

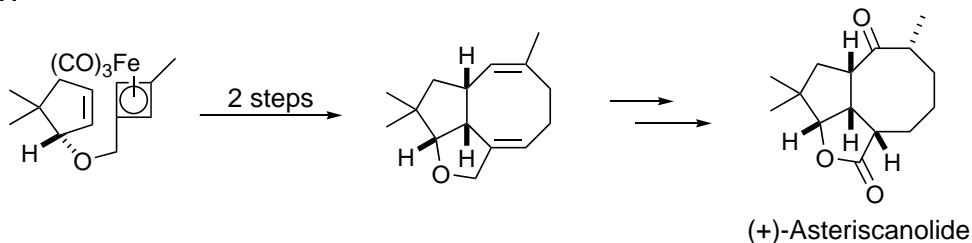


CYCLOBUTADIENE IN ORGANIC SYNTHESIS



Usage of Unstable Intermediate: Cyclobutadiene as A Case

0. Introduction



difficulty to use in synthesis

high reactivity

unstable species

unique reaction sequences

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Contents

1. General feature of cyclobutadiene
2. Stabilization by iron tricarbonyl complex
3. Reaction sequences of cyclobutadiene
4. Total synthesis of (+)-Asteriscanolide

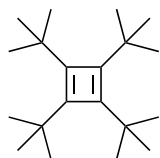
1. General feature of cyclobutadiene

- + antiaromatic
- + unstability from ring strain

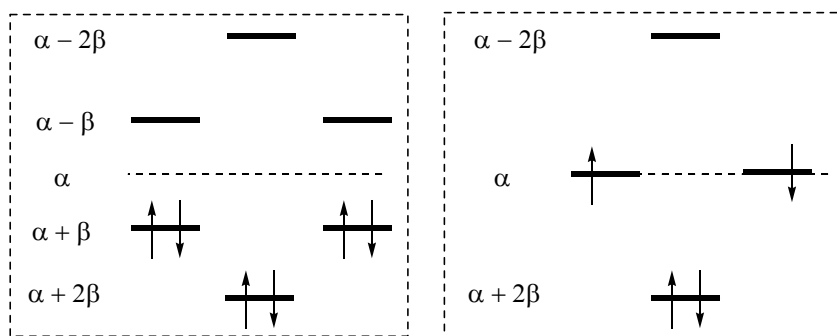
- + rapid dimerization and oligomerization



cf. stable cyclobutadiene

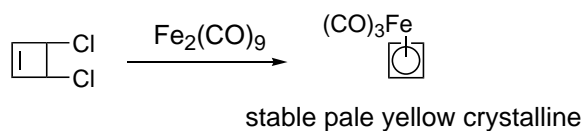


Huckel orbital energy

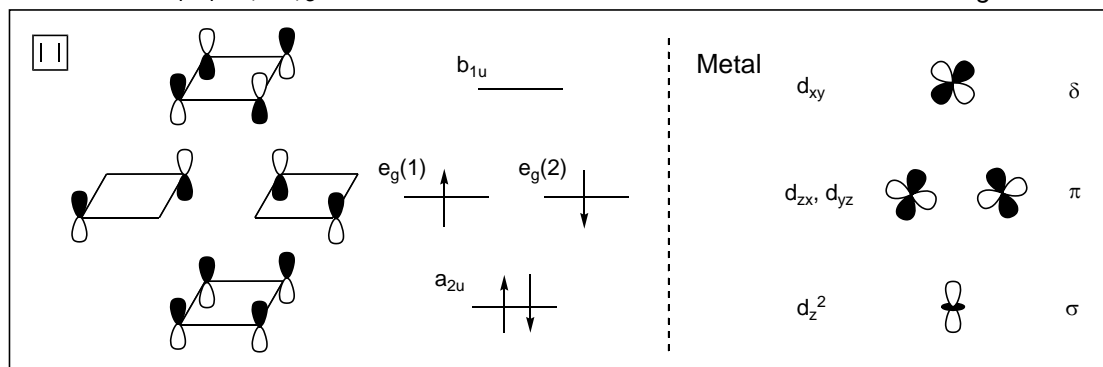


2. Stabilization by iron tricarbonyl complex

- + in 1965, the first preparation of cyclobutadiene-iron tricarbonyl

ref. *JACS* **1965**, 87, 132.

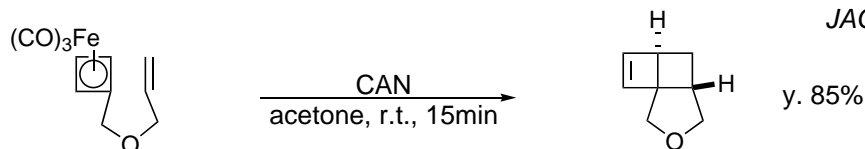
- + Molecular orbital of $C_4H_4Fe(CO)_3$

ref. *Inorg. Chem.* **1979**, 18, 1760.

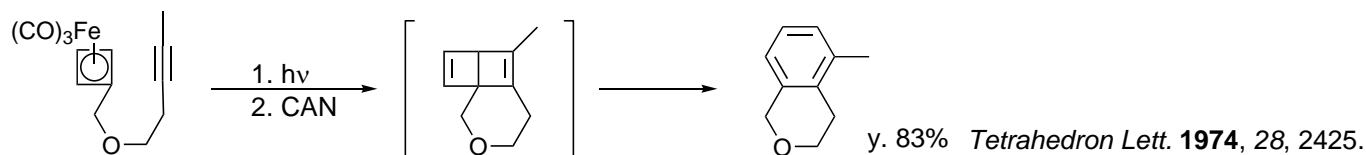
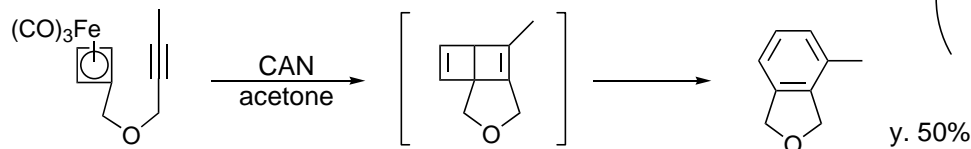
3. Reaction sequences of cyclobutadiene

3.1. Intramolecular cycloadditions between cyclobutadiene and alkenes

ref. *JACS*, **1996**, *118*, 9196.
JACS, **2002**, *124*, 14748.

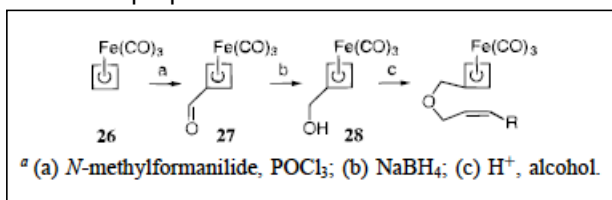


Precedents



Scope and limitations

substrate preparation



+ intramolecular = the key to success with unactivated olefin
+ intermolecular cycloadditions ----- oligomerization

+ 11 & 14

transfer of stereochemical information ----concerted mechanism

+ 20: sterically restricted tether -----oligomerization
higher temp. & short rxn. time -----works well

+ 23: sterically encumbered alkene -----two adjacent
quaternary
carbon centers

Oxidative decomplexation of $(\text{CO})_3\text{Fe}$ -cyclobutadiene complex

substrates prone to undergo intramolecular cycloaddition

||

CAN (5eq.), acetone(1-2mM), r.t., 15min

substrates less prone to undergo intramolecular cycloaddition

||

trimethylamine-*N*-oxide(TMAO, 8-20eq.), acetone(2-20mM),
reflux, 6-24h

Table 1. Intramolecular Cyclobutadiene–Olefin Cycloadditions

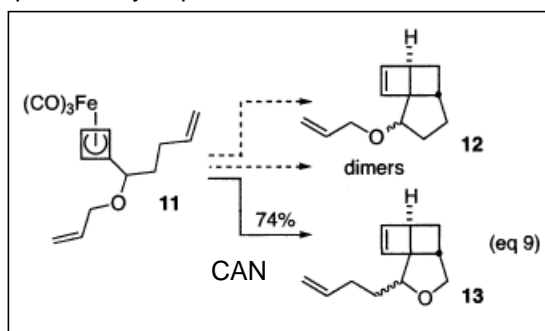
Entry	Substrate ^a	Cycloadduct ^b	Thermal Product ^b
(1)			
	5 95%	6 H 85%	7 H 85%
(2)			
	8 67%	9 92%	10 86%
(3)			
	11 98%	12 H 70%	13 Pr 97%
(4)			
	14 95%	15 H 64%	16 Pr 80%
(5)			
	17 78%	18 70%	19 92%
(6)			
	20 85%	21 60%	22 51%
(7)			
	23 85%	24 65%	25 88%

^a Isolated yields from alcohol precursor 28. ^b Isolated yields.

No involvement of Fe in the cycloaddition

Tether effect

preliminary experiment



- * Three-atom heteroatom-containing tethers
- * Three-atom all-carbon tethers
- * Four-atom heteroatom-containing tethers
- * Four-atom all-carbon tethers

Table 1. Cycloadditions of Chiral Cyclobutadiene Complexes

entry	SM (% ee)	conditions ^a	yield	product ratio (ee)
1	14 (35%)	CAN	66%	16:17 = 16 (0%):1 (0%)
2	14 (35%)	TMAO	55%	16:17 = 14 (0%):1 (0%)
3	18 (35%)	CAN	48%	20:21 = 1 (0%):1 (0%)
4	18 (35%)	TMAO	54%	20:21 = 1 (0%):1 (0%)

^a CAN (room temperature, 2 mM, 15 min); TMAO (56 °C, 20 mM, 6 h).

+ Three-atom heteroatom-containing tethers

Table 2. Intramolecular Cycloadditions with Three-Atom Heteroatom-Containing Tethers

entry	substrate	cycloadduct	method ^a	yield ^b
(1)	22 R ₁ =R ₂ =H	23	A	85%
(2)	24 R ₁ = <i>n</i> -Pr, R ₂ =H	25	A	64%
(3)	26 R ₁ =H, R ₂ = <i>n</i> -Pr	27	A	70%
(4)	28 R ₁ =R ₂ =Me	29	A	70%
(5)	30	31	A	65%
(6)	32	33	A	90%
(7)	34 allene	35	A	35% (4.5:1.0 dr)
(8)	36	37	A, B, C	20%, 49%, 64%
(9)	38 R=SO ₂ <i>p</i> -Tol	39	A	93%
(10)	40 R=allyl	41	A	70%

^a Reaction conditions: method A, CAN (5 equiv), acetone (1–2 mM), room temperature, 15 min; method B, CAN (10 equiv), DMF (1 mM), 80 °C, 5 min; method C, TMAO (10 equiv), acetone (45 mM), reflux, 12 h.
^b Isolated yields.

A: CAN, acetone, rt
 B: CAN, CH₃CN, rt
 C: CAN, DMSO-H₂O, rt
 D: TMAO, acetone, reflux

Table 3. Intramolecular Cycloadditions of Carboxylate Derivatives

entry	substrate	cycloadduct	method ^a	yield ^b
(1)	42	43	A, B, C	55%, 70%, 88%
(2)	44	45	A, D	0% ^c , 0% ^c
(3)	46	47	A, D	47%, 30%

*hydrolysis
 *cinnamyl alcohol was recovered

^a Reaction conditions: method A, CAN (5 equiv), acetone (1–2 mM), room temperature, 15 min; method B, CAN (5 equiv), CH₃CN (1 mM), room temperature, 15 min; method C, CAN (10 equiv), DMSO:H₂O (1:1), room temperature, 15 min; method D, TMAO (8–10 equiv), acetone (20 mM), reflux, 12 h. ^b Isolated yields. ^c 20–30% starting material recovered, as well as 65% *trans*-cinnamyl alcohol.

unactivated olefins: OK
 oxidant : CAN is OK

+ Three-atom all-carbon tethers

Table 4. Intramolecular Cycloadditions with Three-Atom All-Carbon Tethers

entry	substrate	cycloadduct	method ^a	yield ^b (dr)		
(1)				A: CAN, r.t. B: TMAO, reflux C: CAN, reflux		
(1)	48 R ¹ = Et, R ² = H	49	50	A trace B 49% 49:50 (2.9:1.0)	unactivated alkene: CAN: X	
(2)	51 R ¹ = H, R ² = <i>n</i> -Pent	52	53	A or B trace		
(3)					A 53% B 55%	trans slightly activated alkene CAN: OK
(4)					A trace B 53%	cis secondary orbital interaction ?
(5)					A 92% 59:60 (2.3:1.0)	trans activated alkene good yield
(6)					A 66% 62:63 (2.5:1.0)	cis secondary orbital interaction ?
(7)					C 34%	restricted freedom of the tether

^a Reaction conditions: method A, CAN (5 equiv), acetone (1–10 mM), room temperature, 15 min; method B, TMAO (10 equiv), refluxing acetone (20 mM), 6–8 h; method C, CAN (10 equiv), refluxing acetone:CH₂Cl₂ (7:1, 1 mM), 3 min. ^b Isolated yields.

Table 5. Cycloadditions with Enone Substrates

entry	substrate	cycloadduct	method ^a	yield ^b	
(1)			A: CAN, acetone B: TMAO C: CAN, MeOH	A 0% B 70%	
(2)	68 R = <i>n</i> -Pent	69	A 0% B 51%	sp ²	
(3)	70 R = <i>t</i> -Butyl	71	A 0% B 27%		
(4)	72 R = CO ₂ Me	73	A 91%		
(5)					overall yield (ketalization) C 70%(100%) ^c C 57%(75%) ^c C 29%(95%) ^c
(6)	74 R = Ph	(67) ^d		sp ³	
(7)	75 R = <i>n</i> -Pent	(69) ^d			
(7)	76 R = <i>t</i> -Butyl	(71) ^d			
(8)					A 83%

gem-disubstituted
cf. entry 1

+ reactive
heteroatom-containing > all-carbon

shorter C-O lengths
compressed C-O-C bond angles

+ how to solve this low reactivity

- *electronic activation of dienophile
- *secondary orbital interaction
- *restriction in the freedom of tether
- *geminal substitution
- *TMAO

+ Four-atom heteroatom-containing or all-carbon tethers

Table 6. Intramolecular Cycloadditions with Four-Atom Ethereal Tethers

entry	substrate	cycloadduct	method ^a (yield ^b)
(1)			A: CAN B: TMAO
(2)	81 R = Ph	82	A (0%), B (22%)
(3)	83 R = CO ₂ Me	84	A (63%), C (55%) A (65%)
(4)			A (0%), B (17%)
(5)			A (0%), B (21%) 88:89 (3.3:1.0)
(6)			A (0%), B (30%)

^a Reaction conditions: method A, CAN, acetone (1 mM), room temperature, 15 min; method B, TMAO (20 equiv), refluxing acetone (1 mM), 24 h; method C, TMAO (8 equiv), refluxing acetone (20 mM), 6 h. ^b Isolated yields.

Table 7. Cycloadditions with Four-Atom All-Carbon Tethers

entry	substrate	cycloadduct	method ^a	yield ^b
(1)			A	<5%
(2)			A	88%
(3)			A	33% ^c

^a Reaction conditions: method A, CAN (5 equiv), acetone (1 mM), room temperature. ^b Isolated yields. ^c The yield represents a two-step sequence: Knoevenagel condensation of the corresponding iron aldehyde with Meldrum's acid followed by CAN-promoted cycloaddition.

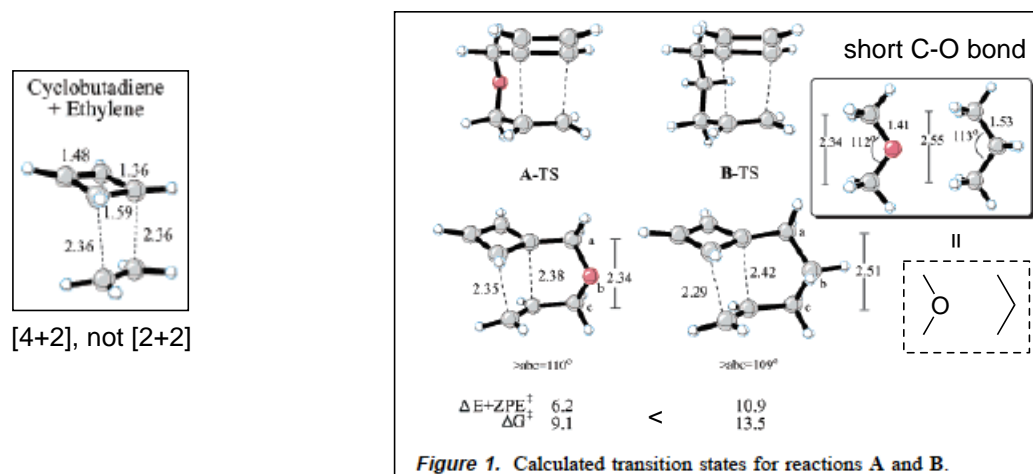
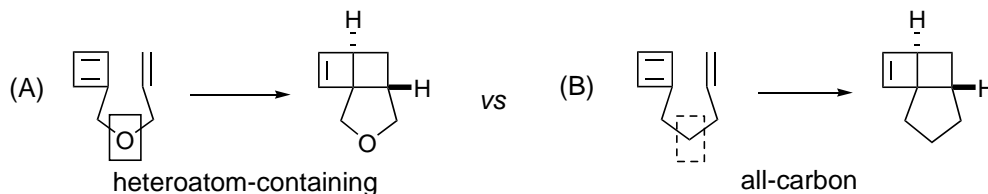
+ reactivity
three-atom > four-atom

+ again, some activation (strongly in the case of all-carbon case) is essential

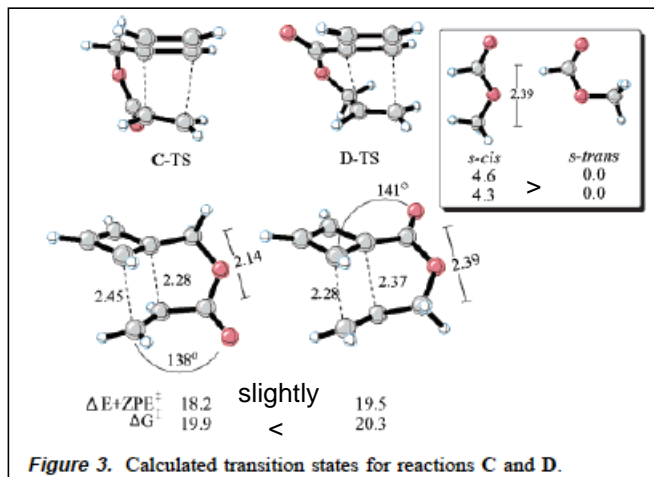
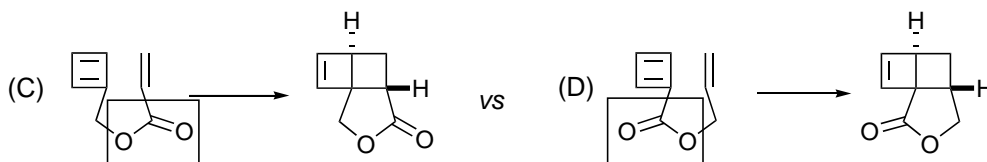
Theoretical calculations

RB3LYP/6-31G(d) as implemented in Gaussian 98

These reactivity was supported by theoretical calculations.



All-carbon tether must be more compressed because of long C-C bond at the expense of angle strain that destabilizes the B-TS.

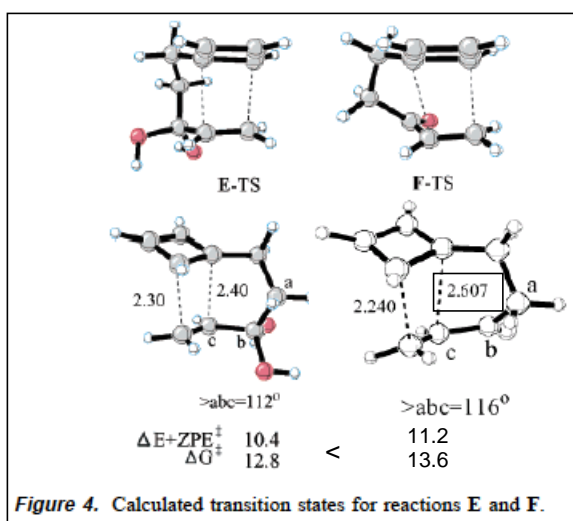
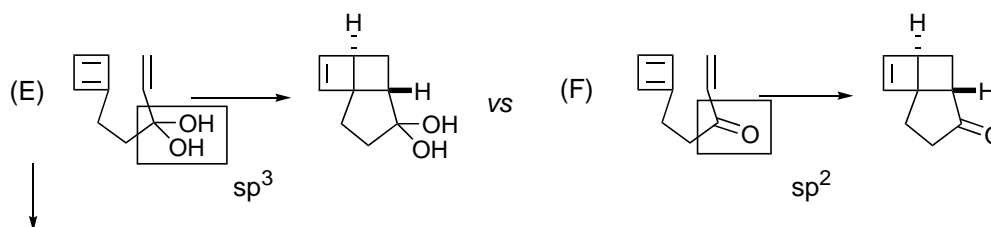


Unexpectedly, these activation energy is higher than A-TS or B-TS. (cf. A: 9.1 kcal/mol)

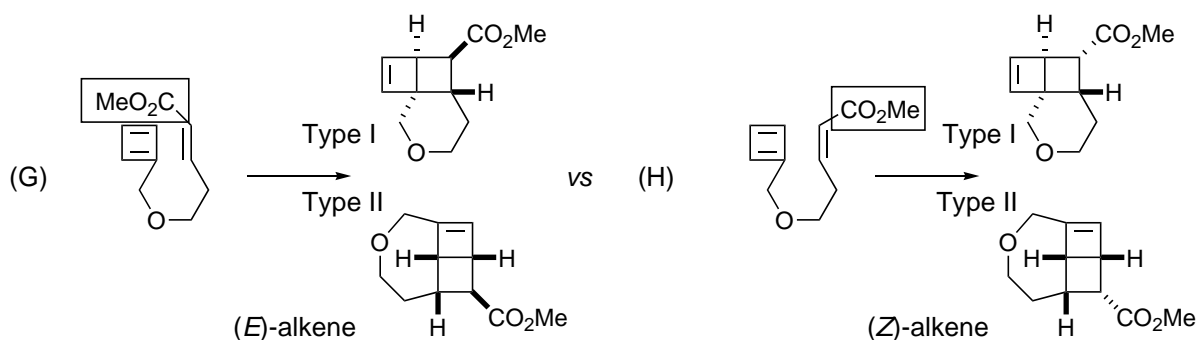
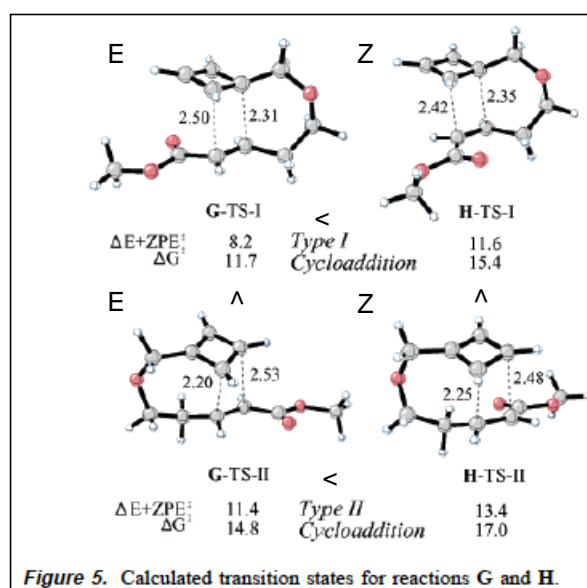
Ester tether is too short to connect two reacting groups without strain?
And because s-cis conformer is unfavorable?

Anyway, there is no inherent difference in cyclization reactivity between C and D.

Low yield of D might be due to
1. less propensity to be oxidized
2. more electrophilicity of ester carbonyl (α -cation is stabilized by the complex)



clearly, sp^2 carbon makes the compressed TS difficult



The Type I transition structure is lower in energy than the Type II transition.

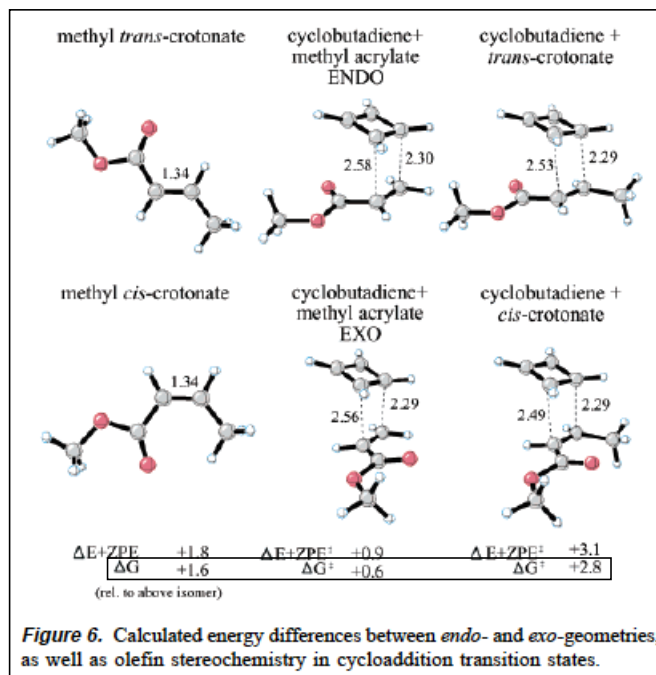
(disagreement with experiment in H-TS)

Type I : Type II = 1.0 : 3.3
(Table 6, entry 5)

E-alkene leads to lower energy transition structure compared to *Z*-alkene.

A quantitative measurement of the factors →
(simplified model)

Transition energy difference	2.8
Dienophile's energy difference	1.6
<i>Endo/exo</i> energy difference	0.6
Strain in the <i>cis</i> -transition structure	0.6
	(kcal/mol)



Conclusions

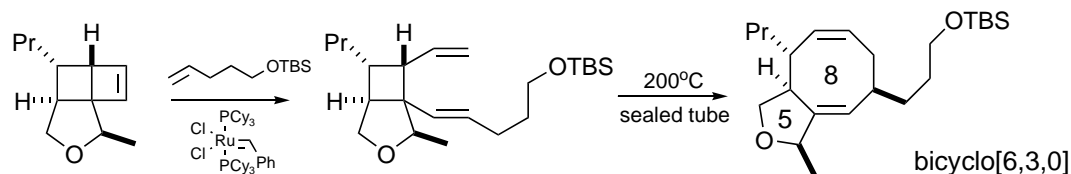
Oxidatively liberated cyclobutadiene could be trapped intramolecularly with olefins to afford functionalized cyclobutene-containing cycloadducts.

This reaction was affected by several factors including

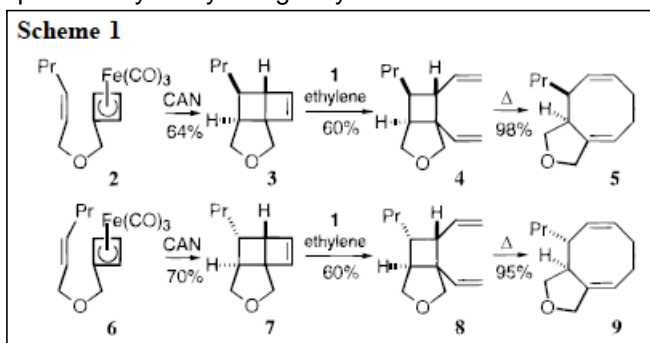
- 1) oxidant (CAN vs TMAO)
- 2) electronical activation (conjugated olefin)
- 3) tether length (heteroatom-containing vs all-carbon, 3 atoms vs 4 atoms)
- 4) tether's freedom (sp^2 vs sp^3 , restriction by phenyl group)
- 5) alkene configuration (*E* vs *Z*)

3.2. Rapid entry into functionalized bicyclo[6,3,0] ring system

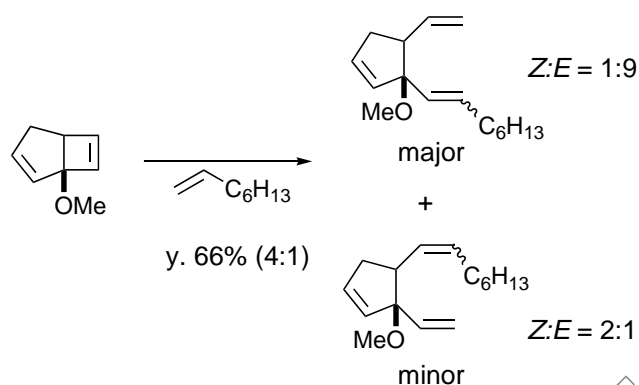
ref. JACS 1997, 119, 1478.



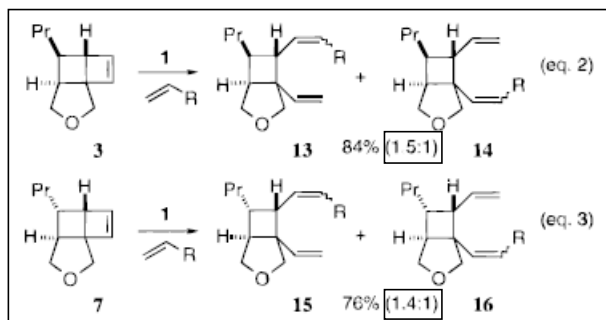
preliminary study using ethylene



model study using substituted alkene
(substituted alkene: regio- & stereo-chemical issue)

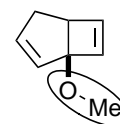


substituted alkene (R = 4-penten-1-ol)



reconsideration of the steric factor

little regiocontrol
(1.5:1 & 1.4:1)

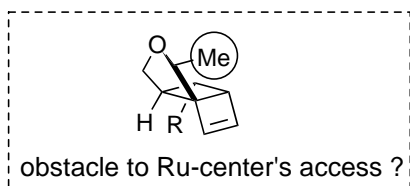


conformation of the methoxy group may play a role in dictating the reaction outcome ?

entry	substrate	major product	yield ^b (regioisomer ratio)
1			72% (8:1)
2			60% (10:1)
3		-	0%
4			57% (1.9:1)

^a Cross-metathesis of cyclobutene substrates with TBS-pent-4-en-1-ol. ^b Isolated yields after silica gel chromatography.

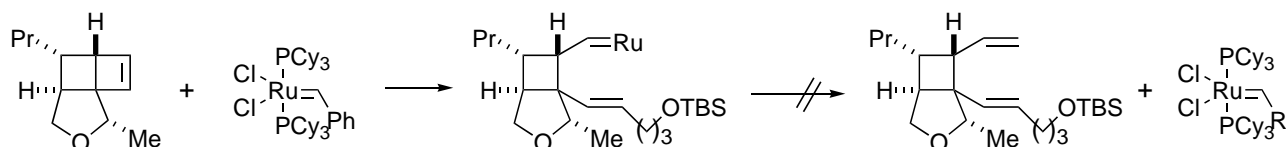
clear contrast between **17** and **21**.



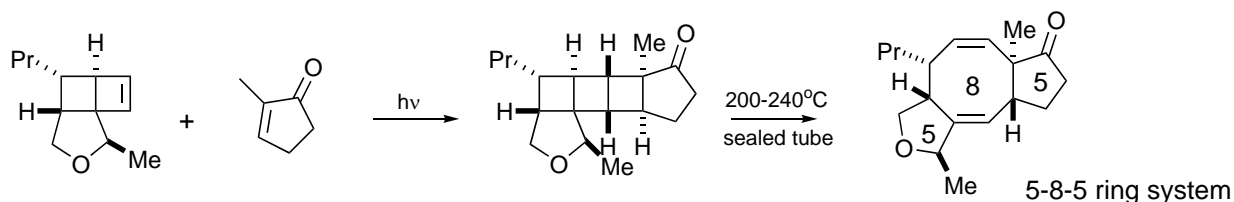
entry	substrate	product ^b	yield ^c
1			70%
2			97%
3			90%
4			96%
5			99%

^a Typical conditions: Substrates heated (200 °C, 1 h) in benzene [0.01 M]. ^b Structural and stereochemical assignments were made through degradative and spectroscopic techniques. ^c Isolated yields after silica gel chromatography.

Alkylidene complex was observed by ¹H, ¹³C, ³¹P NMR, which does not undergo subsequent turnover.



3.3. [2+2] photocycloaddition/thermal retrocycloaddition; a new entry to functionalized 5-8-5 ring system



ref. *JACS* **1999**, *121*, 4534.
OL **2001**, *3*, 2819.

JACS **2005**, *127*, 1201.

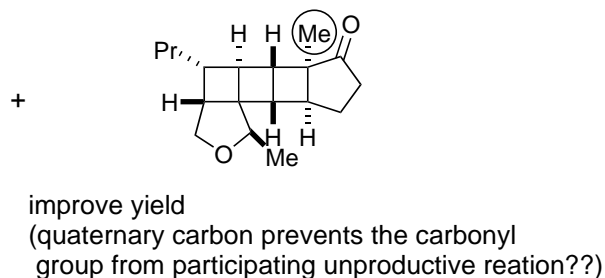
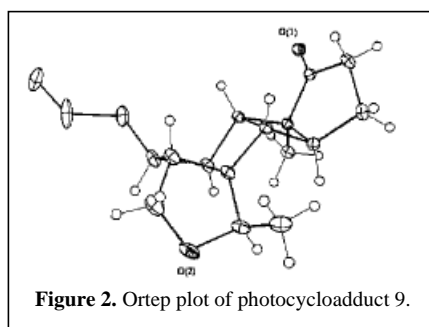
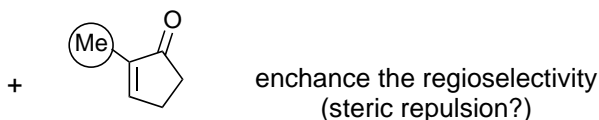
Table 1. Intermolecular Photo[2 + 2]cycloaddition

Entry	Cyclobutene	Enone	Major Product ^a	Yield (conv.) Isomeric ratio ^a	regioisomer
(1)				91% (89%) 1.2:1	
(2)				55% (83%) only isomer	
(3)				84% (71%) only isomer	
(4)				52% (68%) only isomer	
(5)				52% (80%) 8:1	

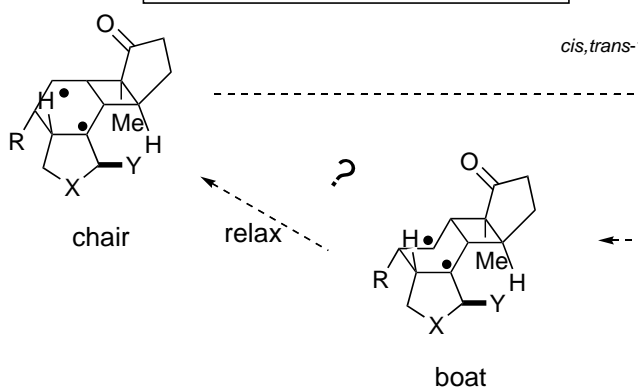
^a Minor isomer has carbonyl group on opposite side of cyclopentane ring.

Table 2. Thermal Fragmentation of Photoadducts

Entry	Cycloadduct	Thermal Product	Yield (conv.)
(1)			41% (70%)
(2)			99% (100%) inversion
(3)			68% (100%) inversion
(4)			70% (100%) inversion
(5)			88% (76%) inversion



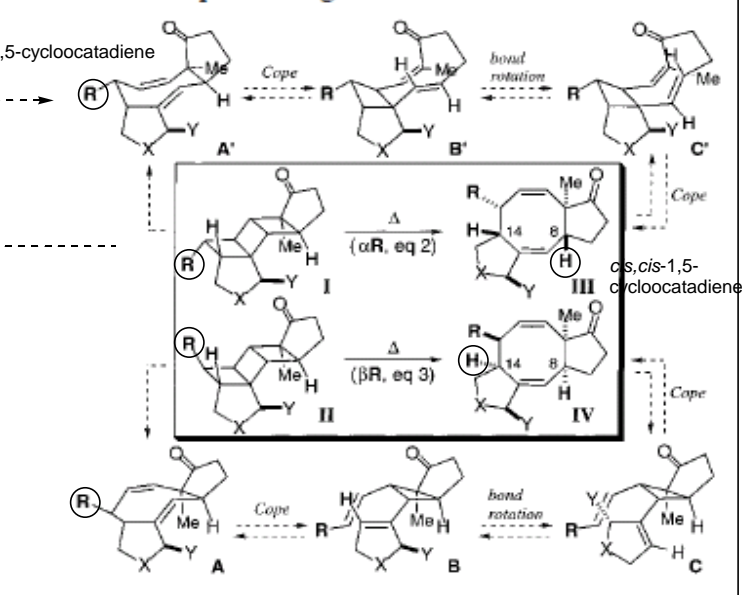
+ stereochemical inversion
@C8 in entry 2 & 3
@C14 in entry 4 & 5



+ Configuration of R determines which pathway (A or A') is prevailed. R favors exo face ?

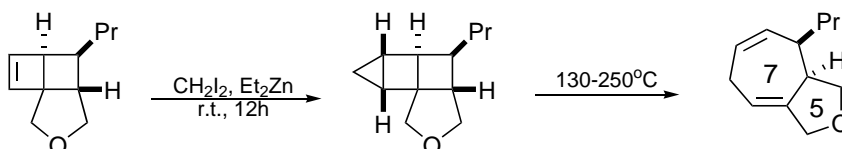
+ *cis,trans*-1,5-cyclooctadiene relaxes leading to *cis,cis*-1,5-cyclooctadiene through rearrangement.

Scheme 1. Proposed Fragmentation Mechanism



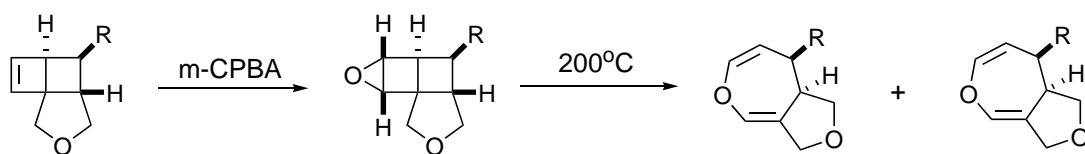
3.4. Approach to bicyclo [5,3,0] ring system through cyclopropane opening

ref. *JACS* 2001, 123, 5152.
OL 2005, 7, 5785.
OL 2006, 8, 5183.



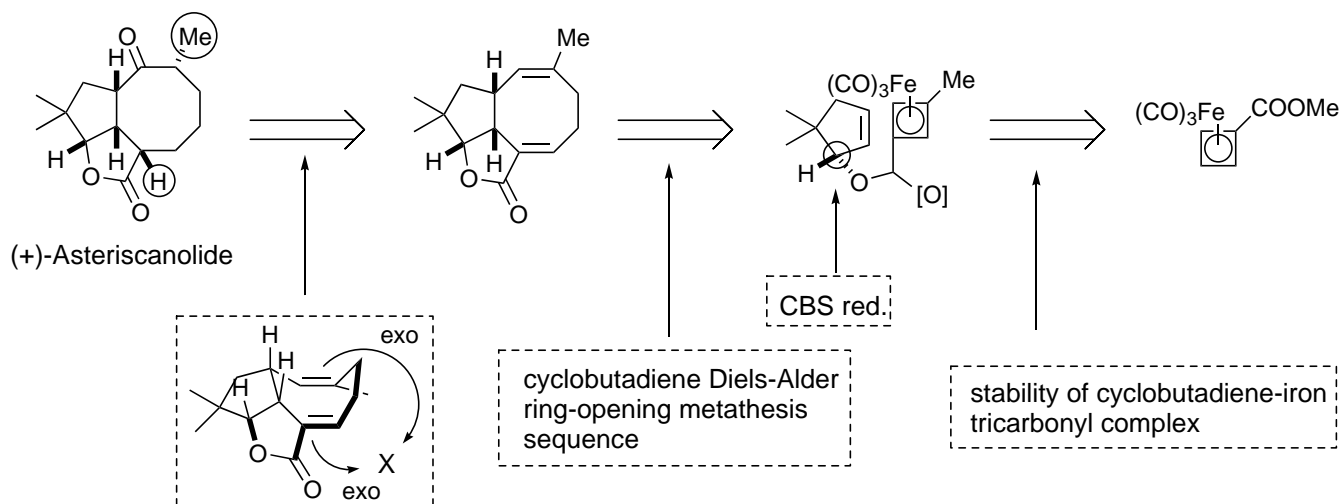
bicyclo [5,3,0]

+ Oxepines are also available.



4. Total synthesis of (+)-Asteriscanolide

ref. *JACS* **2000**, 122, 8071.



Total Synthesis of (+)-Asteriscanolide

