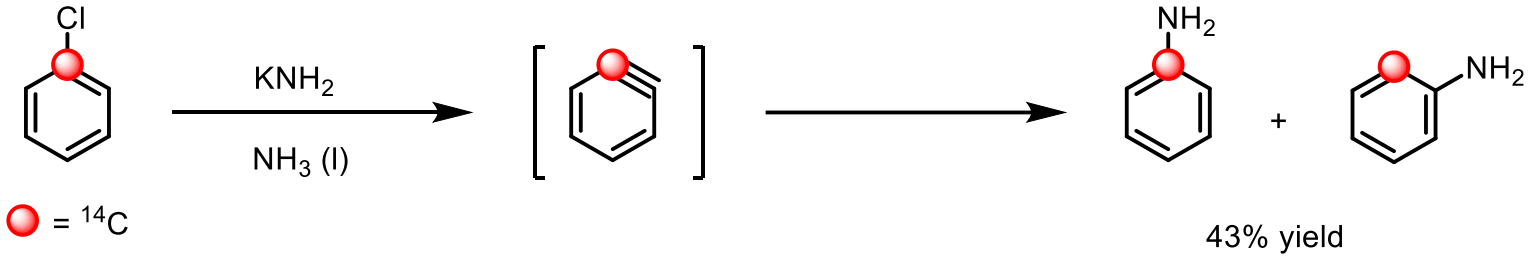
Strained Cyclic Allenes – Transient Intermediates with Expanding Synthetic Applications

Carter Cunningham
Denmark Group Meeting
February 27th, 2024

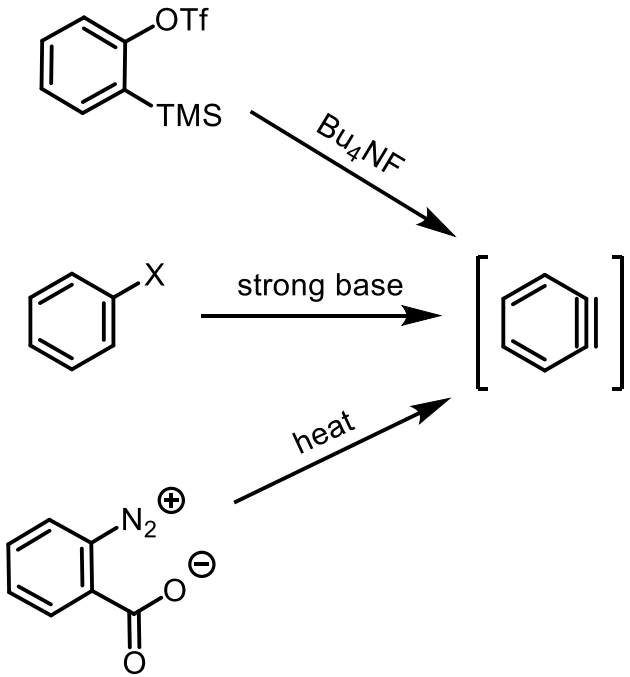
Discoveries of Strained Organic Molecules with Traditionally Linear Geometries

Roberts (1953):



43% yield

Approx. 1:1 ratio



CHEMICAL REVIEWS

Review

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A Comprehensive History of Arynes in Natural Product Total Synthesis

Pamela M. Tadross and Brian M. Stoltz*

Angewandte Minireviews

Natural Product Synthesis

Arynes and Cyclohexyne in Natural Product Synthesis

*Christian M. Gampe and Erick M. Carreira**

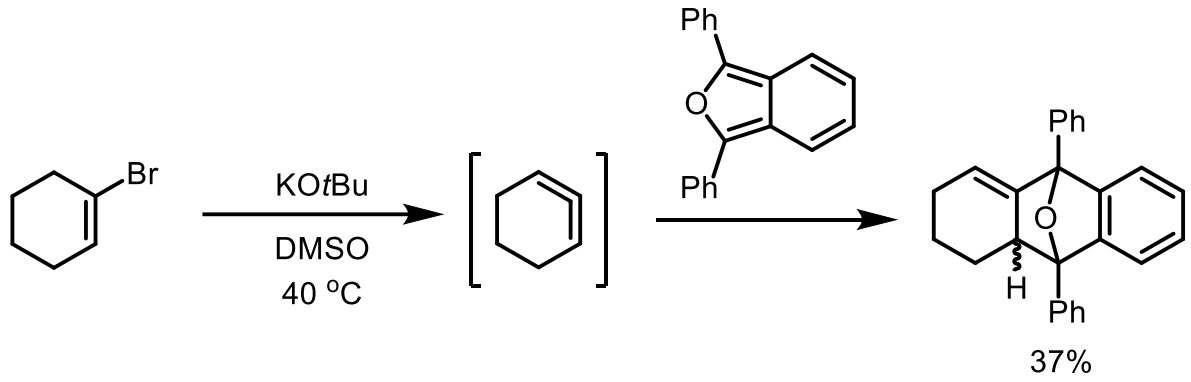
Roberts *et. al.; J. Am. Chem. Soc.* **1953**, *75*, 3290–3291.

Roberts *et. al.; Tetrahedron*, **1957**, *1*, 343-344.

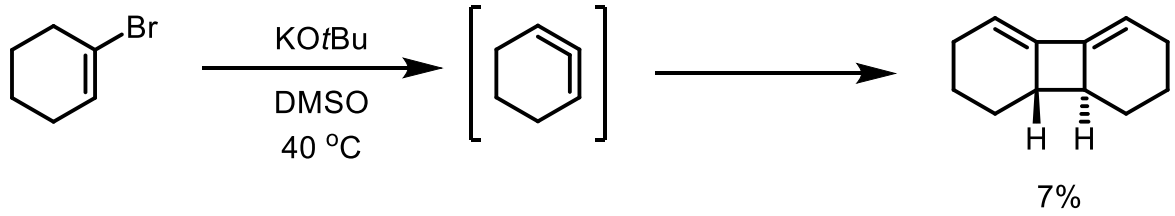
Should also note contributions made by Wittig *et. al.*

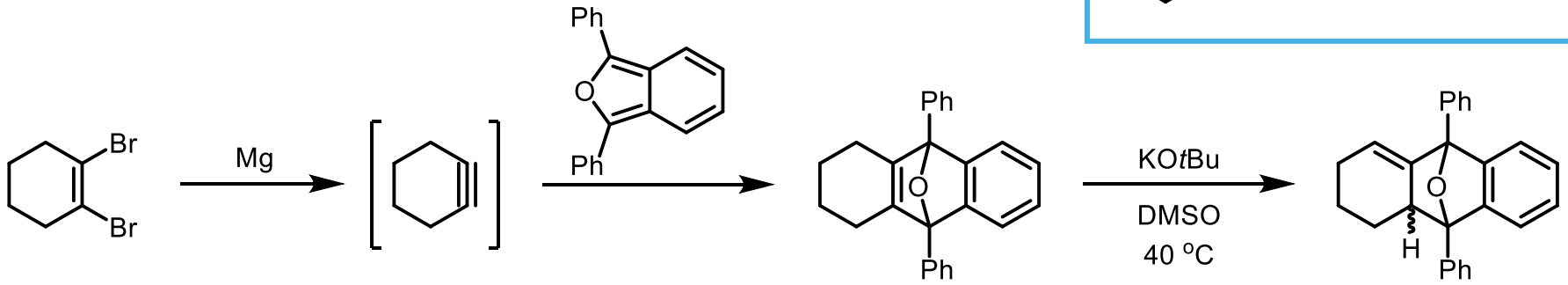
Discovery and Utility of 1,2-Cyclohexadiene

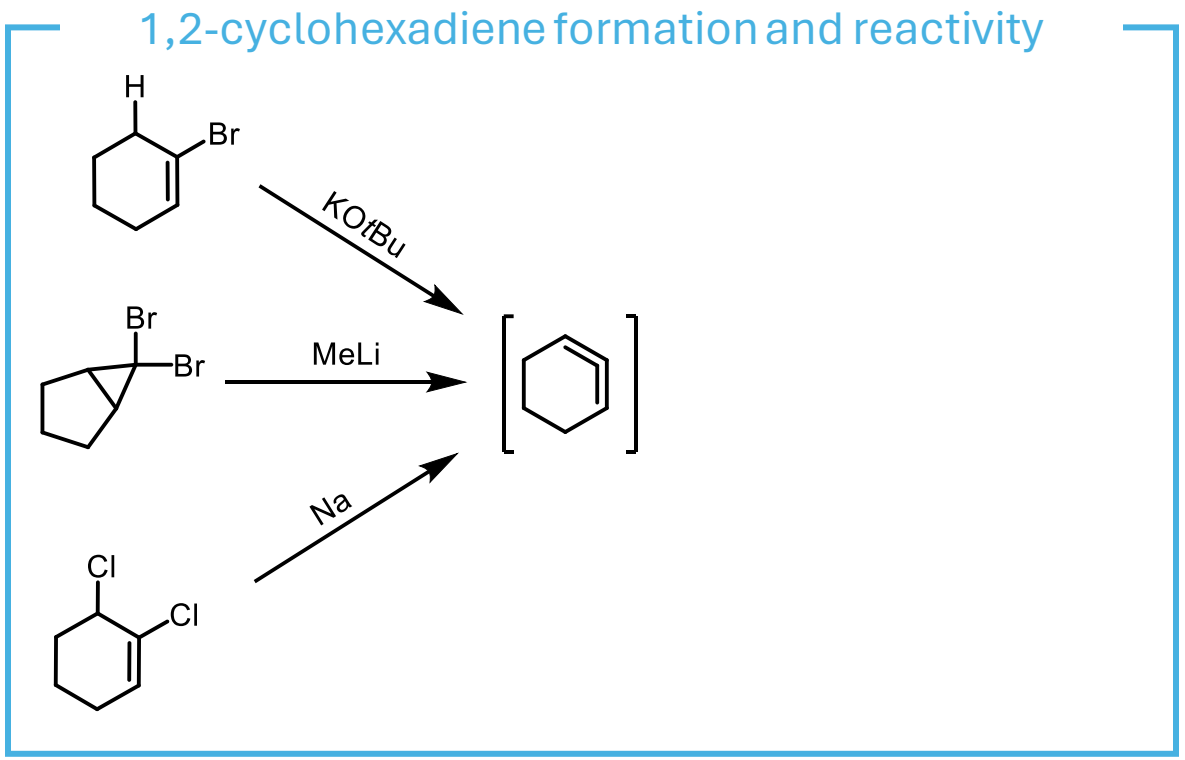
Wittig (1966):



Control Experiments:







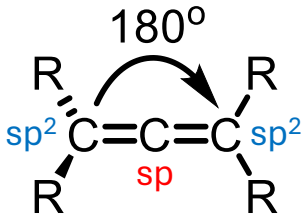
Fritze, P.; Wittig, G. *Angew. Chem. Int. Edn. Engl.* **1966**, *5*, 846.

Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111-1124

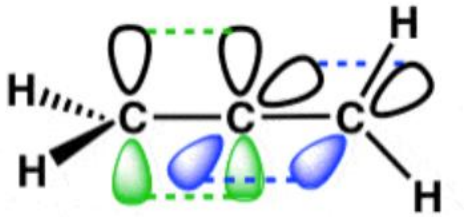
Presentation Overview

- ❑ Defining “strained” cyclic allenes via experimental and computational data
- ❑ Novel approaches for utilizing cyclic allenes
- ❑ Perspective/Summary

Characteristics of Acyclic Allenes vs Cyclic Allenes



Acyclic allenes are not inherently "strained" since strain implies a deviation from normal bonding geometry



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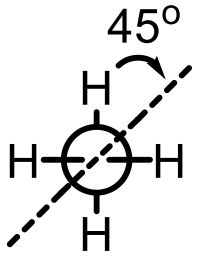
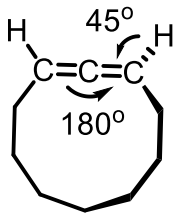


90° dihedral angle or 45° bend out-of-the-plane defined by the median between the two substituents

Stable and only dimerizes at room temperature

Rapidly dimerizes at room temperature and only observable via low temp NMR

Even cyclooctyne can be isolated as their parent structure



Ring Size ←

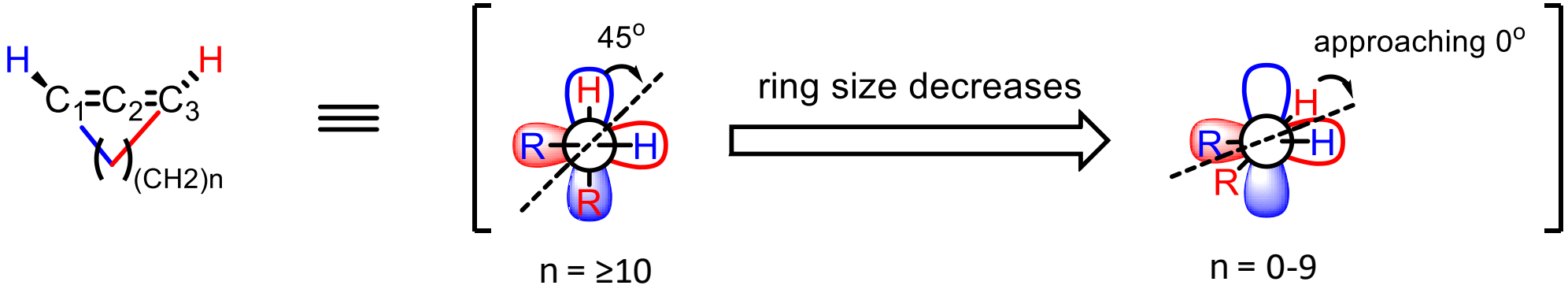
Compression of allene C_1-C_2-C_3 bond increases and out-of-plane bending of H decreases

Tapia *et. al.; J. Chem. Soc., Perkin Trans.* ***1985****, 2,* 363-366.

Johnson *et. al.; J. Am. Chem. Soc.* **1985**, *107*, 532-537.

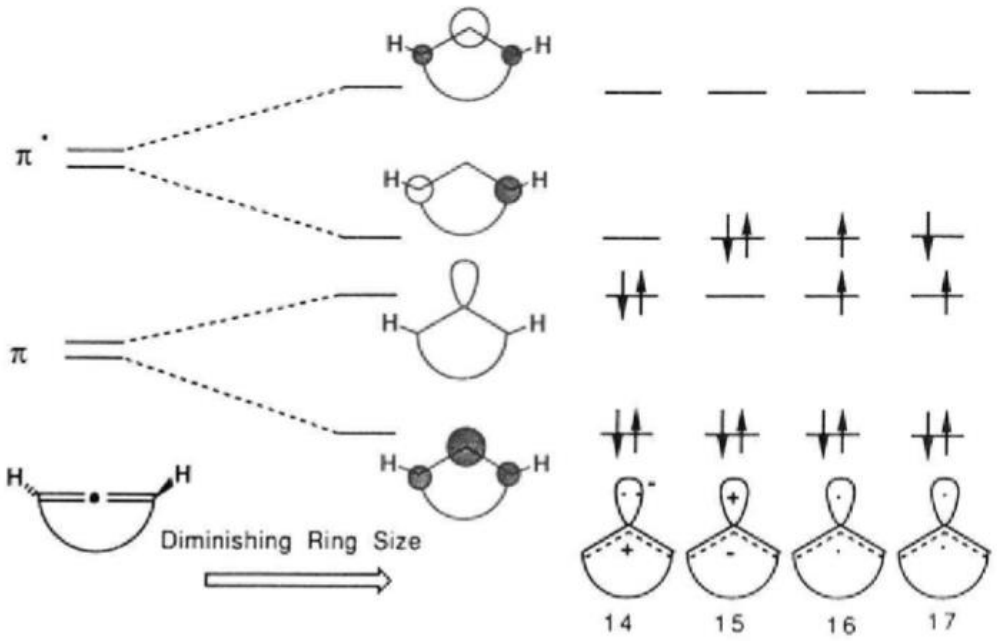
Consequences of Decreasing Ring Size in Cyclic Allenes

- Bending imparts modest strain, but majority of strain comes from torsion that weakens the π-bonds and destroys their degeneracy



- At what point does π-bonding yield to ring strain to give a planar allene, and how does the electronic configuration of the planar allene exist as?

Planar cyclic allenes can be better viewed as an allyl system with an orthogonal sp^2 hybrid orbital



Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111-1124.

Theoretical Studies on the Electronic Structure of Cyclic Allenes

Table I. Ab Initio Computational Results for 1,2-Cyclopentadiene

basis set	computational method	5(^{1}A)[b]	5-^{1}D(^{1}A$_2$)[c]	5-^{3}D(^{3}A$_2$)[c]	5-^{1}Z$_1$(^{1}A$_1$)[d]
		state energies (hartrees)[a]			
STO-3G	RHF/ROHF[e]	−190.31037 (0.0)	−190.36874 (−36.6)	−190.37294 (−39.3)	
3-21G	RHF/ROHF[e]	−191.58548 (0.0)	−191.62131 (−22.5)	−191.62488 (−24.7)	−191.56213 (14.7)
3-21G & STO-3G	RHF/ROHF[e]	−191.11159 (0.0)	−191.14984 (−24.0)	−191.15332 (−26.2)	−191.08564 (16.3)
3-21G + pol	RHF/ROHF[e]	−191.69779 (0.0)	−191.72666 (−18.1)		−191.67802 (12.4)
3-21G & STO-3G	UHF		−191.18672 (s^2 = 1.26)	−191.16713 (s^2 = 2.11)	
3-21G & STO-3G	RMP2/UMP2[f]	−191.49527 (0.0)	−191.49614 (−0.5) (s^2 = 1.19)	−191.49090 (2.74) (s^2 = 2.08)	
3-21G & STO-3G	RMP3/UMP3[f]	−191.52958 (0.0)	−191.53639 (−4.3) (s^2 = 1.19)	−191.53105 (−0.92) (s^2 = 2.08)	
3-21G & STO-3G	FORS[g]	−191.19929 (0.0)	−191.20093 (−1.03)		

[a] Relative energies for comparable species are given in kcal/mol. [b] All calculations at STO-3G/RHF geometry in C_2. [c] STO-3G/ROHF geometry. [d] At geometry for ^{1}D state. [e] RHF or ROHF for closed- or open-shell species. [f] Second- or third-order Möller–Plesset calculation with RHF or UHF wave functions. [g] 12- or 8-configuration MCSCF.

Under all methods of computation, 1,2-cyclopentadiene favors either the excited singlet state 5-^{1}D or triplet state 5-^{3}D but may be within range of error to favor chiral cyclic allene

Table II. Ab Initio Computational Results for 1,2-Cyclohexadiene[a-g]

basis set	computational method	6(^{1}A)[b]	6-^{1}D(^{1}A)[c]	6-^{3}D(^{3}A)[c]	6-^{1}Z$_1$(^{1}A)[d]
		state energies (hartrees)[a]			
STO-3G	RHF/ROHF[e]	−228.95597 (0.0)	−228.96296 (−4.4)		−228.79919 (98.4)
3-21G	RHF/ROHF[e]	−230.46297 (0.0)	−230.45734 (3.5)		
3-21G & STO-3G	RHF/ROHF[e]	−229.74931 (0.0)	−229.74613 (2.0)	−229.74941 (−0.06)	
3-21G + pol	RHF/ROHF[e]	−230.56712 (0.0)	−230.56095 (3.9)		−230.49076 (47.9)
3-21G & STO-3G	UHF		−229.78341 (s^2 = 1.26)	−229.76355 (s^2 = 2.11)	
	RMP2/UMP2[f]	−230.18044 (0.0)	−230.14565 (21.8) (s^2 = 1.18)	−230.14006 (25.3) (s^2 = 2.07)	
	FORS[g]	−229.81769 (0.0)	−229.79679 (13.1)		

[a-g] See corresponding footnotes in Table I.

The opposite trend is now observed, where 1,2,-cyclohexadiene now favors the ground singlet state (the chiral cyclic allene structure)

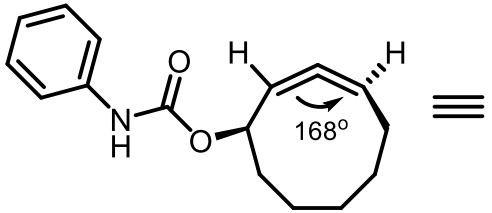
Johnson, *et. al.; J. Am. Chem. Soc.* **1985**, *107*, 532-537.

Theoretical Studies on the Electronic Structure of Cyclic Allenes

Table III. MNDO Results for Cyclic Allenes

species	ΔH_f (kcal/mol) SCF	ΔH_f (kcal/mol) CI	C_1–C_2–C_3 (deg)	out-of-plane hydrogen bending[a] (deg)
4	156.9 (0.0)[b]	166.2 (0.0)	93.0	0.7
4-^{1}D	134.4 (−22.5)	134.4 (−31.8)	99.5	0.0
4-^{3}D	132.4 (−24.5)		99.5	0.0
5	104.3 (0.0)	93.5 (0.0)	121.0	13.0 (20.9)[a]
5-^{1}D	90.2 (−14.1)	90.2 (−3.3)	119.9	0.0
5-^{3}D	89.0 (−15.3)		119.9	0.0
6	67.7 (0.0)	63.5 (0.0)	138.46	22.9 (30.4)[a]
6-^{1}D	69.2 (1.5)	69.2 (5.7)	135.36	0.0
6-^{3}D	68.5 (0.8)		135.36	0.0
7	44.2		153.4	27.6
8	32.7		161.5	31.0
9	29.2		170.4	33.7
15	122.9	117.4	111.7	
allene			180.0	45.0

[a] Defined as the angle made by the C–H bond with the plane defined by C_1–C_2–C_3. Corresponding ab initio values are given in parentheses. [b] Relative energies (kcal/mol).



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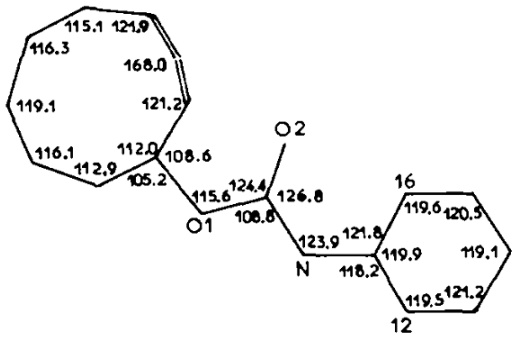
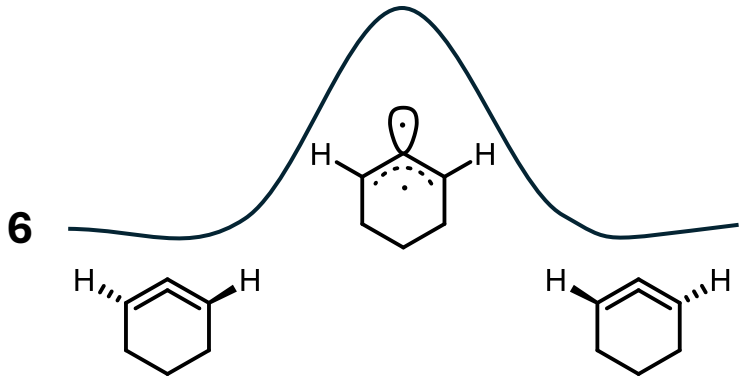


Fig. 1. Structure cristalline du phényluréthane **5**; distances interatomiques (Å) et angles de valence (d°).

6-^{1}D/^{3}D



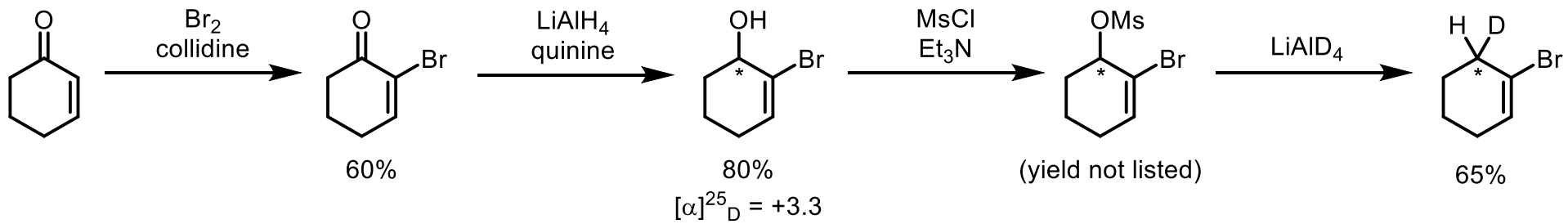
Low barrier between chiral cyclic allene and excited singlet/triplet state means low barrier to racemization

Johnson, *et. al.; J. Am. Chem. Soc.* **1985**, *107*, 532-537.

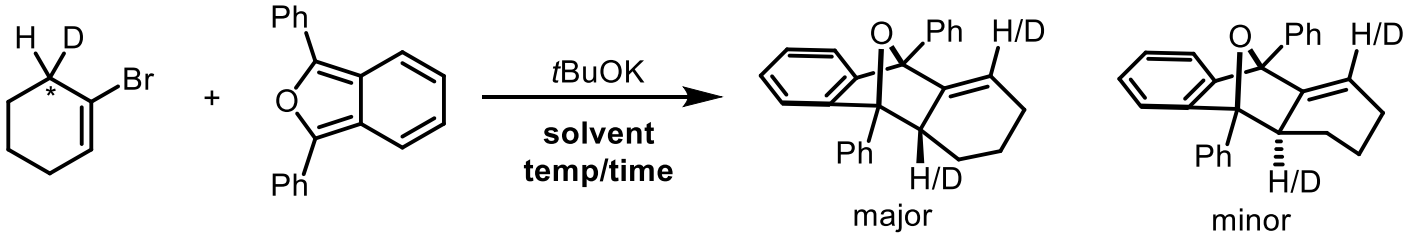
Crabbe, *et. al. Tetrahedron.* **1977**, *33*, 961-964.

Experimental Capture of Chiral Cyclic Allenes

Balci and Jones (1980):



Chiral allene precursor



Not noted which regioisomer formed

Temp (°C)	$[\alpha]^{25}_D$, deg (major)	$[\alpha]^{25}_D$, deg (minor)	Solvent and Time
53	-0.3 ± 0.09	+1.6 ± 0.11	THF, 20 h
80	0.0 ± 0.11	+0.3 ± 0.20	Diglyme, 6 h
100	0.0 ± 0.06	0.0 ± 0.06	Diglyme, 1 h

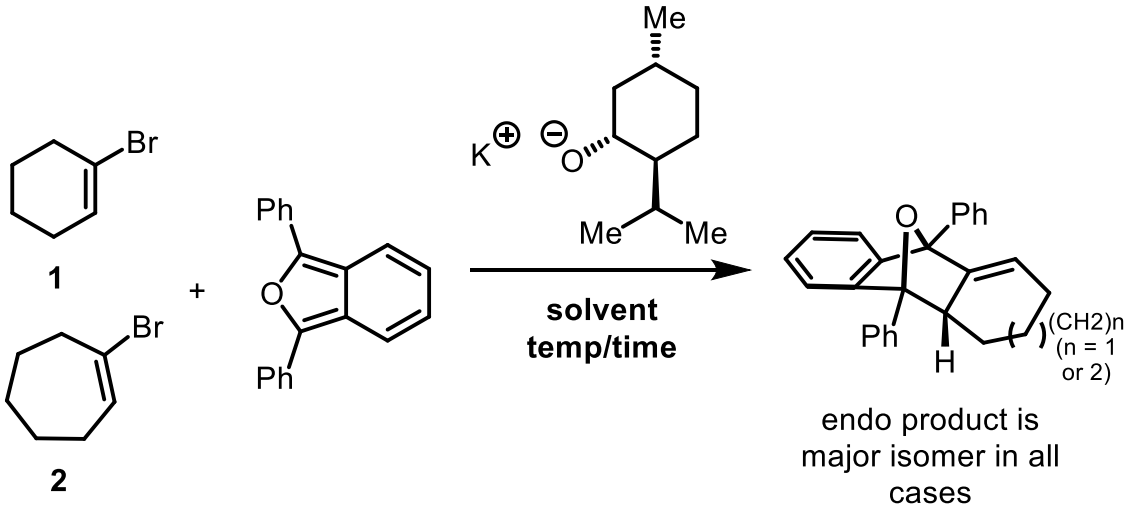
Taking advantage of kinetic isotope effect to generate non-racemic cyclic allene

Racemization at 80 °C is consistent with the predicted barrier of ~15 kcal/mol by Johnson et. al.

Balci, M.; Jones, W. M. *J. Am. Chem. Soc.* **1980**, *102*, 7608-7610.

Experimental Capture of Chiral Cyclic Allenes

Balci and Jones (1981):



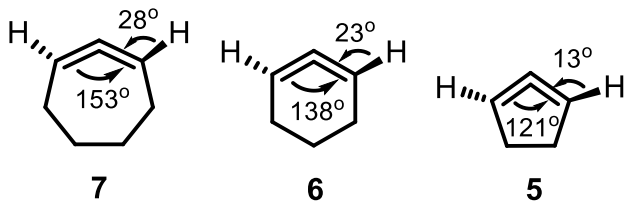
Cyclic Allene Precursor	Base	Temp (°C)	$[\alpha]^{25}_{D}$, deg	Solvent/Time
1	potassium menthoxide	53	-0.4	THF, 20 h
		80	0.0	Diglyme, 6 h
2	potassium menthoxide	53	-1.9	THF, 20 h
		100	-1.7	Diglyme, 6 h
1-bromo-6-deutero-cyclohexene	*t*BuOK	53	-0.3	THF, 20 h
		80	0.0	Diglyme, 6 h

Both chiral cyclic allene precursors w/ achiral base and achiral cyclic allene precursors w/ chiral base give optically active products

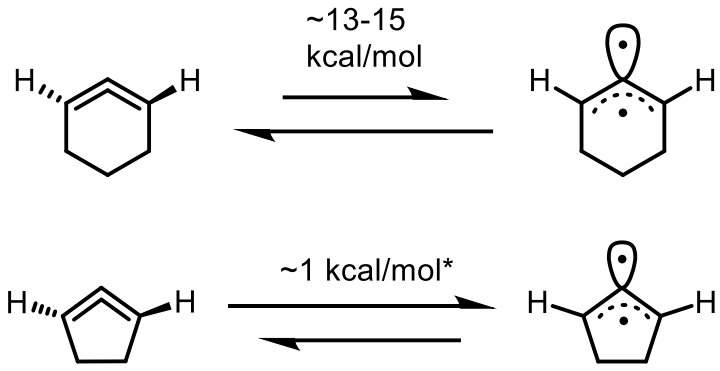
Balci, M.; Jones, W. M. *J. Am. Chem. Soc.* **1981**, *103*, 2874-2876.

Summary of Cyclic Allene Characteristics

Ring size imparts bending of allene bond and pushes H atoms towards planarity

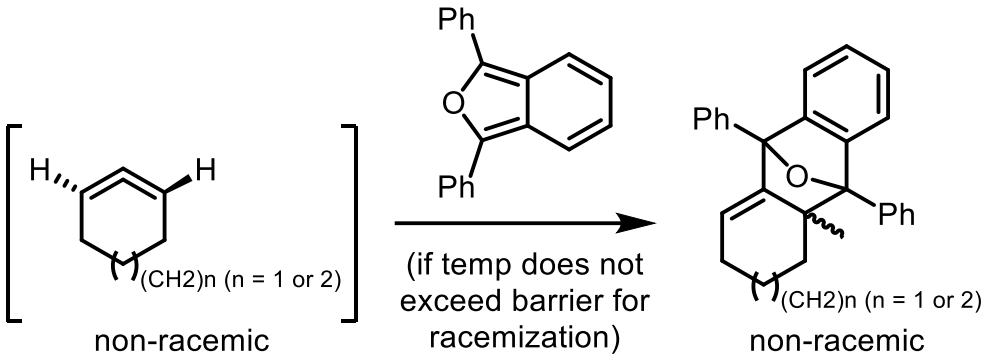


Greater degree of planarity begins to favor excited singlet/triplet states and not chiral cyclic allene



*Authors note calculations are within the range of error to show that the ground singlet state may be favored

Precedence for existence of chiral cyclic allenes is shown by generated in non-racemic form and trapping to form optically active adducts



<u>Other general things to note:</u>

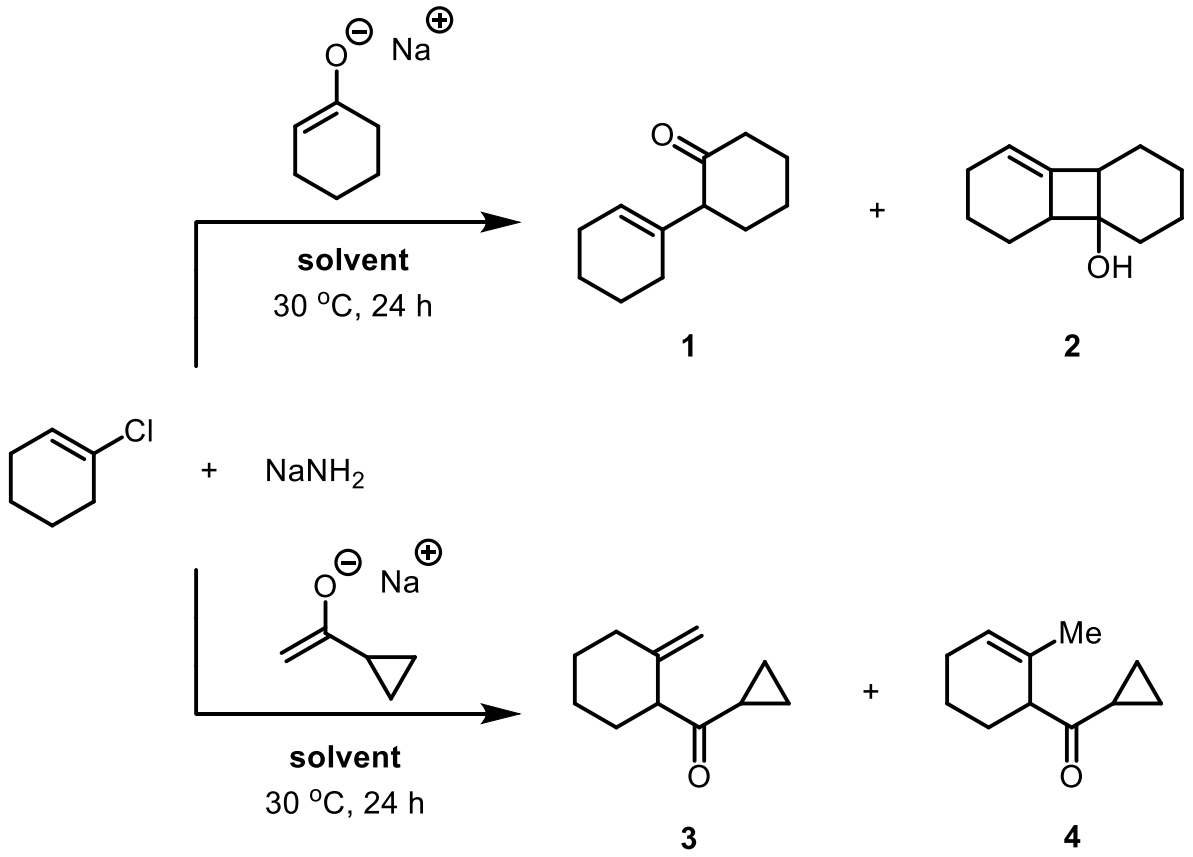
Ring strain for 1,2-cyclo-hepta/hexa/pentadiene are calculated as 15, 20, and 30 kcal/mol, respectively

IR for 1,2-cyclonona/octadiene are reported as 1956 cm^{-1} and 1950 cm^{-1}, respectively

(acyclic allenes usually range 1950-1960 cm^{-1} for asymmetric stretching)

NMR data for 1-*tert*-butyl-1,2-cyclooctadiene: ^{13}C (202.2, 117.7, and 94.4 ppm)

Group Problem



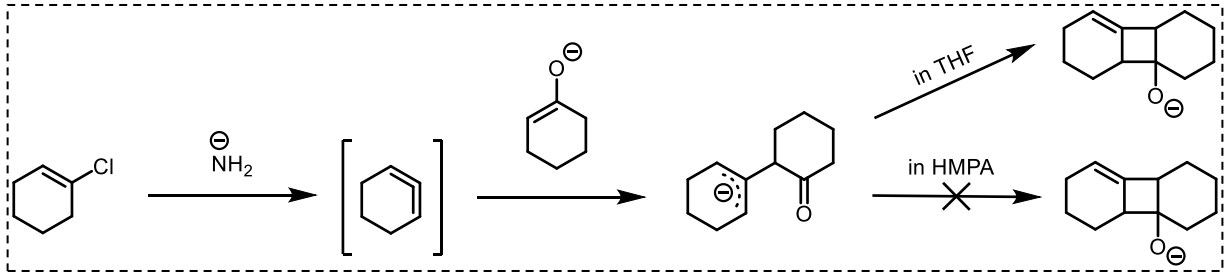
Sole formation of **1** in HMPA
Sole formation of **2** in THF

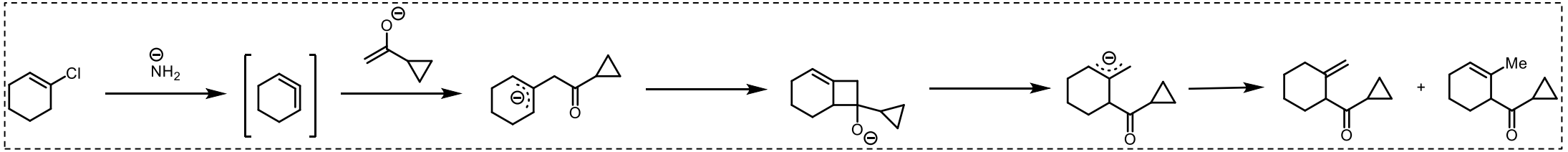
70:30 mixture of 3:4 in THF
No data for HMPA

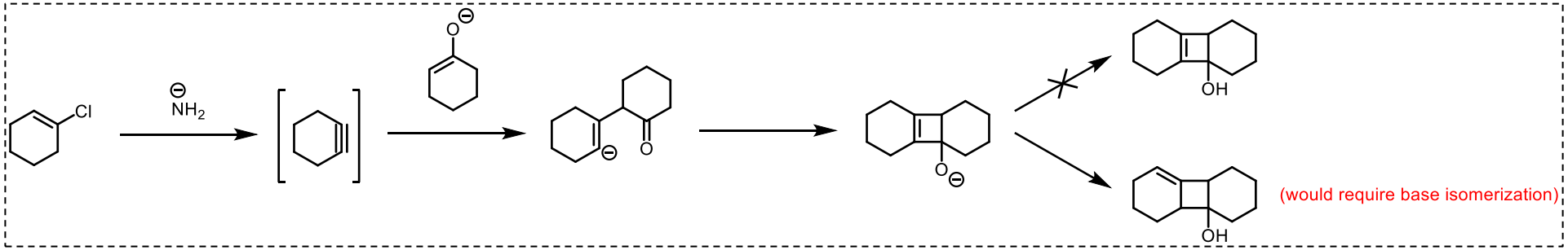
1. Propose a reason for the change in product distribution of **1** and **2** when solvents are changed
2. Propose a mechanism for the formation of **3** and **4** given your reasoning for why **2** forms in THF
3. Do you think the same products would be formed if cyclohexyne formed instead of 1,2-cyclohexadiene?

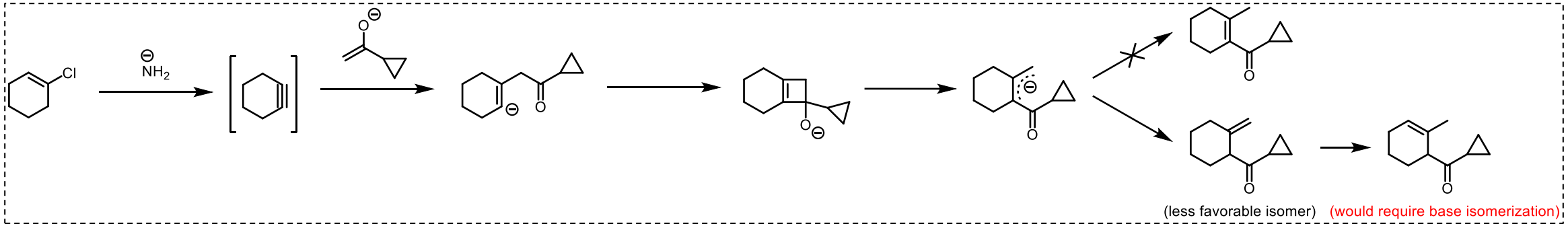
Caubère, P.; Brunet, J. J. *Tetrahedron*, **1972**, *28*, 4835-4845.

Group Problem







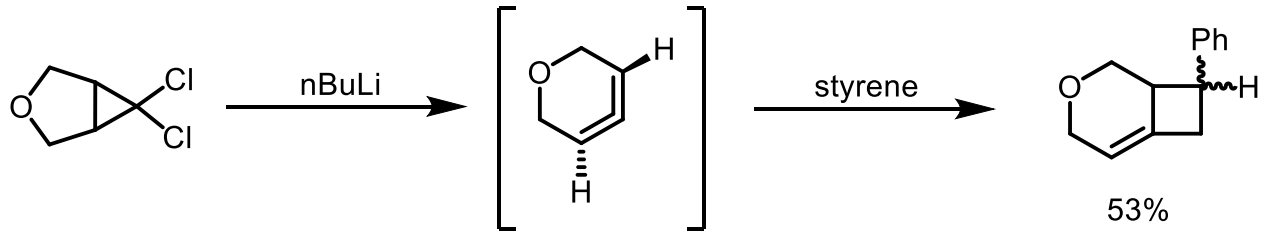


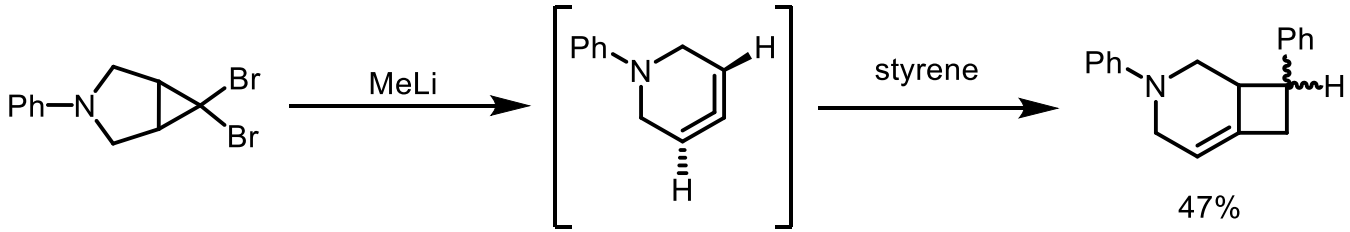
Presentation Overview

- ❑ Defining “strained” cyclic allenes via experimental and computational data
- ❑ Novel approaches for utilizing cyclic allenes
- ❑ Perspective/Summary

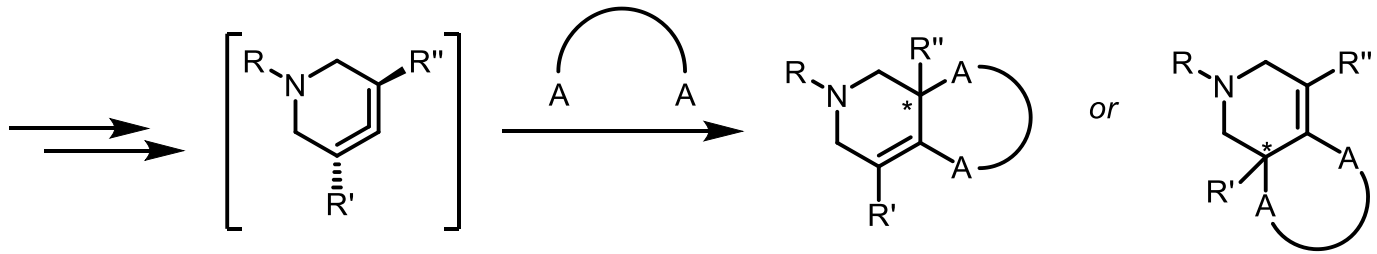
What About Cyclic Allenes Containing Heteroatoms?

Christl (1987-1994):





Garg (2018):



Harsh conditions required for generation and little synthetic utility displayed

Employ milder methods for generating cyclic allene then trap in a regioselective manner to yield sp^3-rich piperidine fused scaffolds

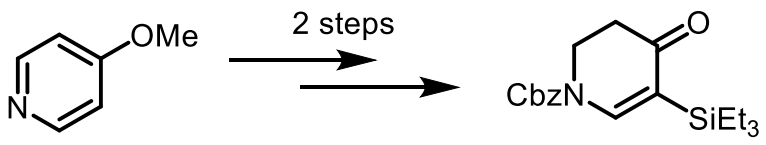
Schreck, M.; Christl, M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 690-692.

Christl *et. al. Chem. Ber.* **1994**, *127*, 1137- 1142.

Garg *et. al.; Nat. Chem.* ***2018***, *10*, 953-960.

Generation and Interception of Strained Azacyclic Allenes

Azacyclic Allene Precursor Synthesis



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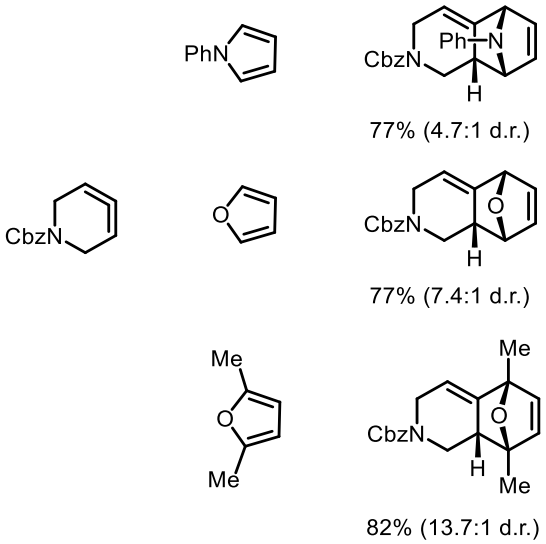
Fluoride-induced elimination of organosilanes to yield strained intermediates has been known, with Guitián et. al. being the first to employ the method for generating 1,2,-cyclic allenes

Garg *et. al.; Nat. Chem.* ***2018***, *10*, 953-960.

Guitián *et. al. Eur. J. Org. Chem.* **2009**, 5519–5524.

Scope of Diels-Alder Cycloaddition with Azacyclic Allenes



Modest diastereoselectivity for the endo product when using non-substituted azacyclic allenes

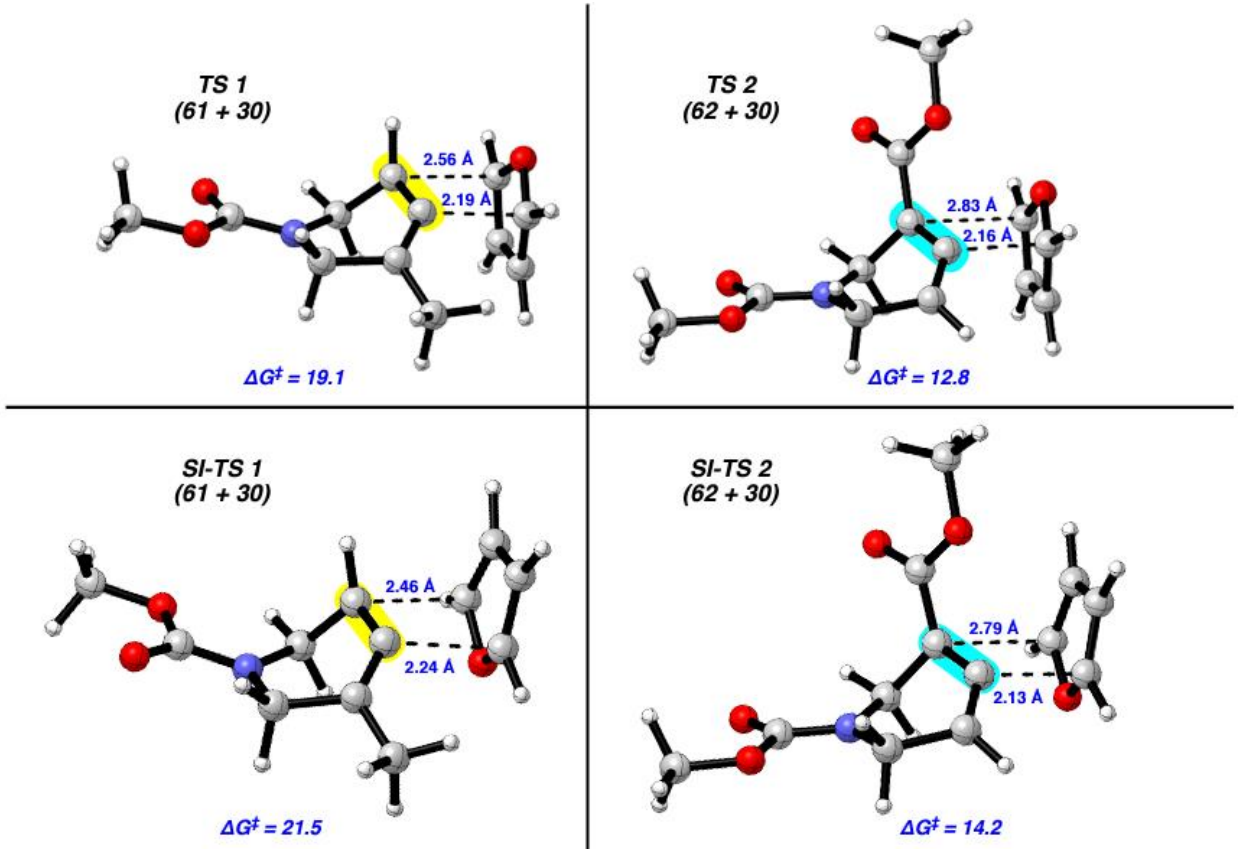
Diastereoselectivity for the endo product increases when using substituted azacyclic allenes

Highly regioselective and diastereoselective reaction when using non-C_2 symmetric azacyclic allene

Garg *et. al.; Nat. Chem.* ***2018***, *10*, 953-960.

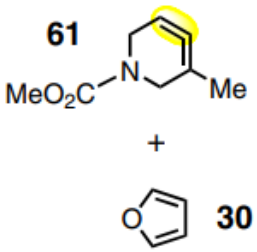
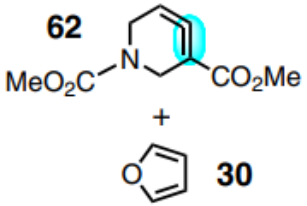
Origin of Regio- and Diastereoselectivity

Evidence for Endo Selectivity



Highly asynchronous concerted transition state with initial binding to allene central carbon due to its large MO coefficient

Evidence for Regioselectivity

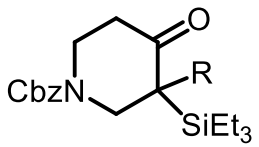
Diels–Alder partners	ΔG and ΔE (major regioisomer)	ΔG and ΔE (minor regioisomer)	$\Delta\Delta G$ and $\Delta\Delta E$
 **61** + **30**	TS1		
	$\Delta G^{\ddagger} = 19.1$	$\Delta G^{\ddagger} = 20.6$	$\Delta\Delta G^{\ddagger} = -1.5$
	$\Delta E^{\ddagger} = 4.6$	$\Delta E^{\ddagger} = 6.2$	$\Delta\Delta E^{\ddagger} = -1.6$
	$\Delta E_{dist}^{\ddagger} = 10.9$	$\Delta E_{dist}^{\ddagger} = 11.2$	$\Delta\Delta E_{dist}^{\ddagger} = -0.3$
	$\Delta E_{int}^{\ddagger} = -6.3$	$\Delta E_{int}^{\ddagger} = -5.0$	$\Delta\Delta E_{int}^{\ddagger} = -1.3$
 **62** + **30**	TS2		
	$\Delta G^{\ddagger} = 12.8$	$\Delta G^{\ddagger} = 17.7$	$\Delta\Delta G^{\ddagger} = -4.9$
	$\Delta E^{\ddagger} = -1.6$	$\Delta E^{\ddagger} = 3.1$	$\Delta\Delta E^{\ddagger} = -4.7$
	$\Delta E_{dist}^{\ddagger} = 8.2$	$\Delta E_{dist}^{\ddagger} = 7.5$	$\Delta\Delta E_{dist}^{\ddagger} = 0.7$
	$\Delta E_{int}^{\ddagger} = -9.8$	$\Delta E_{int}^{\ddagger} = -4.4$	$\Delta\Delta E_{int}^{\ddagger} = -5.4$

DI/AS analysis shows greater stabilization for $\Delta E_{int}^{\ddagger}$ of major regioisomer due to greater concentration of the LUMO on double bond distal to EDG (e.g., Me) or proximal to EWG (e.g., CO_2Me)

Garg *et. al.; Nat. Chem.* ***2018***, *10*, 953-960.

Enantioselective Diels-Alder Reaction of Azacyclic Allene

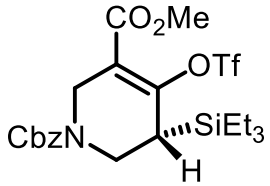
Employing Non-Racemic Azacyclic Allene Precursors



(R = H or Me)

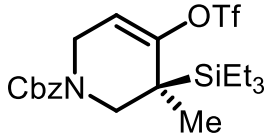
gram-scale purification by chiral SFC

remainder of allene precursor synthesis

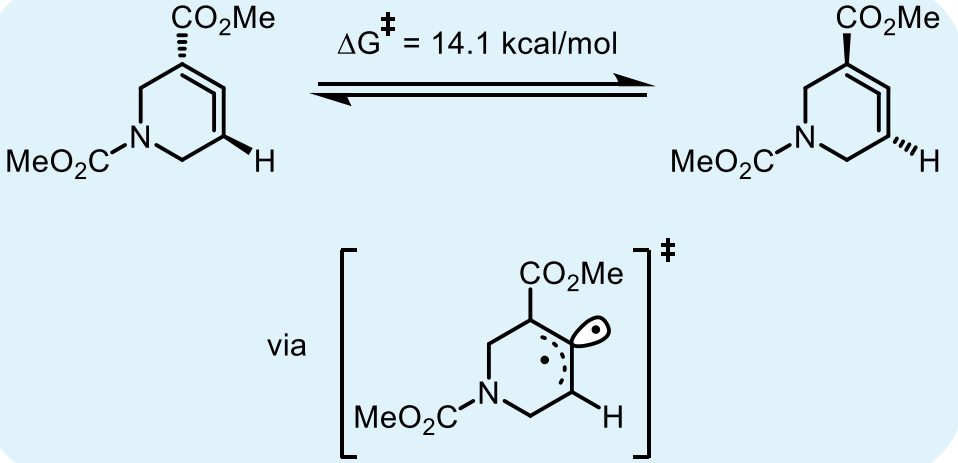


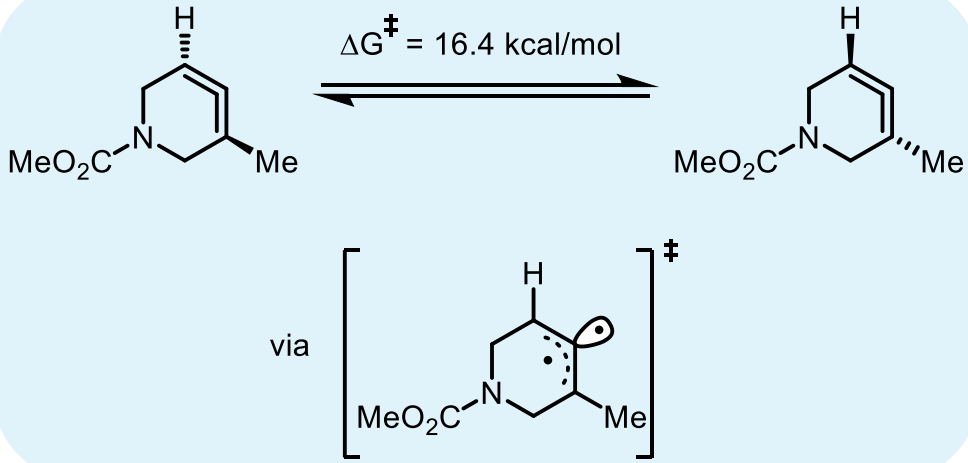
(+)-5a (87% ee)

and



(+)-3b (99% ee)

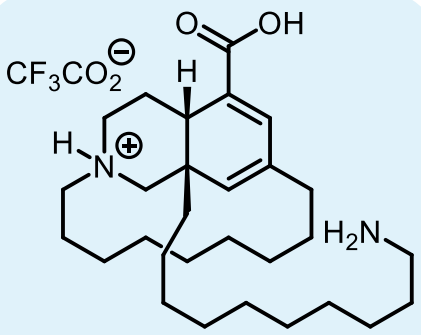




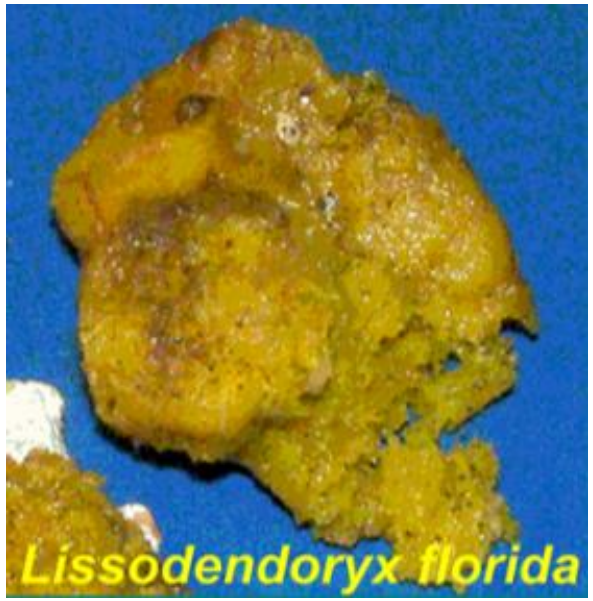
Garg *et. al.; Nat. Chem.* ***2018***, *10*, 953-960.

Application of Strained Cyclic Allenes in Total Synthesis

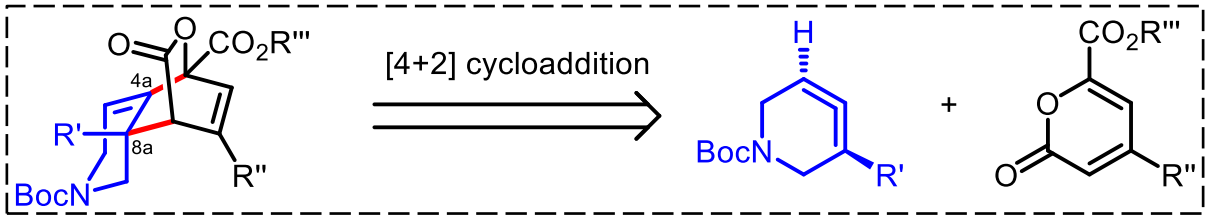
Concise Synthesis of Manzamine Alkaloid Lissodendoric acid A



Lissodendoric acid A



- Member of the family of marine natural products known as manzamine alkaloids
- Isolated in 2017 from the marine sponge *Lissodendoryx florida*
- Shown to "*reduce reactive oxygen species (ROS) in a Parkinson's disease model consisting of Neuro2a cells treated with 6-hydroxydopamine (~50% reduction in ROS levels at concentrations of 0.1 and 10mM)*" – Stonik *et. al.*



Rapidly assembles azadecalin core while simultaneously incorporates the C8a quaternary center

Masks 1,3-diene as the [2.2.2]-bicyclic system and can be revealed upon thermal expulsion of CO_2

Stonik *et. al. Org. Lett.* **2017**, *19*, 5320–5323.

Garg *et. al.; Science* **2023**, *379*, 261–265.

Optimization of Diels-Alder Reaction

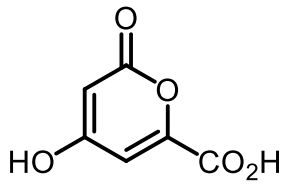
Combination of pyrone and alkyl substituted cyclic allenes would be an Inverse-Demand Diels Alder reaction, swapping regioselectivity observed from before

*Difficulty generating **1** in high ee without the use of chiral separation techniques required evaluation of other chiral cyclic allene precursors*

*Low yield using **9** but modest enantioselectivity permitted its use in the forward synthesis*

Forward Synthesis of Lissodendoric acid A via Cycloaddition of Azacyclic Allene

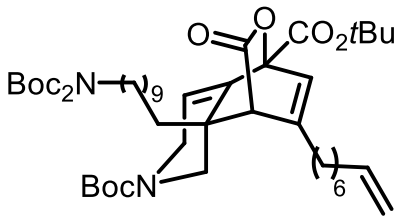
A



1

Garg *et. al.; Science* **2023**, *379*, 261–265.

Forward Synthesis of Lissodendoric acid A via Cycloaddition of Azacyclic Allene

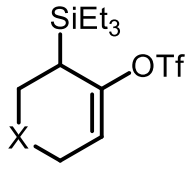


7

12 steps LLS; 0.8% overall yield

Garg *et. al.; Science* **2023**, *379*, 261–265.

Capturing Chiral Cyclic Allene Intermediates via Asymmetric Nickel Catalysis



1
racemic

*Dynamic kinetic resolution of racemic silyl triflate **1** into enantioenriched polycyclic products*

Very few examples of catalytic asymmetric trapping of strained cyclic intermediates

1. *Catalyst must be compatible with conditions for generating strained intermediates*
2. *Generate significant quantities of the active catalytic species to react with the fleeting allene intermediate*
3. *Be amenable to the development of an asymmetric variant*

Garg *et. al.*; *Nature* **2020**, *586*, 242-247.

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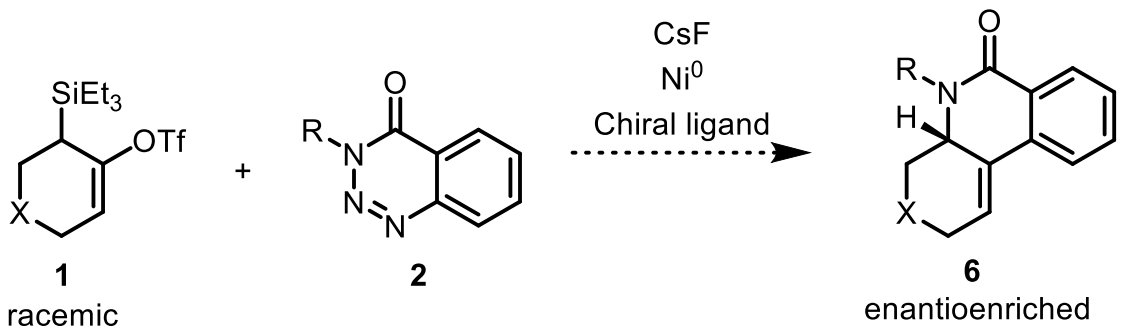

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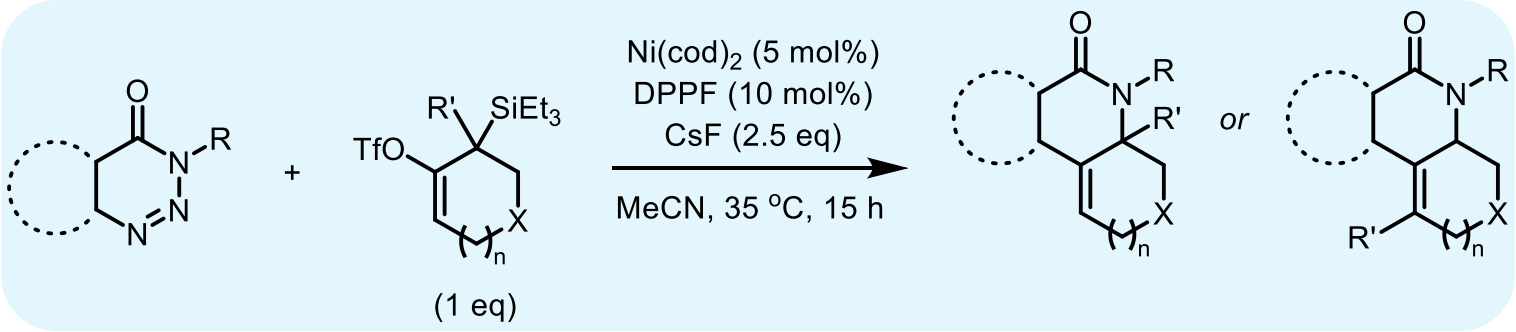
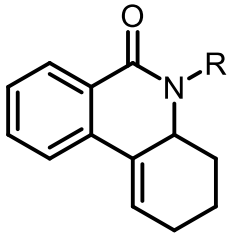
Garg *et. al.*; *Nature* **2020**, *586*, 242-247.

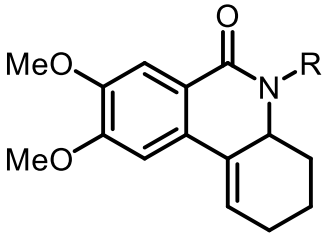
Initial Survey of Reactivity for Racemic Transformation



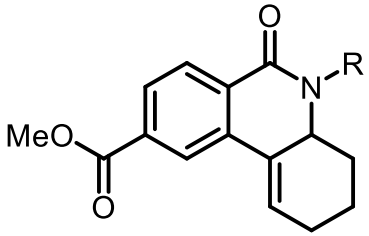
Benzotriazinone scope:



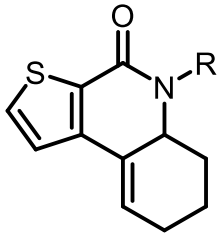
R = *p*-tol, 91%
R = Me, 83%
R = Bn, 95%



84%

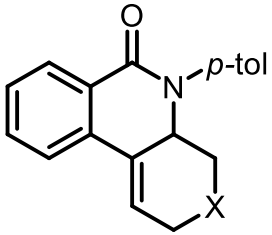


85%

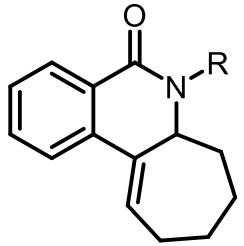


73%

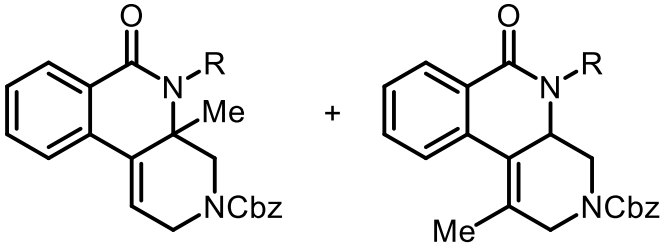
Strained cyclic allene scope:



X = O, 99%
X = *N*-Cbz, 88%
X = *N*-Boc, 92%



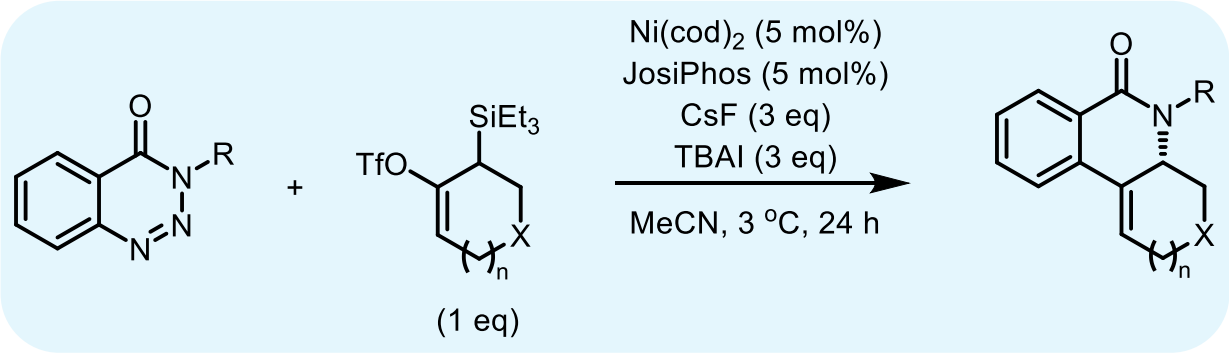
64%

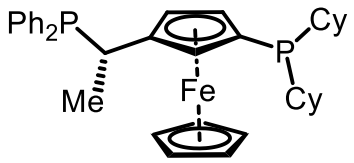


89%
3.8:1

Garg *et. al.*; *Nature* **2020**, *586*, 242-247.

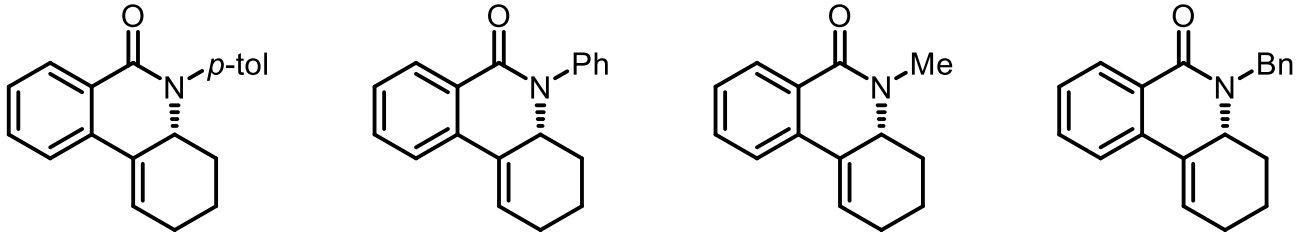
Asymmetric Denitrogenative Annulation of Benzotriazinones





JosiPhos

Benzotriazinone scope:



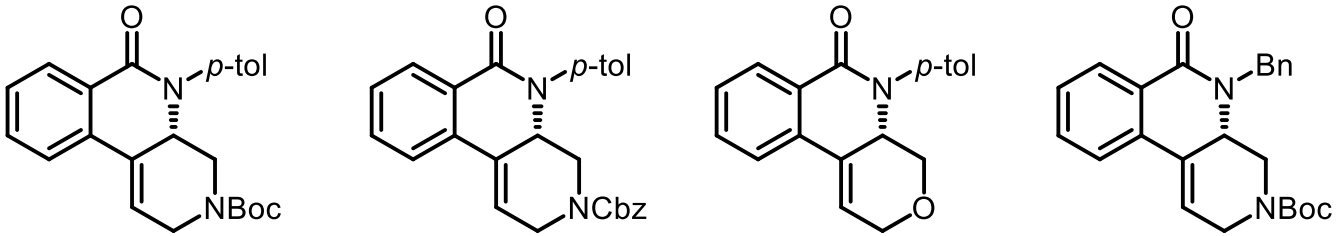
85%
94% ee

81%
92% ee

78%
88% ee

73%
81% ee

Strained cyclic allene scope:



70%
81% ee

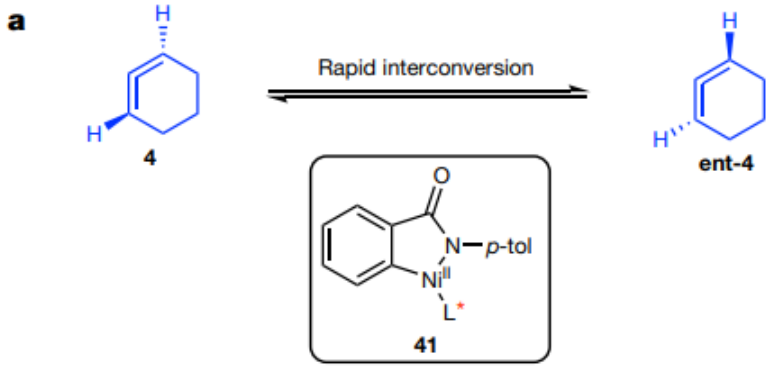
63%
81% ee

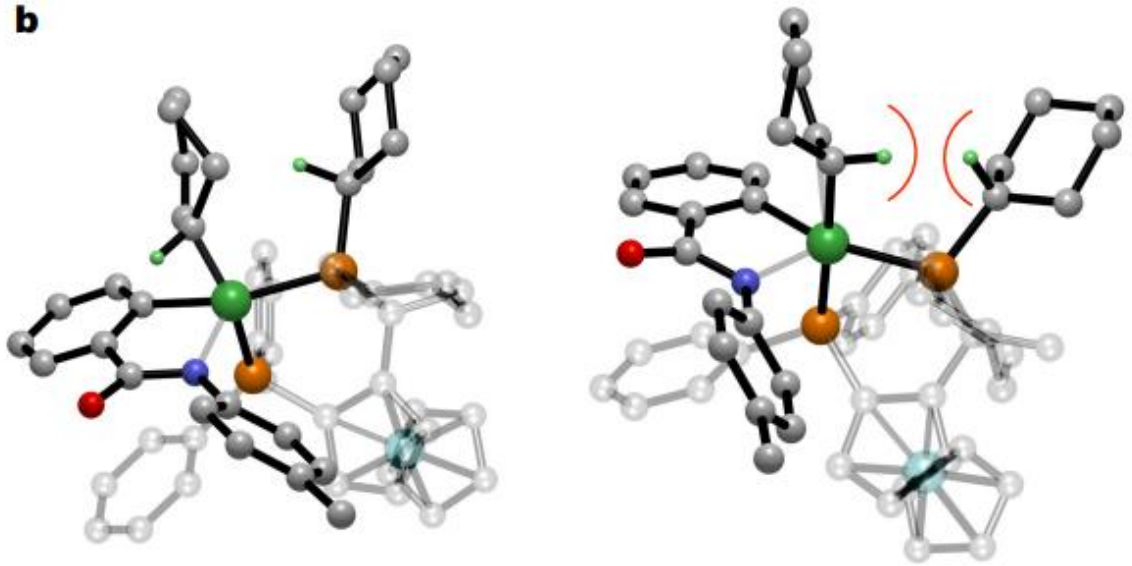
84%
81% ee

66%
84% ee

Garg *et. al.*; *Nature* **2020**, *586*, 242-247.

Computational Study for Origin of Enantioselectivity





TS-1
$\Delta E_{dist,\ allene}^{\ddagger} = 7.9$
$\Delta E_{dist,\ Ni}^{\ddagger} = 33.2$
$\Delta E_{int}^{\ddagger} = -56.6$

$\Delta\Delta E_{dist,\ allene}^{\ddagger} = -5.3$
$\Delta\Delta E_{dist,\ Ni}^{\ddagger} = 1.8$
$\Delta\Delta E_{int}^{\ddagger} = -4.7$

TS-1a
$\Delta E_{dist,\ allene}^{\ddagger} = 13.2$
$\Delta E_{dist,\ Ni}^{\ddagger} = 31.4$
$\Delta E_{int}^{\ddagger} = -51.9$

Computational study raises two questions:

1. **Why is the predicted e.e. significantly higher than the experimentally observed e.e.?**
2. **Why is the obtained product the enantiomer of that predicted from the favored transition state?**

Garg *et. al.*; *Nature* **2020**, *586*, 242-247.

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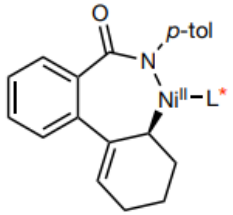
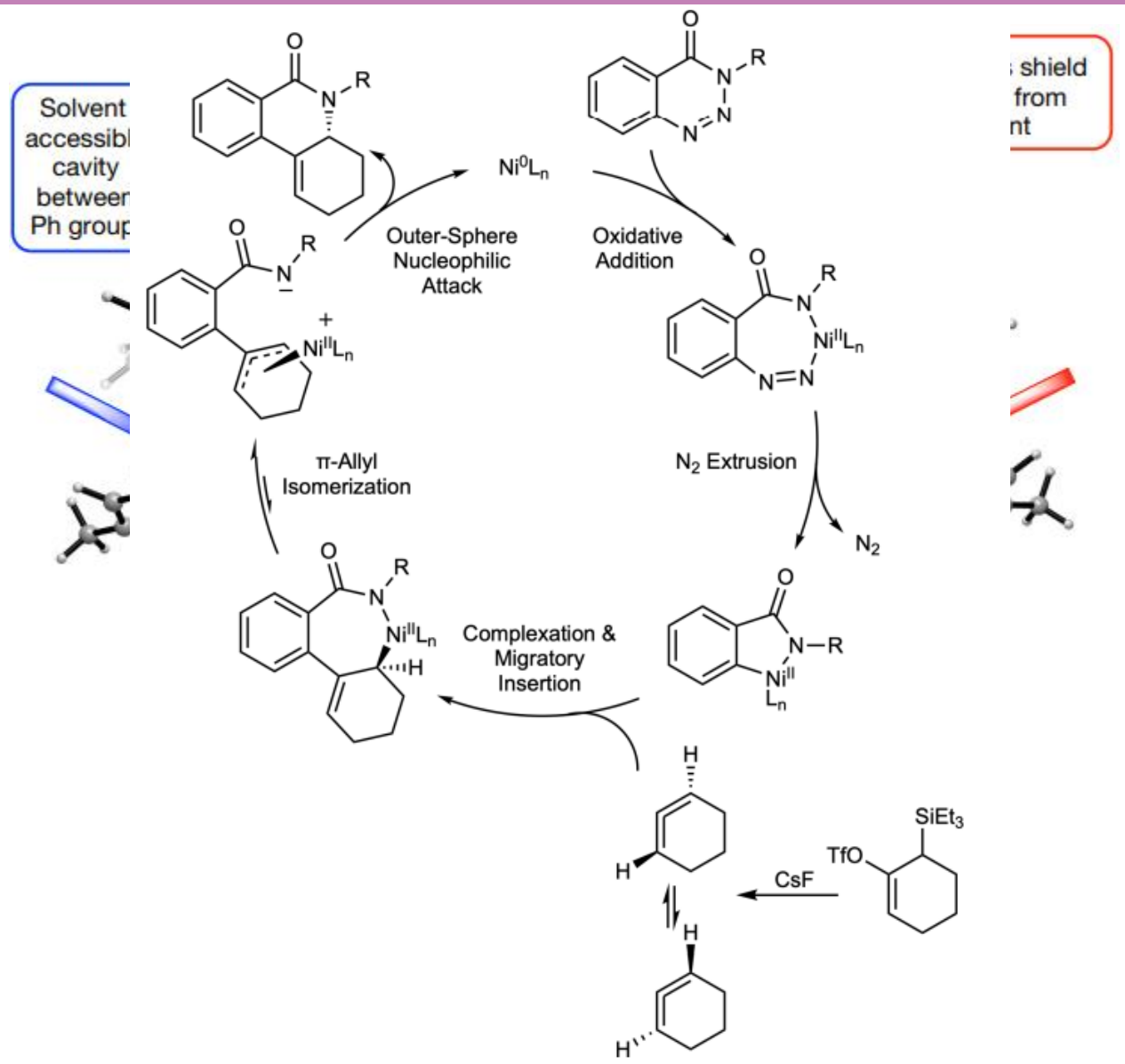


42 (0.0)



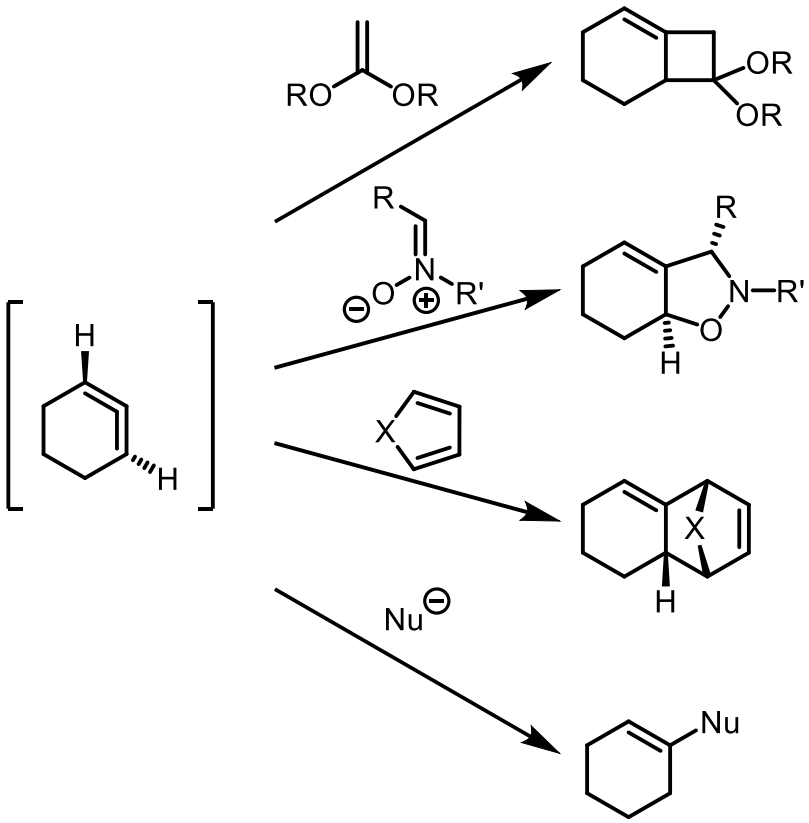
Garg *et. al.*; *Nature* **2020**, *586*, 242-247.

Presentation Overview

- ❑ Defining “strained” cyclic allenes via experimental and computational data
- ❑ Novel approaches for utilizing cyclic allenes
- ❑ Perspective/Summary

Perspective/Summary

- **General reactivity of strained cyclic allenes is analogous to that of other strained cyclic intermediates such as benzyne or cyclohexyne**
  - Able to undergo [2+2], [3+2], and [4+2] cycloadditions, along with other general captures of nucleophiles to yield vinyl functionalized products



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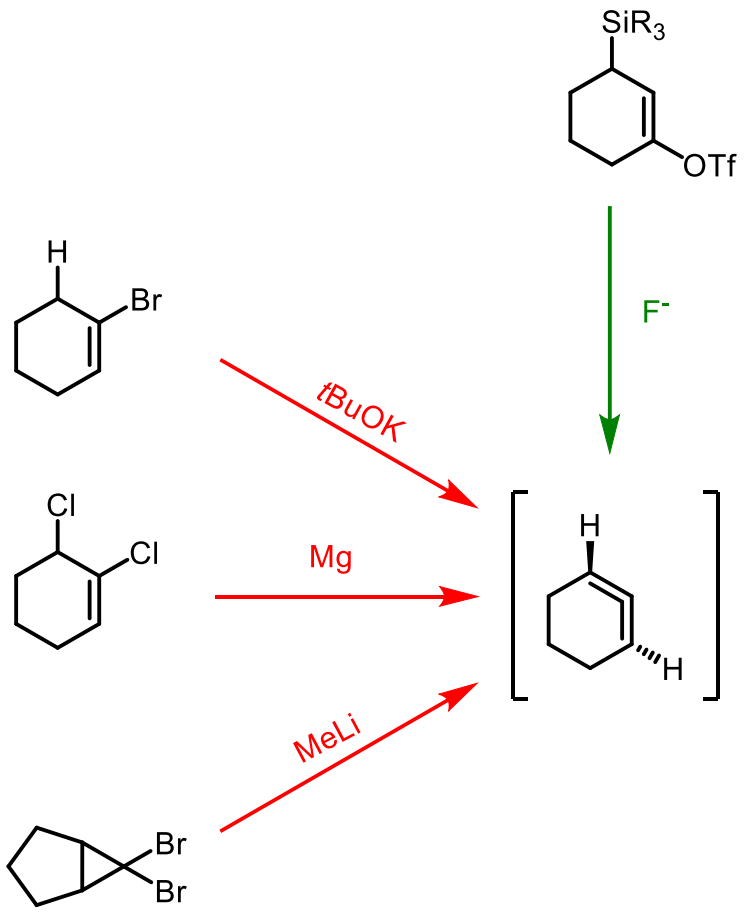
- **Initial methods to generate 1,2-cyclic allenes required harsh conditions but can now be generated mildly at room temperature via easily synthesized precursors**
  - Previous requirements of organolithiums or other strong bases limited the application of 1,2-cyclic allenes, but the implementation of milder methods for generation should expand the applications (as demonstrated by Garg and coworkers)



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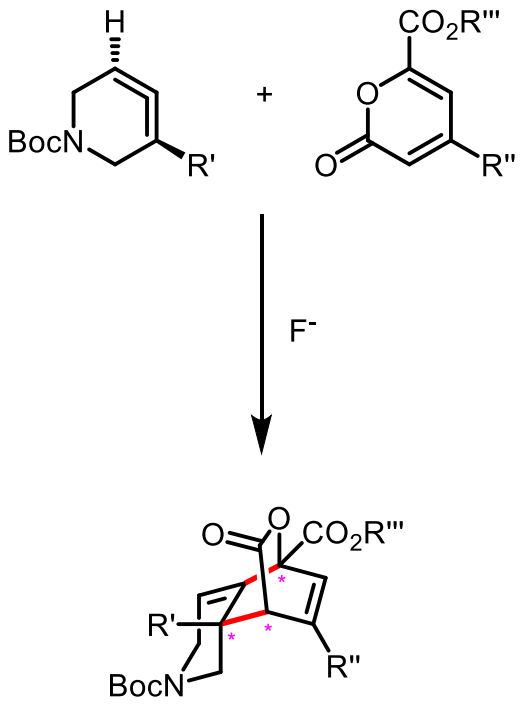
  - Previous requirements of organolithiums or other strong bases limited the application of 1,2-cyclic allenes, but the implementation of milder methods for generation should expand the applications (as demonstrated by Garg and coworkers)
- **May never see the same applicability as benzyne intermediates, but offers benefits that are not able to be achieved through cyclic alkyne chemistry**
  - Inherent chirality in molecule can be leveraged to form up to three sp^3 stereocenters in one step



Useful Reviews

Chem. Rev. **1989**, *89*, 1111–1124

Strained Cyclic Cumulenes

RICHARD P. JOHNSON

Chem. Rev. **1989**, *89*, 1111-1124

Leveraging Fleeting Strained Intermediates to Access Complex Scaffolds

Sarah M. Anthony, Laura G. Wonilowicz,[†] Matthew S. McVeigh,[†] and Neil K. Garg*

JACS Au **2021**, *1*, 897–912

6

Cyclic Allenes Up to Seven-Membered Rings

Manfred Christl

Christl, M. Cyclic Allenes Up to Seven-Membered Rings. Modern Allene Chemistry; Krause, N., Hashmi, A. S. K.; Wiley-VCH Verlag GmbH & Co., 2004; Vol.1, pp 243–357

Questions?