodoniums: Total synthesis of (–)-Muscarine



Knight, D.; *Eur. JOC;* **2004**, 1973.

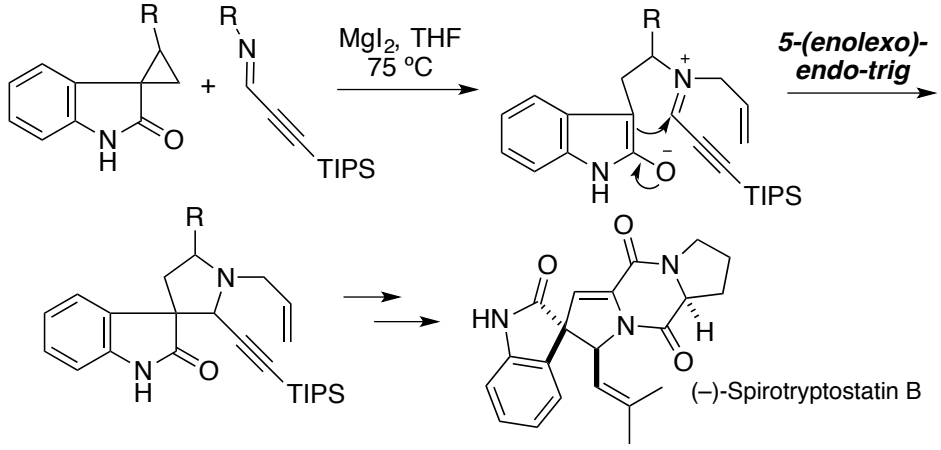
Mercuronium-mediated *5-endo:* (+)-Castanospermine and analogues



Dhavale, D.; *JOC*, **2006**, *71*, 4667.

Iminium and Oxonium Cyclizations:

Ring-expansion/Iminium 5-endo to (–)-Spirotryptostatin B



Carreira, E.; *JACS,* **2005**, *127*, 11505.

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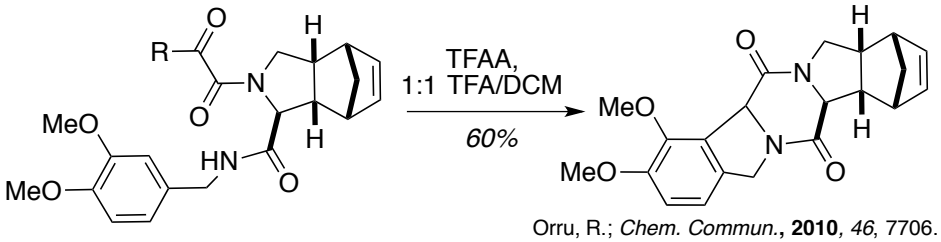
Breaking the Rules: "Anti-Baldwin" Cyclizations

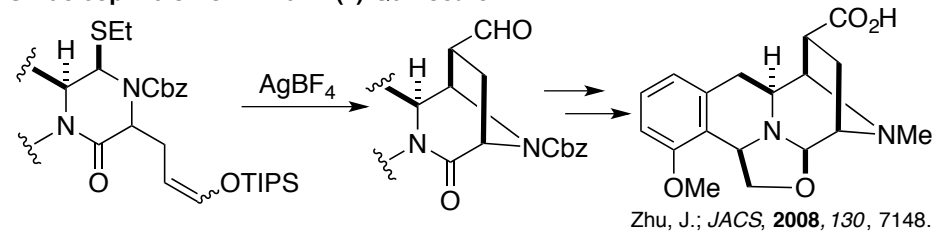
Sarah Wengryniuk

Pictet-Spengler to 2,5-Diketopiperazines: *"MUPS" Sequence*



Orru, R.; *Chem. Commun.*, **2010**, *46*, 7706.

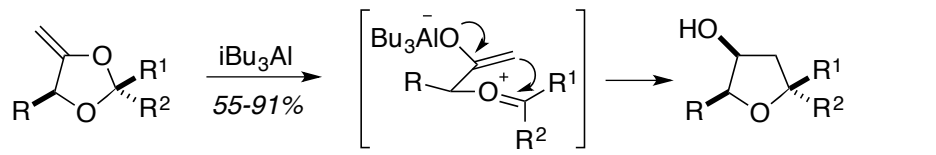
O-nucleophile onto Iminium: (–)-Quinocarcin



Zhu, J.; *JACS*, **2008**, *130*, 7148.

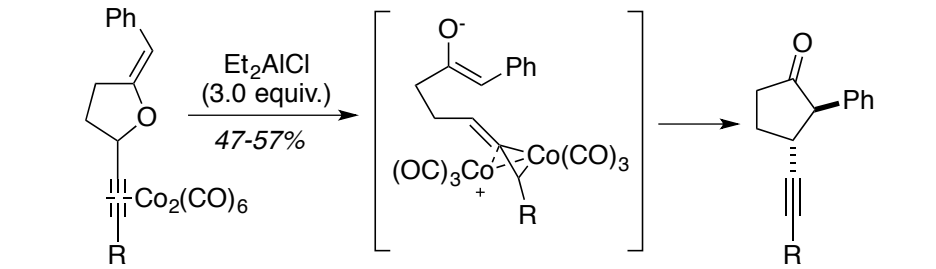
5-(enolendo)-exo/endo-trig

Onto an oxonium: THFs from 1,3-Dioxolan-4-ones



Petasis, N.; *JACS*, **1995**, *117*, 6394.

5-(enolendo)-exo-trig in Co-mediated O-->C Rearrangement

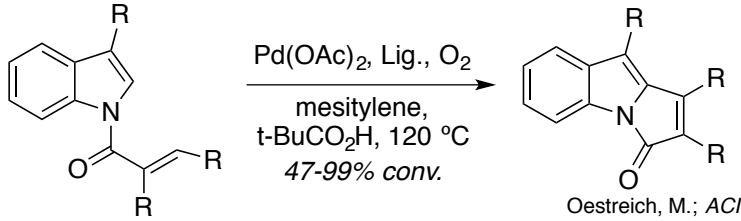


Harrity, J.; *JOC*, **2005**, *70*, 10046.

5-endo Heck Reactions

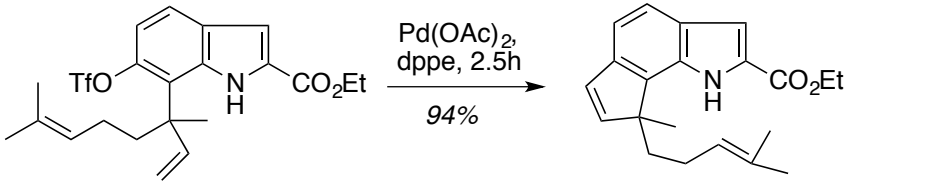
IHR typically proceed via exo-pathway
- For 5-endo requires harsh reaction conditions and/or specially designed substrates and yields are typically low.

Diastereoselective C-2 Alkenylation of Indoles via 5-endo "Fujiwara-Moritani"



Oestreich, M.; *ACIE*, **2012**, *51*, 1265.

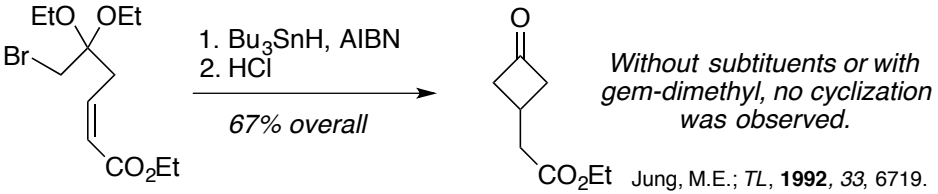
Unexpected result in synthesis of Teleocidin B



Tanner, D.; *Synlett*, **2006**, *18*, 3140.

Radicals: Focus on 4-exo vs 5-endo
- Despite being a favored process, not many examples of 4-exo in literature
- Examples of 5-endo radicals are scare, often involve heteroatoms.

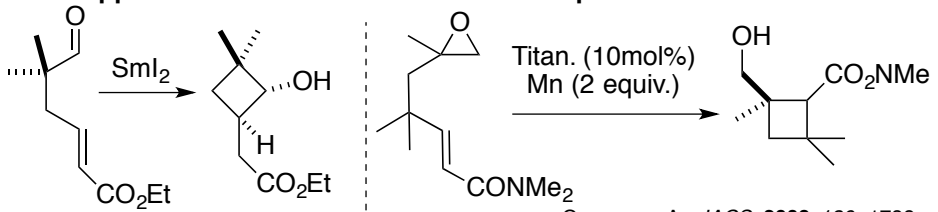
4-exo-trig-rad: Employing the *gem*-dialkoxy effect



Without subtituents or with gem-dimethyl, no cyclization was observed.

Jung, M.E.; *TL*, **1992**, *33*, 6719.

Other approaches: Substituent effects still important



Proctor, D. *Synlett*, **2012**, *23*, 6.

Ganauser, A.; *JACS*, **2008**, *130*, 1788.

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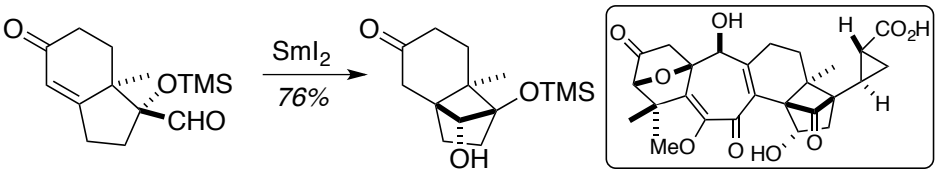
Breaking the Rules: "Anti-Baldwin" Cyclizations

Sarah Wengryniuk

4-exo-trig-rad: Synthesis of strained ring of Solanoeclepin

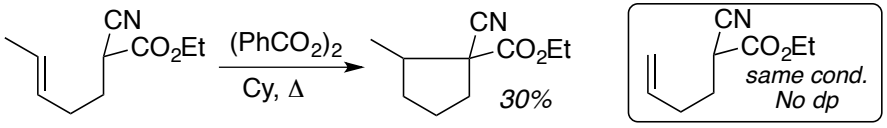


Nishikawa, T.; *Chem. Lett.*, **2012**, *41*, 287.

5-endo-trig-rad:

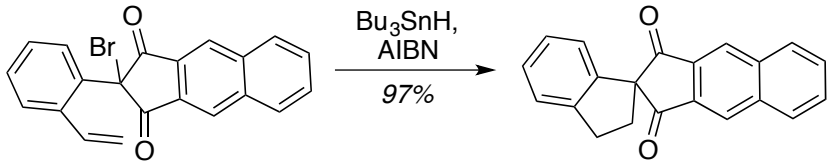
Review: Ishibashi, H.; *Synthesis*, **2002**, *6,* 695. Lots of things that don't work.
5-endo-trig rad, disfavored?: Gimisis, T.; *JACS*, **2002**, *124*, 10765.

First "successful" example: Similar substrates don't work



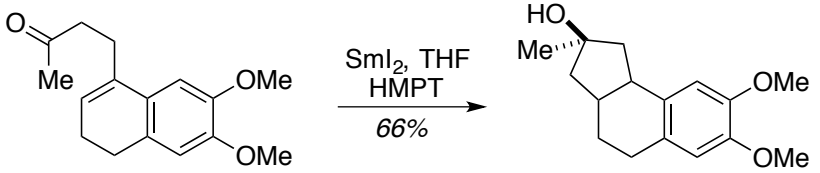
Julia, M.; *Bull. Soc. Chim. Fr.,* **1965,** 1550.

Aided by radical stabilizing group: leads to high yields



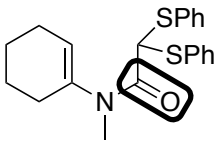
Reddy, K.M.; *TL*, **1993**, *34*, 2665.

Aided by radical stabilizing group: Reverse regioselectivity of SmI_2



Bats, W.J.; *ACIE*, **1995**, *34*, 2383.

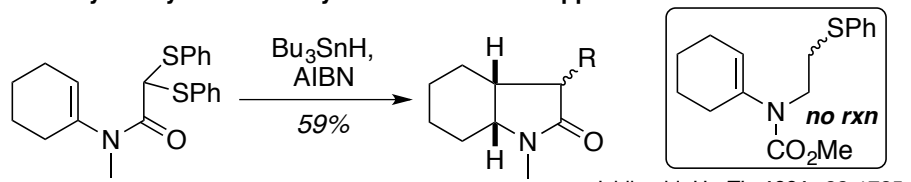
Carbamoylmethyl Radicals: By far most common approach



General Notes

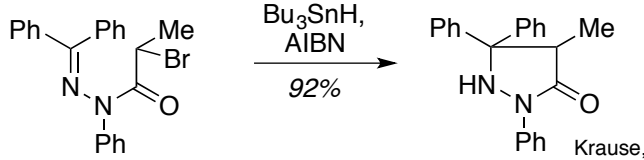
-Must have carbonyl incorporated into 5-mem ring
-Initiators: Bu_3SnH/AIBN; Ni/AcOH, CuCl/bipyridine
-X: Cl, Br, I, SPh, Se
-Alkene: Isolated, benzylic, α,β-unsaturated carbonyl

Carbamoylmethyl Radicals: By far most common approach



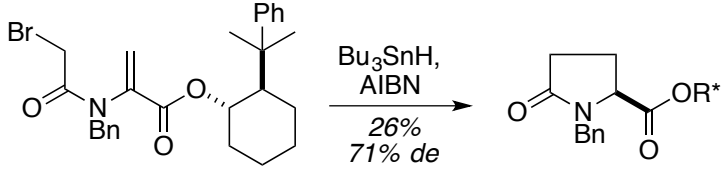
Ishibashi, H.; *TL*, **1991**, *32*, 1725.

Carbamoylmethyl Radicals: Hydrazone Derivative



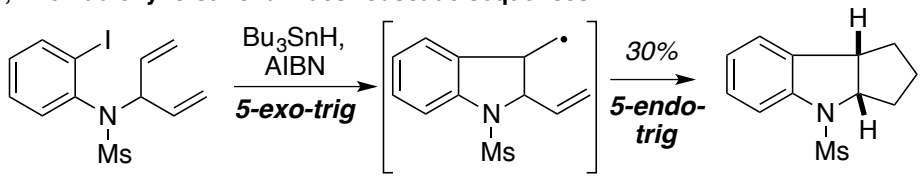
Krause, J.; *TL,* **1993**, *34,* 797.

Carbamoylmethyl Radicals: Attempt at stereoselectivity



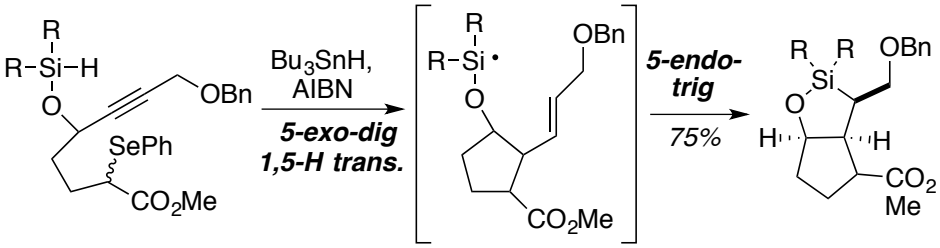
Parsons, A.F.; *TL*, **1997**, *38,* 491.

1,4-Pentadienyl-3-sulfonamides: Cascade sequences



Murphy, J.; *OL*, **2001**, *3,* 3405.

Silicon Radical: Prostaglandin Synthesis



Clive, D.; *JOC*, **1999**, *64*, 2776.

Baran Group Meeting

Breaking the Rules: "Anti-Baldwin" Cyclizations

Sarah Wengryniuk

Alkyne Cyclizations: "Dig"

-Recent theoretical and mechanistic work in field by Igor Alabugin from FSU
-Review: Alabugin, I.; *Chem. Rev.* **2011**, *111,* 6513
-Alkyne cyclizations display most deviation from Baldwin's Rules
-***Alabugin proposes modified set of "rules" for alkyne cyclizations***

Baldwin says:

Nuc, Elec, Rad				
-dig	3	4	5	6
endo	y	y	y	y
exo	n	n	y	y

"Favored" Trajectory for Digonal Closure

Baldwin — *Acute angle of attack 60 °* — *based on X-ray studies and preference for endo- closure*

Revised — *Obtuse angle of attack 120 °* — *theoretical calculations, avoidance of π*-nodal plane, analogous to Burgi-Dunitz angle*

The obtuse trajectory should translate into stereoelectronic preference for exo-cyclization as opposed to endo!

Stereoelectronic Differences in Nucleophilic vs Electrophilic Cylization

Nucleophilic: Nu- LUMO — *Exo*; Nu- LUMO — *Endo*

Electrophilic: E+ HOMO — *Endo/Exo*

Nuc: Secondary orbital interaction is ***destabilizing***

Elec: Secondary orbital interaction is ***stabilzing***

Three Modes of Cyclization to Consider

Electrophilic Closure

Nu-Promoted Electrophilic Closure (NPEC)

E+-Promoted Nucleophilic Closure (EPNC)

This section will cover: 3-exo vs. 4-endo (rad, anionic, cationic)
4-exo vs. 5-endo (rad, anionic, cationic)
Not covered: 5-exo vs 6-endo. Both favored. See review for details.

3-exo vs. 4-endo: By Baldwin's Rules, 4-endo should be favored.

Radical

No examples of either 3-exo and 4-endo radical cyclizations in literature.

Theoretical studies reveal that both processes are endothermic and as such they are not likely to be practically viable.

Hope for development of a 3-exo-dig radical method?

vs.

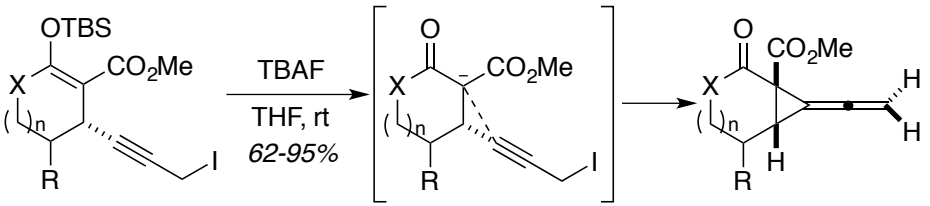
ΔE_r 8.2 kcal/mol — ΔE_r 2.4 kcal/mol

Significant drop in endothermicity suggets that a properly designed system may be able to shift equilibrium.

Anionic

3-exo-dig

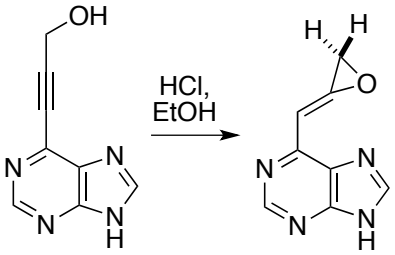
Carbon Nucleophile: *Vinylidene Cyclopropanes from E⁻-deficient Alkenes*



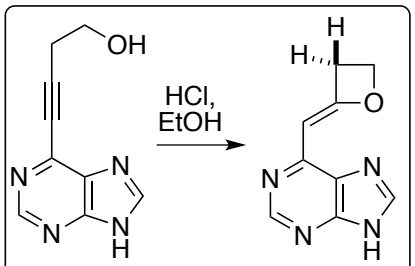
X= C, O R= *i*-Pr, H,

Johnson, J.; *JACS,* **2008**, *130*, 9180.

Oxygen Nucelophile: *Vinyl Oxiranes*



Berg, C.; *Eur. J. Org. Chem.* **2005**, 4988.

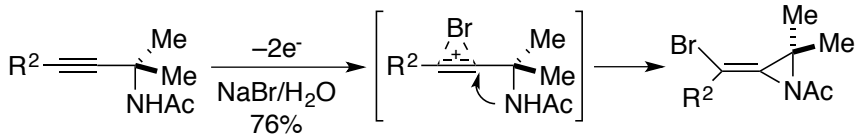


Bonus: 4-exo-dig (10% conv.)

Breaking the Rules: "Anti-Baldwin" Cyclizations

Sarah Wengryniuk

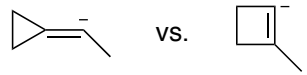
Nitrogen Nucleophile: *Vinyl aziridines via electrohalogenation of propargyl amides*



Torii et. al.; *J. Org. Chem.*, **1992**, *57*, 5023.

4-endo-dig???

Despite being "Favorable" by Baldwins rules, these types of nucleophilic cyclizations remain **unknown**.
This is not surprising based on activation barrier:



E_a	**7.8**	**27.0**
ΔE_r	-4.5	-13.0

~20 kcal/mol higher barrier to activation for 4-endo, which overrides the fact that it is ~7kcal/mol more exothermic than 3-exo

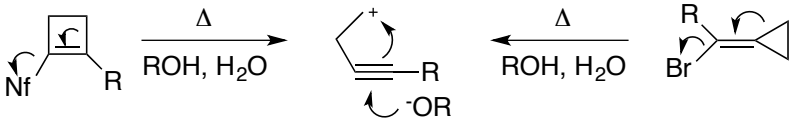
Alabugin, I. et. al.; *JACS*, **2011**, *133*, 12608.

Cationic

Hanack, M.; *JACS*, **1974**, *96*, 6686.
Hanack, M.; *JOC*, **1983**, *48*, 5260.
Wilson, J.W.; *JACS*, **1969**, *91*, 3238.

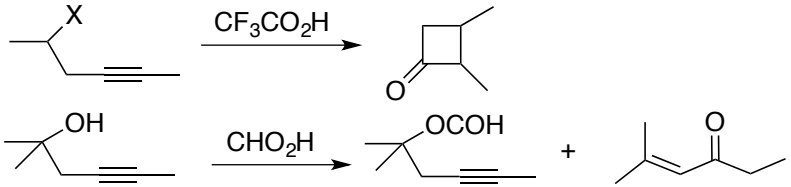
3-exo-dig vs. 4-endo-dig

1° carbocation: Controlled by substitution on alkyne: Example of NPEC



R	3-exo : 4-endo	3-exo : 4-endo
H	0:100	0:100
Me	1:99	1:89
Ph	31:17	--------
An	57:43	54:4

2°/3° carbocations: Similar behavior to 1° or lack of cyclization

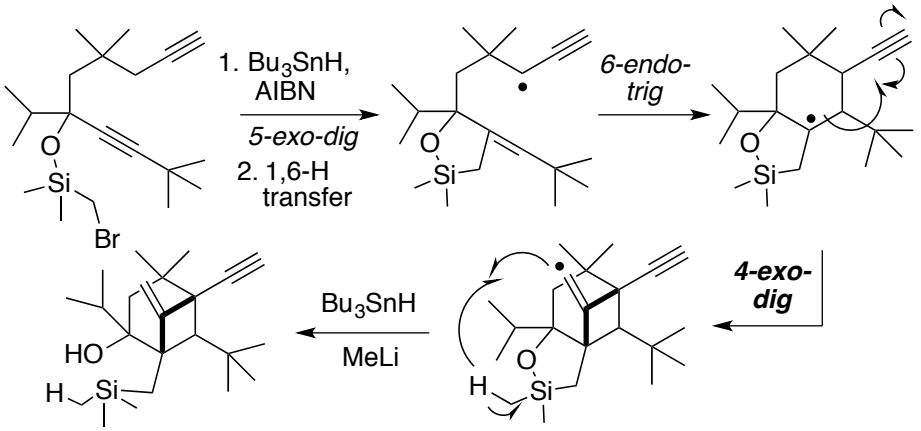


4-exo (Disfav.) vs. 5-endo (Fav.):

-Clear thermodynamic preference for 5-endo (much more exothermic)
-Kinetic preference can often favor 4-exo closure so selectivity is balance of two factors.

Radical

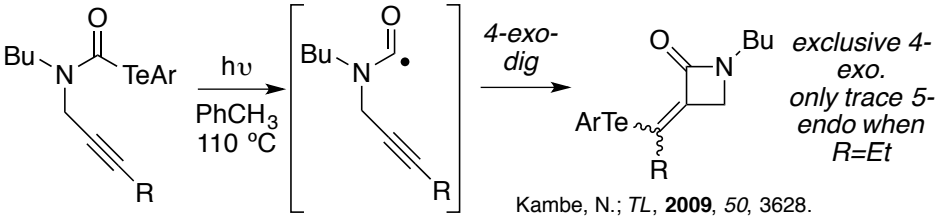
4-exo-dig: Only two examples in literature



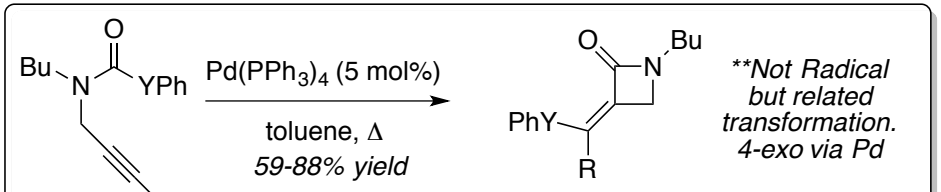
Bicyclo[3.1.1]Heptanes

Malacria, M.; *JACS*, **1997**, *119*, 5037.

Carbamoyl Radicals via photolysis of carbamotelluroates



Kambe, N.; *TL*, **2009**, *50*, 3628.



Kambe, N.; *JACS*, **2005**, *127*, 9706.

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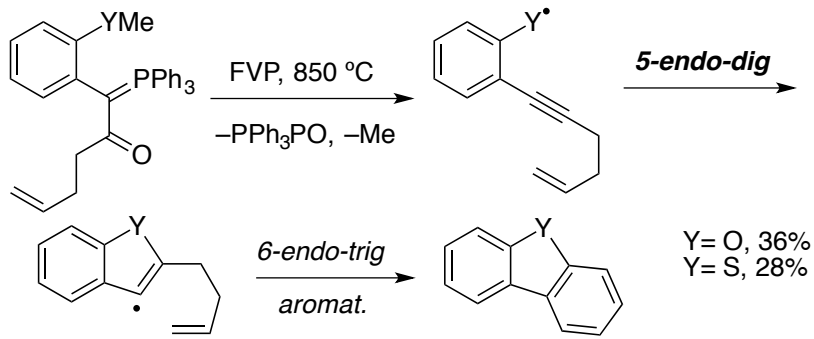
Breaking the Rules: "Anti-Baldwin" Cyclizations

Sarah Wengryniuk

5-endo-dig: Examples employing O, S, Si, C radicals

***Is a favored process by Baldwin's Rules**, but examples are scarce! Went 40 years without example of carbon radical 5-endo-dig cyclization!*

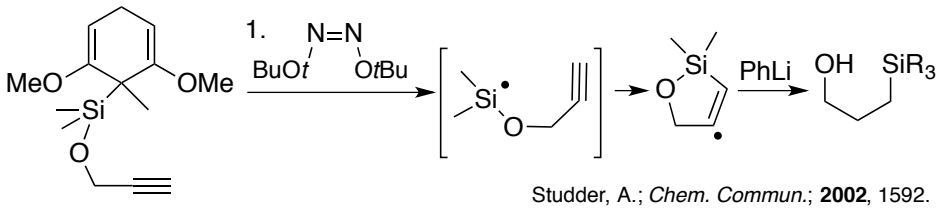
O and S require flash vaccum pyrolysis



Aitken, R. A.; *Synlett*, **1995**, 53.
Aitken, R. A.; *JCS PT1,* **1994**, 2455.

Other "O" example: Barton, T.; *JOC*, **1985**, *50*, 158.

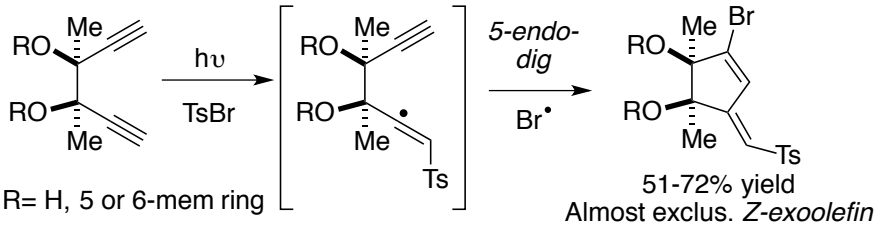
Si-Centered Radical: Intramolecular radical hydrosilylation



Studder, A.; *Chem. Commun.*; **2002**, 1592.

C-Centered Radical: Igor contributes a reaction!

-40 years since Baldwin's Rules and **no 5-endo-dig radical from carbon**
-DFT calculations predicted that while plausible, 5-endo-dig is a slow process
-Bias system with strain effects and prediction that vinyl radical should cyclize fastest
-Use of AIBN/Bu_3SnH led to complex product mixtures



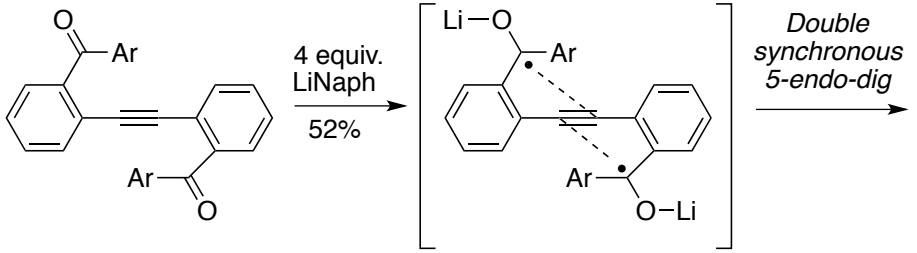
R= H, 5 or 6-mem ring

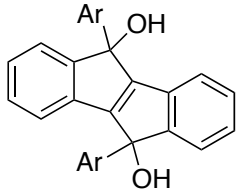
51-72% yield
Almost exclus. *Z-exoolefin*

Alabugin, I.; *JACS*, **2008**, *130*, 10984.

Other Examples of Proposed 5-endo-dig radicals:

Double Synchronous 5-endo-radical cyclization





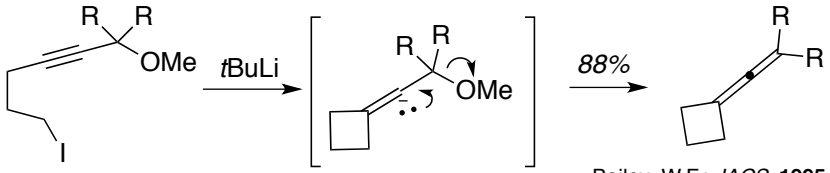
Computational studies support this proposed mechanism. If only one ketone present, dimerization rather than radical cyclization occurs.

Yamaguchi, S.; *OL*, **2009**, *11,* 3076.

Anionic:
-4-exo-dig is disfavored by Baldwin's Rules but is possible!
-5-endo is not easy to facilitate either; diff. btw 4-exo/5-endo is **very small**
-Can facilitate 5-endo:
- Stab/Destab of resulting negative charge
- 4-exo product disfavored by ring strain
- Aromatic Stability of products
- Use of an external electrophile

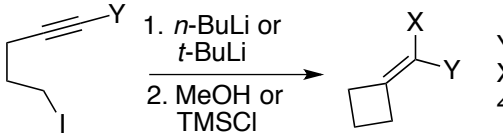
4-exo-dig

Achieving 4-exo is still not easy: Use of Propargylic leaving group



Bailey, W.F.; *JACS,* **1995***, 60,* 754.

Achieving 4-exo is still not easy: Stabilizing negative charge



Y= -$CBMes_2$, -CO_2tBu_2, Ph, TMS
X= H, TMS
48-95% yield

Bailey, W.F.; *TL*, **1990**, *31,* 627.
Bailey, W.F.; *JACS*, **1993**, *115,* 3080.
Cooke, M.; *JOC*, **1994**, *59*, 2930.
Cooke, M.; *JOC*, **1993**, *58*, 6833.

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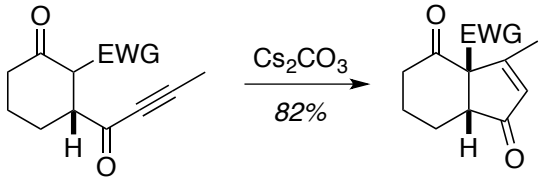
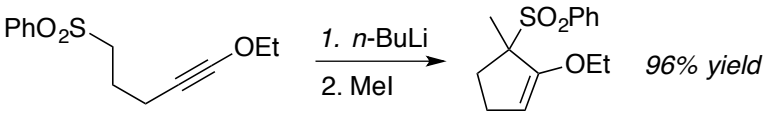
Stabilization of the negative charge: 5-endo-dig onto ynone



Grein, F.; *TL*, **1986**, *27*, 5455.

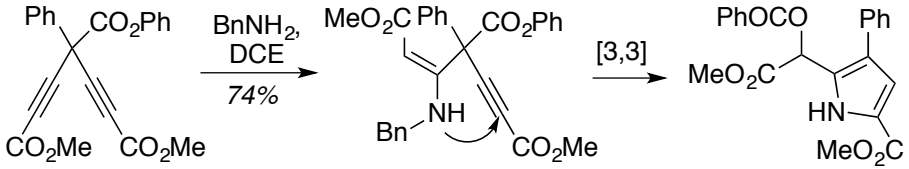
Destabilization via electron-donating group



96% yield

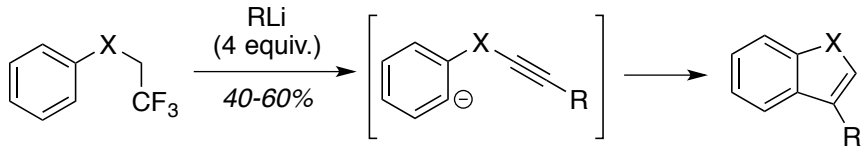
Stallman, J.B.; *JACS*, **1993**, *115*, 7023.

Producing an aromatic product: Pyrroles via 5-endo-dig then [3,3]



Garcia-Tellado, F.; *Chem–Eur. J.*, **2009**, *15*, 838.

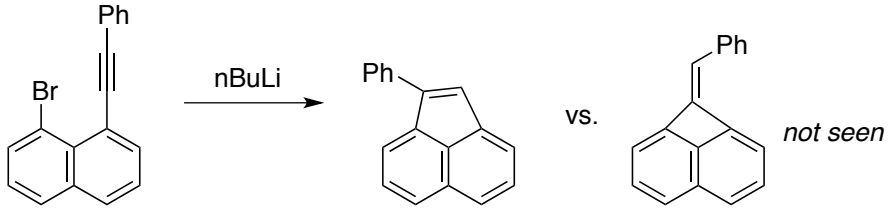
Producing an aromatic product: Carbon Nucleophile



R= nBu, Pr, Ph; X=O, S, N

Johnson, F.; *JOC*, **1986**, *51*, 5040.
For related N-nuc: Knochel, P.; *ACIE*, **2000**, *39*, 2488.

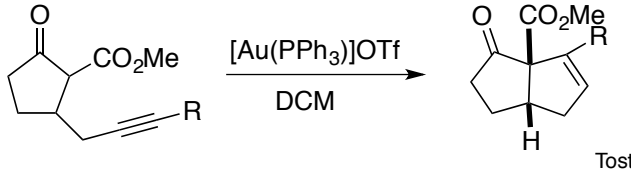
Strained Products: 5-endo favored



not seen

Use of an external electrophile

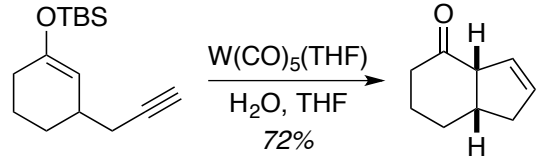
Au: Endo-selective Conia-ene without need for substrate-mediated polarization



R= H, Me, Ph
74-94% yield

Toste, D.; *ACIE*, **2004**, *43*, 5330.

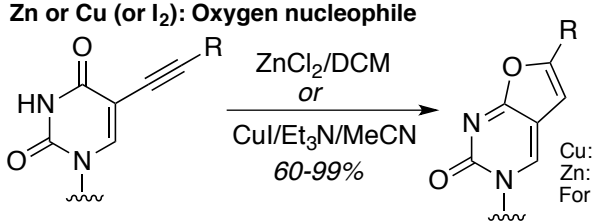
$W(CO)_5$: The use of silyl-enol ether as nucleophile



note: Could proceed via attack on allene intermediate

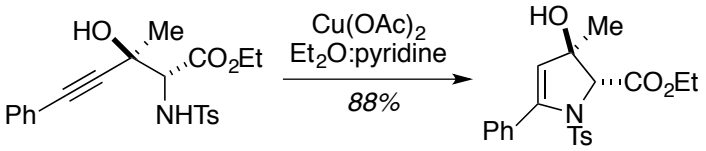
Iwasawa, N.; *OL*, **2002**, *4*, 4463.

Zn or Cu (or I_2): Oxygen nucleophile

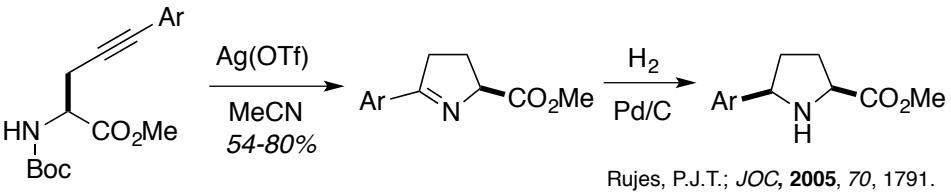


Cu: Robins, M.J.; *J.M.C.*, **2006**, *49*, 391.
Zn: Dembinski, R.; *JOC*, **2008**, *73*, 5881.
For I_2: Knight, D.W.; *TL*, **2001**, *42*, 5945.

Cu(II), Pd, Ag or Hg: Nitrogen Nucleophile



Cu, Pd, Hg: Knight, D.W.; *Synlett*, **2004**, *1*, 119.



Rujes, P.J.T.; *JOC*, **2005**, *70*, 1791.

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Breaking the Rules: "Anti-Baldwin" Cyclizations

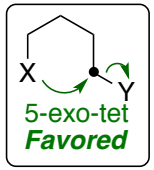
Sarah Wengryniuk

Baldwin's Original Rules: Apply to Nuc⁻, Rad•, Elec⁺

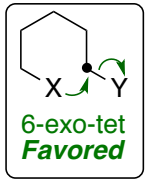
TET

3-exo-tet ***Favored***

4-exo-tet ***Favored***



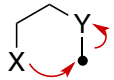
5-exo-tet ***Favored***



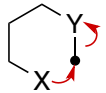
6-exo-tet ***Favored***

3-endo-tet ***????***

4-endo-tet ***????***



5-endo-tet ***Disfavored***



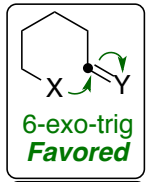
6-endo-tet ***Disfavored***

TRIG

3-exo-trig ***Favored***

4-exo-trig ***Favored***

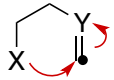
5-exo-trig ***Favored***



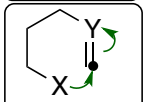
6-exo-trig ***Favored***

3-endo-trig ***Disfavored***

4-endo-trig ***Disfavored***



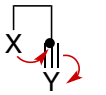
5-endo-trig ***Disfavored***



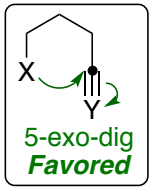
6-endo-trig ***Favored***

DIG

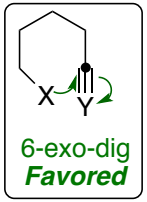
3-exo-dig ***Disfavored***



4-exo-dig ***Disfavored***

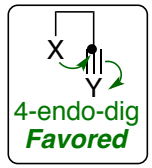


5-exo-dig ***Favored***

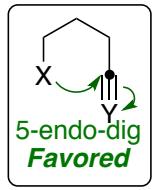


6-exo-dig ***Favored***

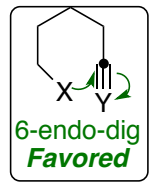
3-endo-dig ***Favored***



4-endo-dig ***Favored***



5-endo-dig ***Favored***



6-endo-dig ***Favored***

Modified Baldwin's Rules:

X = No examples in literature still
√ = Possible, sparse examples
√√ = Many methods available
F = Favored by Baldwin's Rules

TETRAHEDRAL*: Cationic and Radical are as per Baldwin*

Anionic	3	4	5	6
endo	**X**	√	√√	√√
exo	---	---	**F**	**F**

TRIGONAL

Anionic	3	4	5	6
endo	**X**	√	√√	**F**
exo	**F**	**F**	**F**	**F**

Radical	3	4	5	6
endo	**X**	**X**	√	**F**
exo	**F**	**F**	**F**	**F**

Cationic	3	4	5	6
endo	**X**	**X**	√	**F**
exo	**F**	**F**	**F**	**F**

DIGONAL

Anionic	3	4	5	6
endo	**X** (**F**)	**X** (**F**)	√ (**F**)	√ (**F**)
exo	√	√	**F**	**F**

Radical	3	4	5	6
endo	**X** (**F**)	**X** (**F**)	√ (**F**)	**F**
exo	√	√	**F**	**F**

Cationic	3	4	5	6
endo	**X** (**F**)	√ (**F**)	√ (**F**)	**F**
exo	√	√	**F**	**F**