Strain-promoted Reactions of Cyclohexadiene & Cyclohexatriene

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FUDAN UNIV 2023

REPORT

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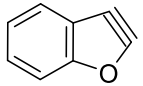
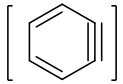
Introduction

Milestones in strained cyclic intermediate chemistry

- high reactivities
- short lifetimes

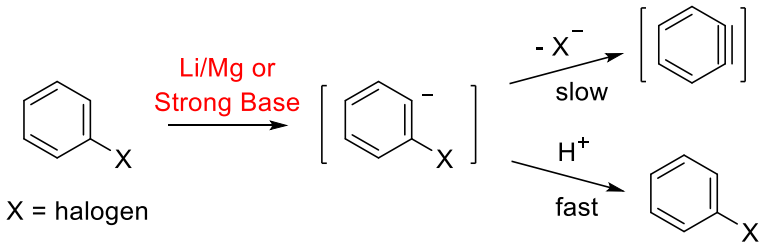
Stoermer & Kahlert	Roberts & Wittig	Roberts	Wittig	Johnson
	validated the intermediacy of benzyne			
 proposed		 cyclohexyne	 cyclohexadiene	 cyclohexatriene
1902	1953	1957	1966	1990

1) R. Stoermer, B. Kahlert, *Ber. Dtsch. Chem. Ges.* **1902**, 35, 1633–1640; 2) J. D. Roberts, *J. Am. Chem. Soc*. **1953**, 75, 3290−3291; 3) G. Wittig, *Angew. Chem*. **1955**, 67, 348; 4) F. Scardiglia, & J. D. Roberts, *Tetrahedron* **1957**, 1, 343−344; 5) G. Wittig, & P. Fritze, *Angew. Chem., Int. Ed. Engl*. **1966**, 5, 846; 6) W. C. Shakespeare, & R. P. Johnson, *J. Am. Chem. Soc.,* **1990**, 112, 8578–8579.

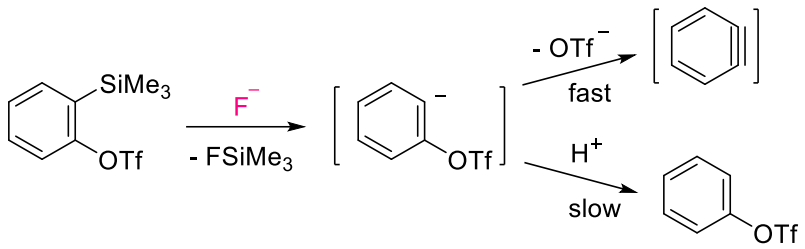
A convenient route to benzyne

Triflate Group (OTf) : Excellent Leaving Group

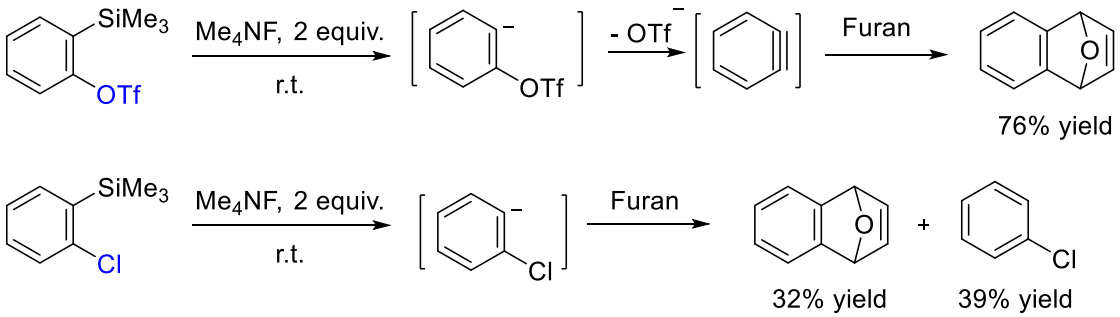
Before 1983: deprotonation of Aromatic Halogen Compounds



Kobayashi, 1983



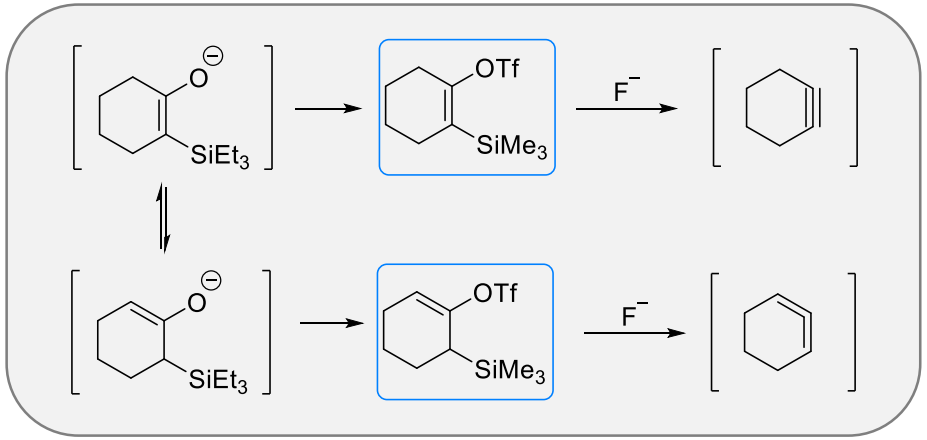
Comparison of Reactivity of Triflate with Chloride



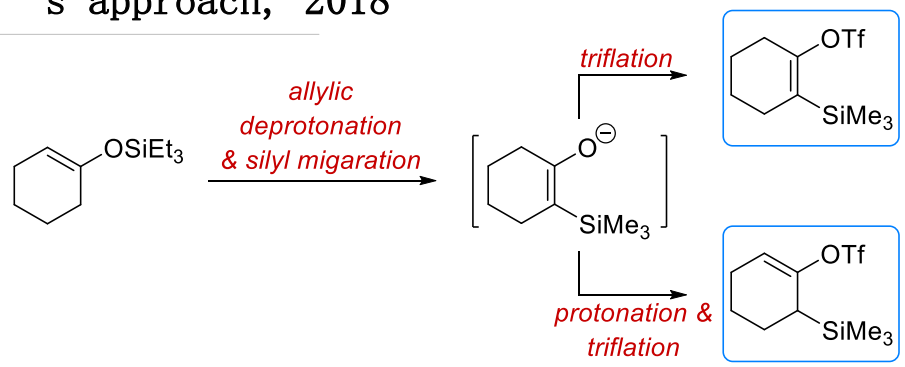
- *tolerate base-sensitive functional groups*
- *under mild conditions*

H. Kobayashi, *Chem. Lett.* **1983**, 12, 1211−1214.

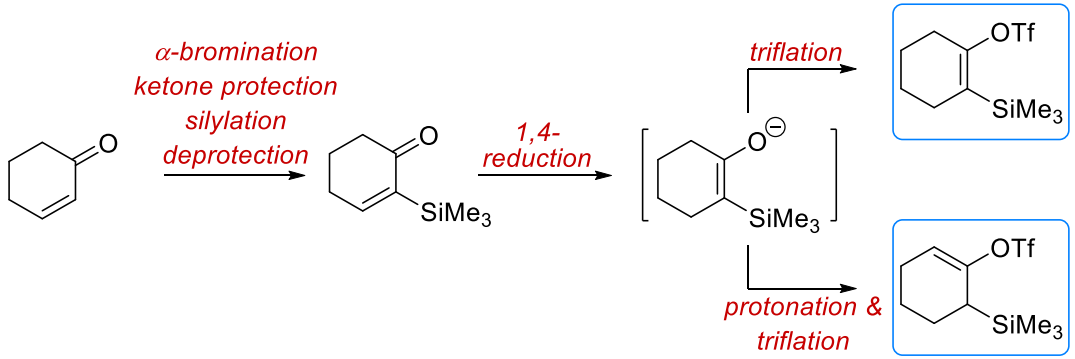
Synthetic approaches to precursors



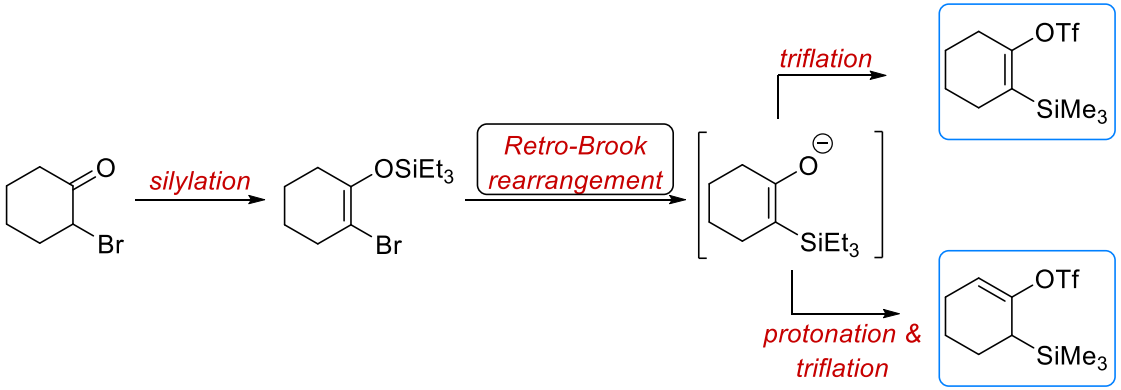
Mori' s approach, 2018



Guitia´n' s approach, 2009

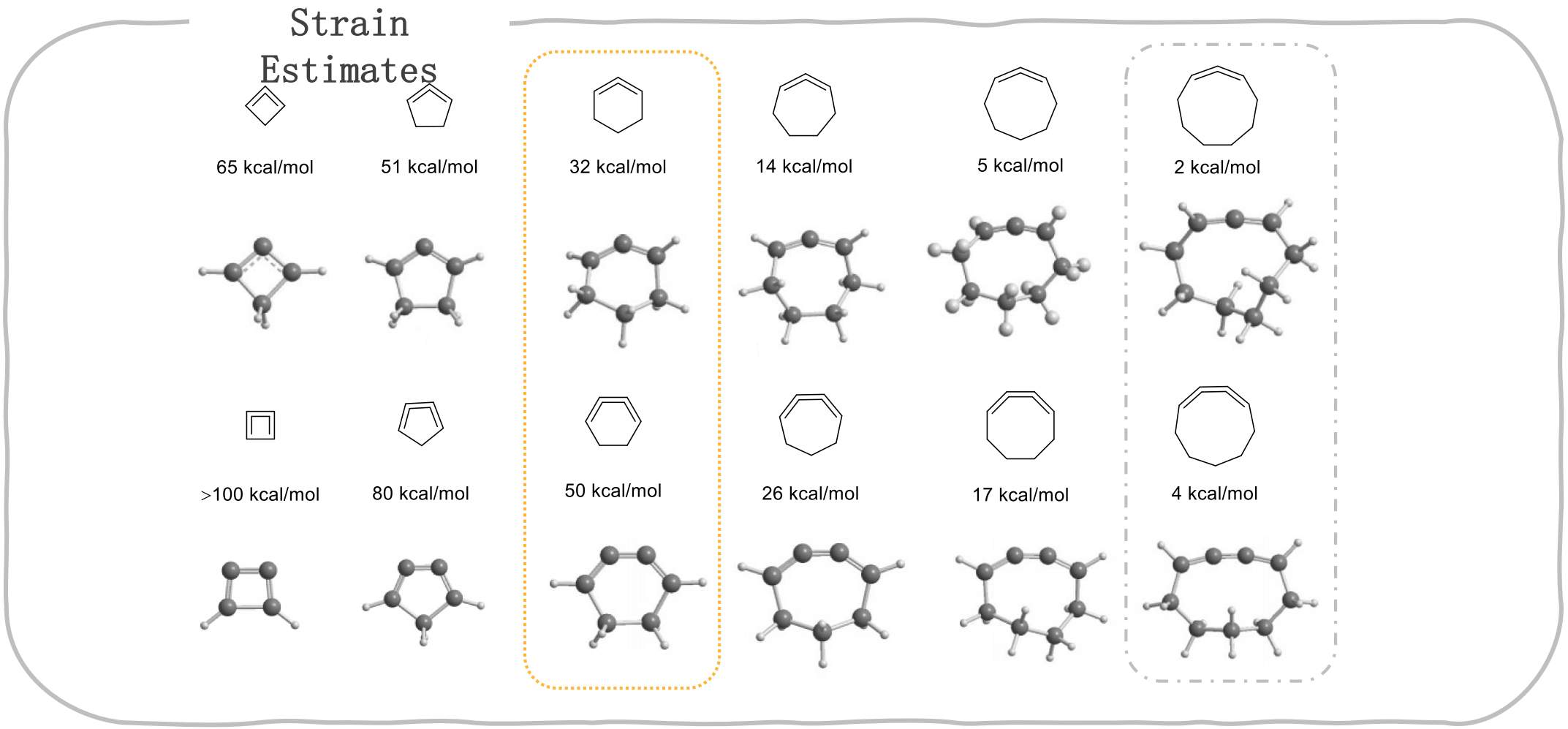


Garg' s approach, 2019



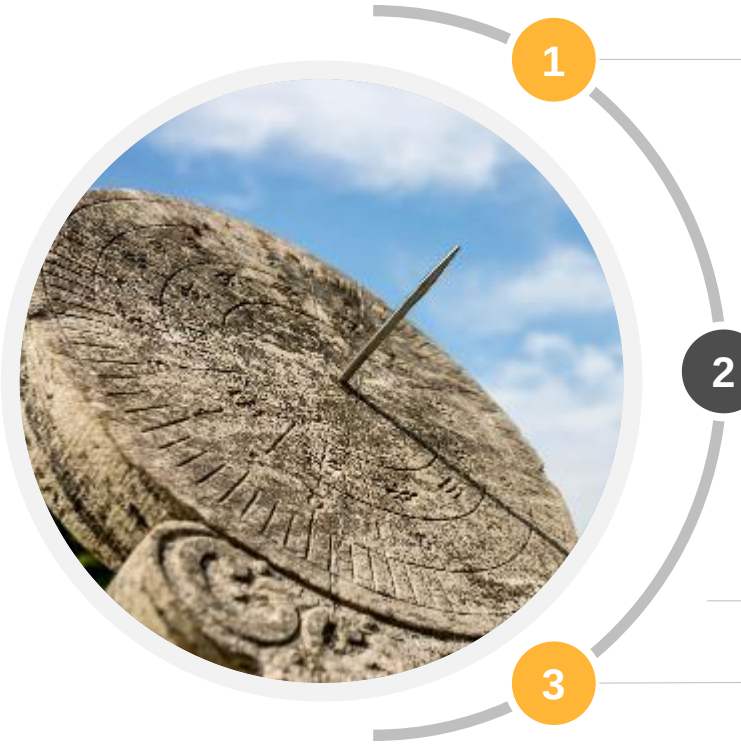
1) E. Guitián, *Eur. J. Org. Chem*. **2009**, 5519−5524; 2) A. Mori, *Eur. J. Org. Chem*. **2018**, 3343−3347; 3) Neil K. Garg, *J. Org. Chem.* **2019**, 84, 3652−3655.

Small-Ring Cyclic Allenes and Butatrienes



R. P. Johnson, *J. Org. Chem*. **2006**, 71, 5708-5714

Overview of the current study



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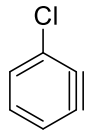
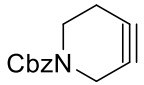


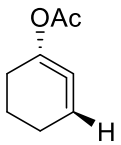
Precursor to
isopyrazam (fungicide)



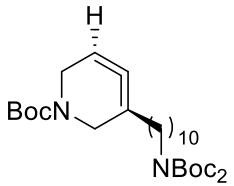
Precursor to
stimulus-responsive materials

About 4,600 reports

2



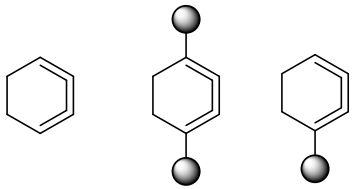
Precursor to
sp^3-rich heterocycles



Precursor to
lissodendoric acid A

About 160 reports

3



Few examples

Neil K. Garg, *Nature*, **2023**, 618, 748-754.

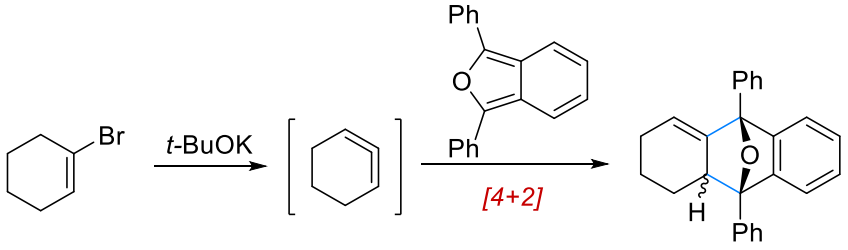
/02

Cyclohexadiene

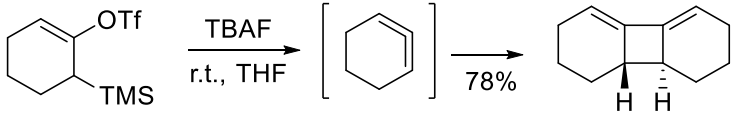
1,2-Cyclohexadiene

1966, Wittig:

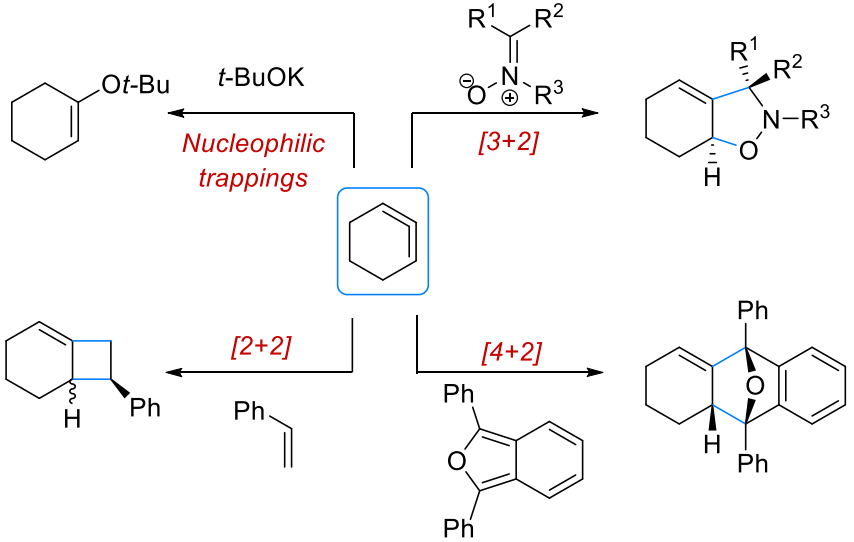
validated the intermediacy of 1,2-Cyclohexadiene



Rapid dimerization



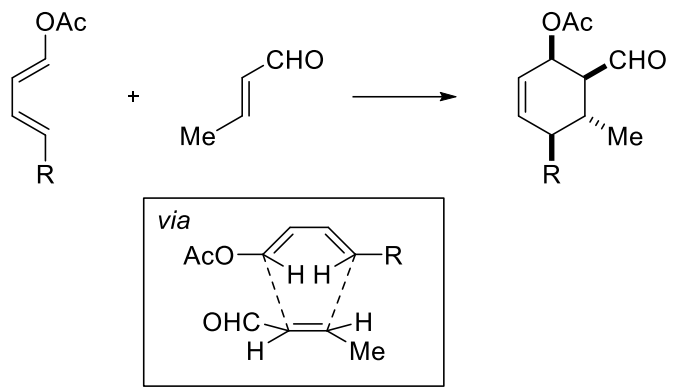
Well studied: Trapping reactions



1) G. Wittig, & P. Fritze, *Angew. Chem., Int. Ed. Engl.* **1966**, 5, 846.2) Neil K. Garg, *J. Am. Chem. Soc.* **2021**, 143, 9338−9342.

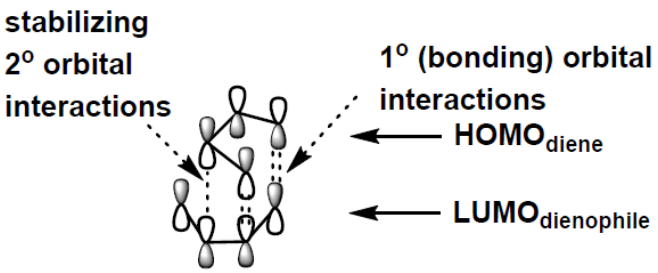
Selectivity in Diels-Alder Reactions

Factors influencing *endo* selectivity of the Diels-Alder reaction

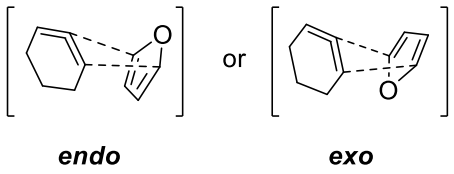


Endo transition state is favored by

- stabilizing secondary orbital interactions
- increase pressure of reaction
- the use of Lewis acid catalysis



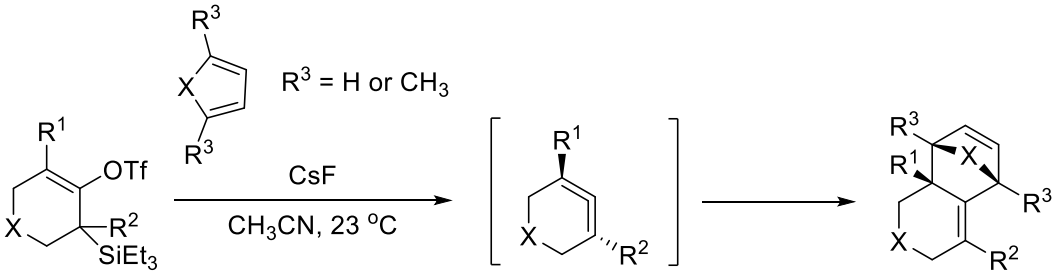
endo and *exo* transition structures

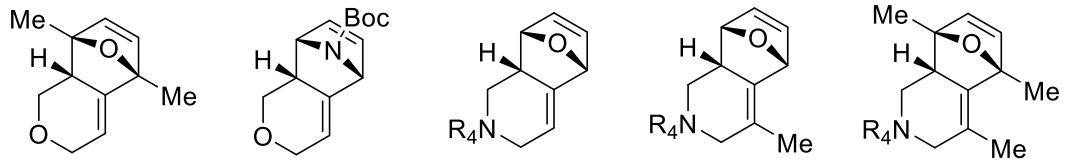


F. Liu, Neil K. Garg, K. N. Houk, *Angew. Chem. Int. Ed.* **2021**, 60, 14989–14997.

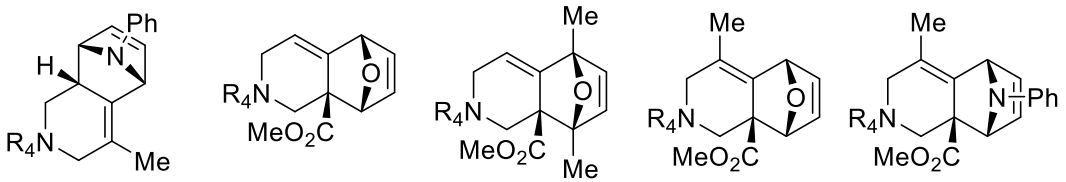
Selectivity in Diels-Alder Reactions

Examples of highly endo selective Diels-Alder reactions





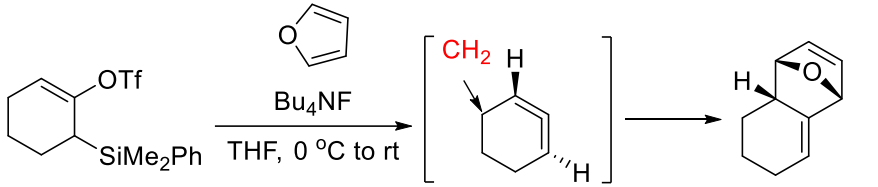
86% yield	74% yield	77% yield	73% yield	56% yield
9.2:1 endo:exo	*6.2:1 endo:exo*	*7.4:1 endo:exo*	*12.8:1 endo:exo*	*>20:1 endo:exo*



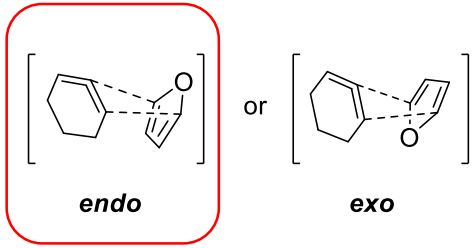
73% yield	74% yield	95% yield	93% yield	95% yield
>20:1 endo:exo	*>9:1 endo:exo*	*>20:1 endo:exo*	*>20:1 endo:exo*	*>20:1 endo:exo*

R^4 = carboxybenzyl.

endo and *exo* transition structures



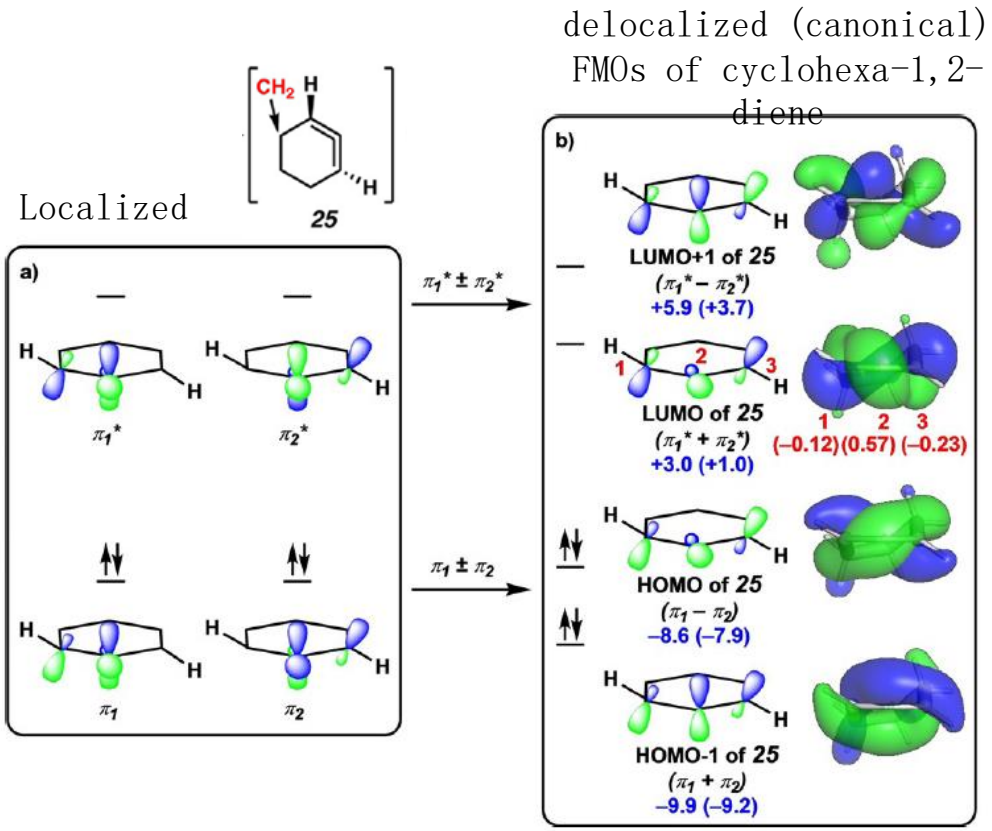
80% yield
11:1 endo:exo



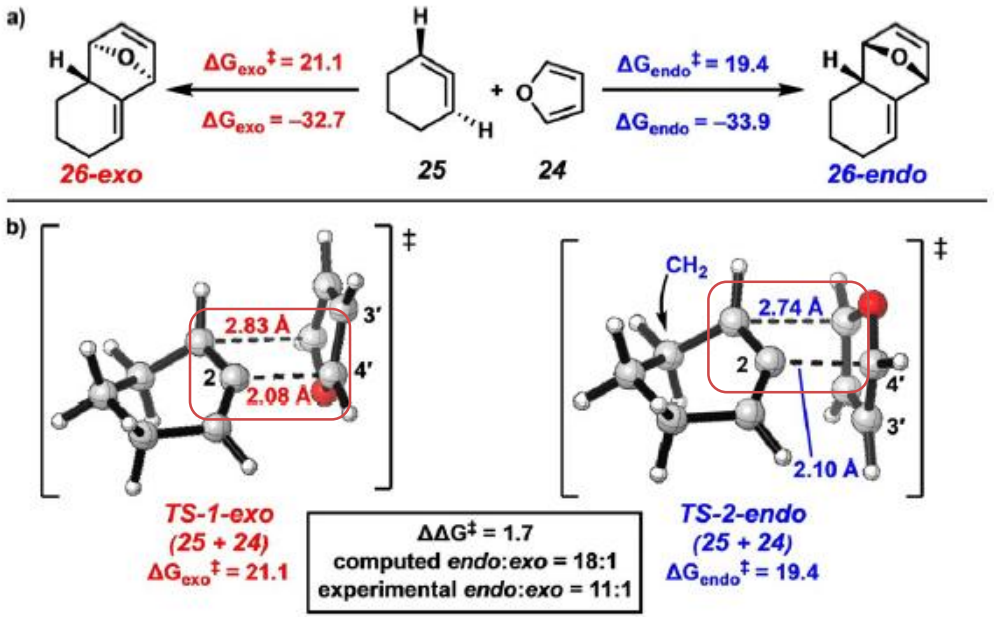
Why the CH_2 group invariably is *endo* in the favored transition state?

F. Liu, Neil K. Garg, K. N. Houk, *Angew. Chem. Int. Ed.* **2021**, 60, 14989–14997.

Endo Selectivity in Diels－Alder Reactions



The LUMO of cyclohexa-1,2-dien has a larger MO coefficient at C2 and DA reactions with electron-rich dienes are expected to occur with preferential bonding at C2 of cyclohexa-1,2-diene.



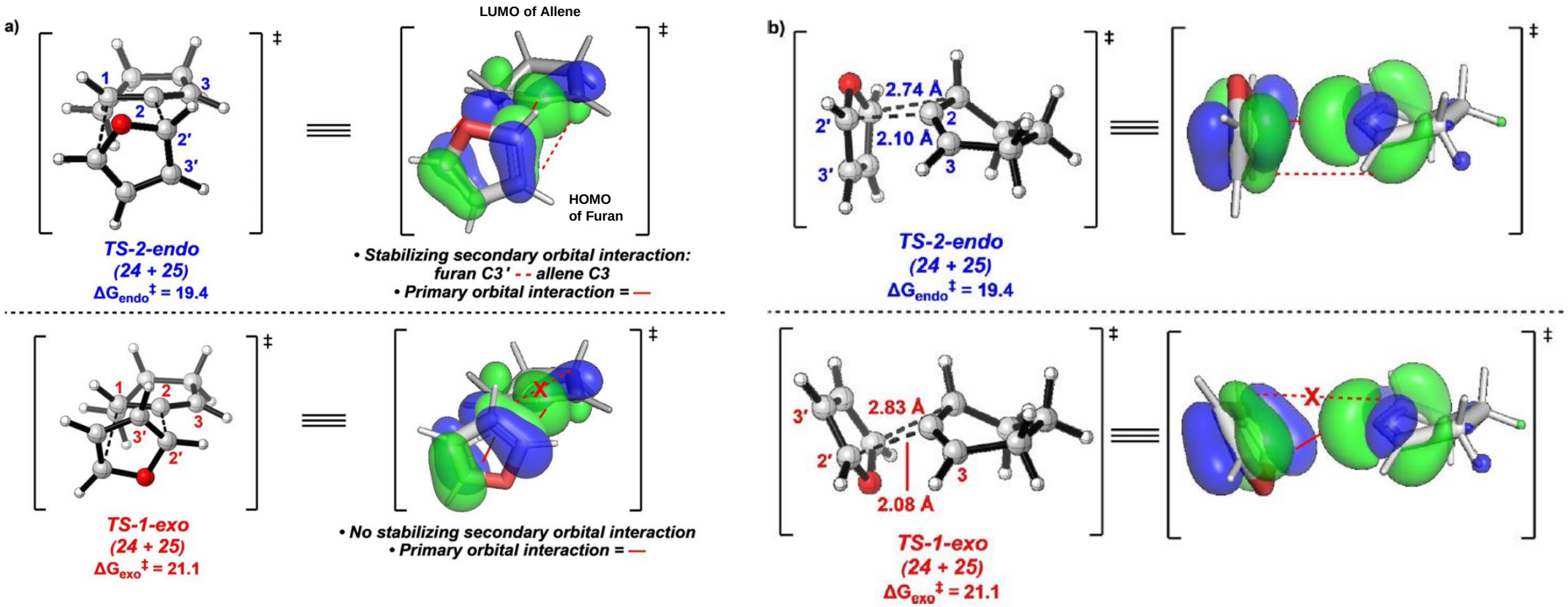
a) Calculated energy barriers for *exo* and *endo* Diels－Alder reaction of cyclohexa-1,2-diene (25) and furan (24).

b) *Exo* and *endo* transition state geometries: orbital overlap of the HOMO of furan with the p orbital on C2 of allene is maximized in the endo

F. Liu, Neil K. Garg, K. N. Houk, *Angew. Chem. Int. Ed.* **2021**, 60, 14989–14997.

Endo Selectivity in Diels－Alder Reactions

Allene LUMO/Furan HOMO interactions in the *endo* and *exo* transition states

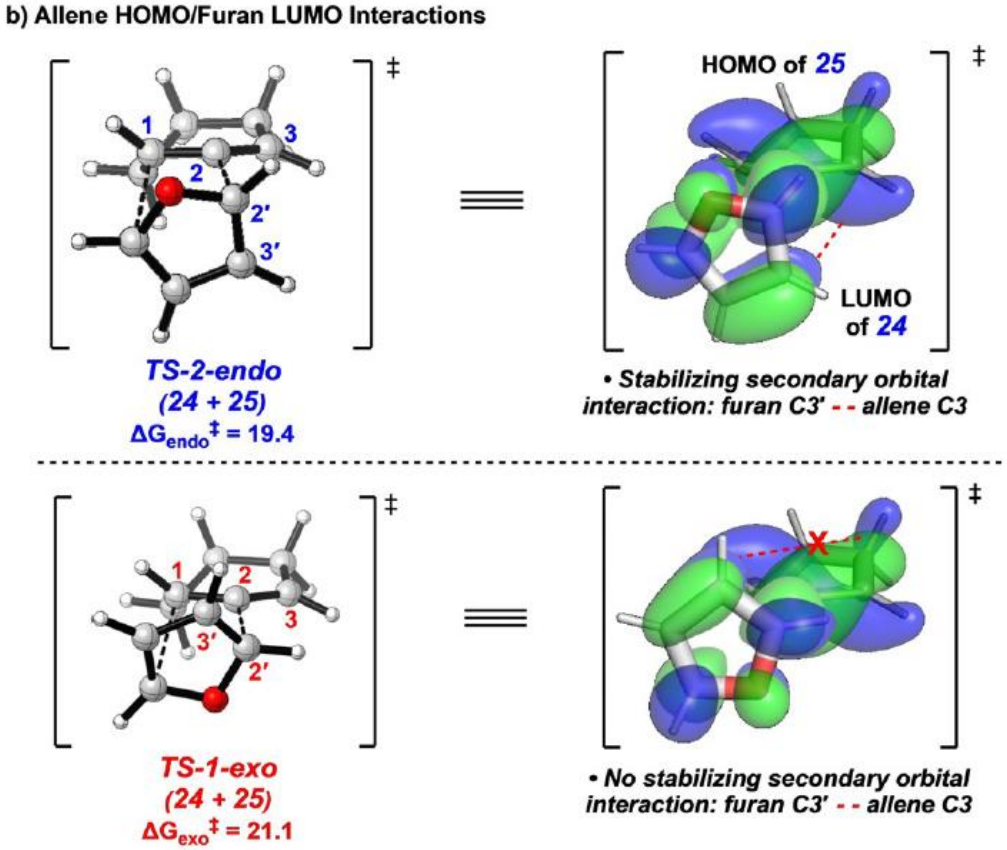


The stabilizing secondary orbital interaction in *TS-2-endo* involves orbital overlap of the HOMO at C3’ of furan with the LUMO at C3 of cyclohexa-1,2-diene.

F. Liu, Neil K. Garg, K. N. Houk, *Angew. Chem. Int. Ed.* **2021**, 60, 14989–14997.

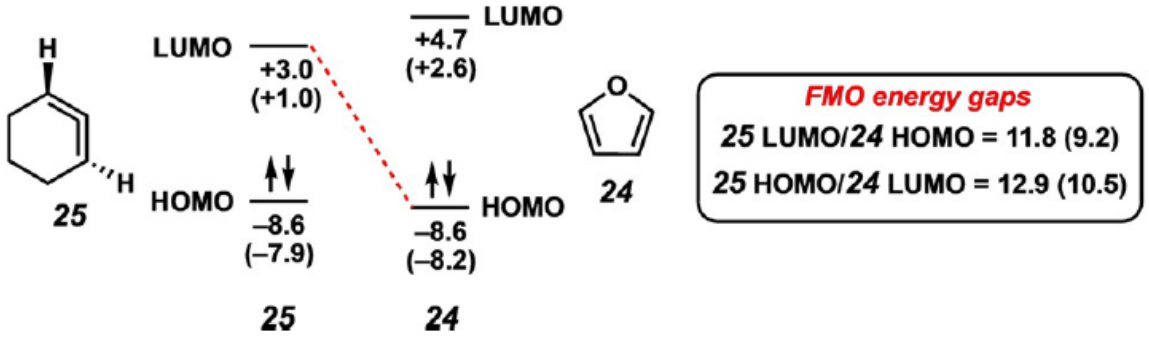
Endo Selectivity in Diels–Alder Reactions

Allene HOMO/Furan LUMO interactions



in both normal and inverse electron-demand Diels–Alder reactions of furan and allene, orbital interactions are more stabilizing along the *endo* pathway

HOMO and LUMO energies



Strongest interaction:
overlap between allene LUMO and furan HOMO

Second strongest interaction:
overlap between allene HOMO and furan LUMO

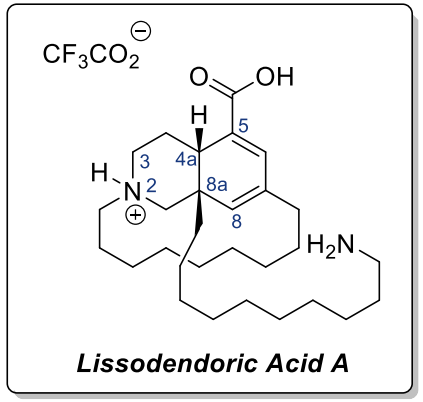
F. Liu, Neil K. Garg, K. N. Houk, *Angew. Chem. Int. Ed.* **2021**, 60, 14989–14997.

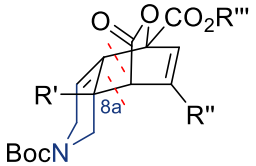
Recent studies of strained cyclic allenes in total synthesis

Synthetic Target: Lissodendoric Acid A

a regioselective, diastereoselective, and stereospecific trapping reaction of a cyclic allene intermediate

manzamine生物碱





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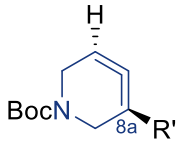

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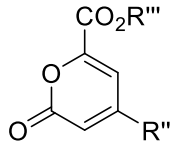


- *Rapid assembly of azadecalin core with C8a quaternary stereocenter*
- *[2.2.2]-bicycle as masked diene*

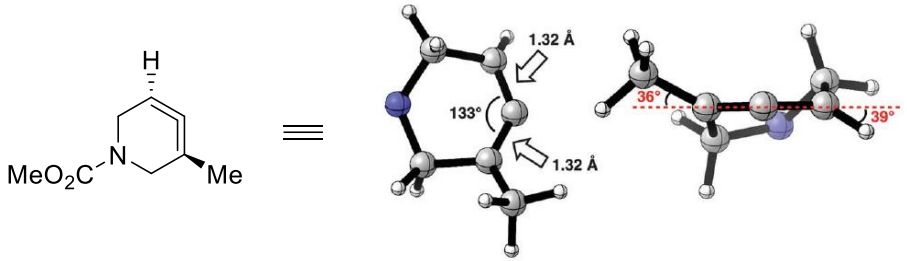
- *Enantioenriched in situ-generated cyclic allenes and enantionspecific trapping studies*

- *Used of pyrone to control regioselectivity*

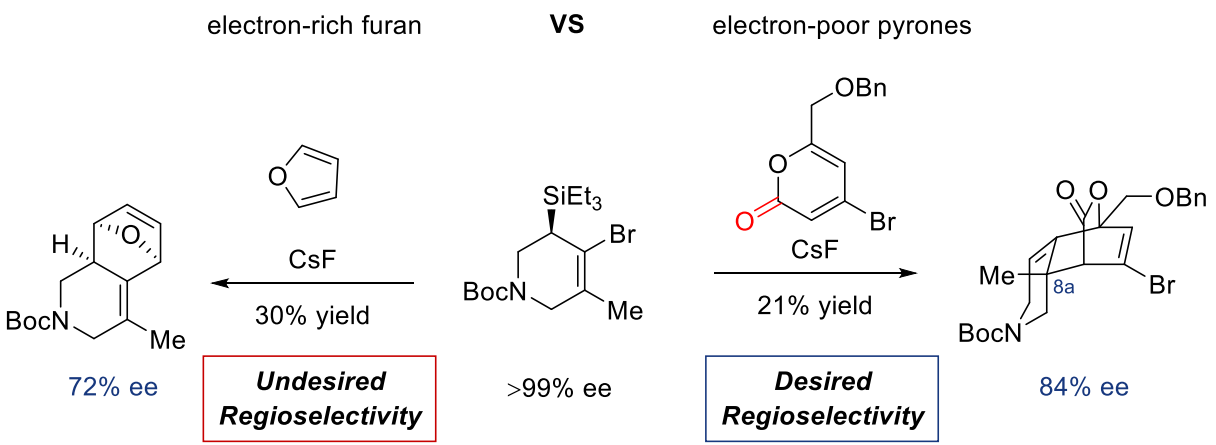
Neil K. Garg, *Science*, **2023**, 379, 261-265.

Recent studies of strained cyclic allenes in total synthesis

Regioselectivity and Stereospecificity Studies



- high reactivity due to strain
- inherently chiral



Regioselectivity:

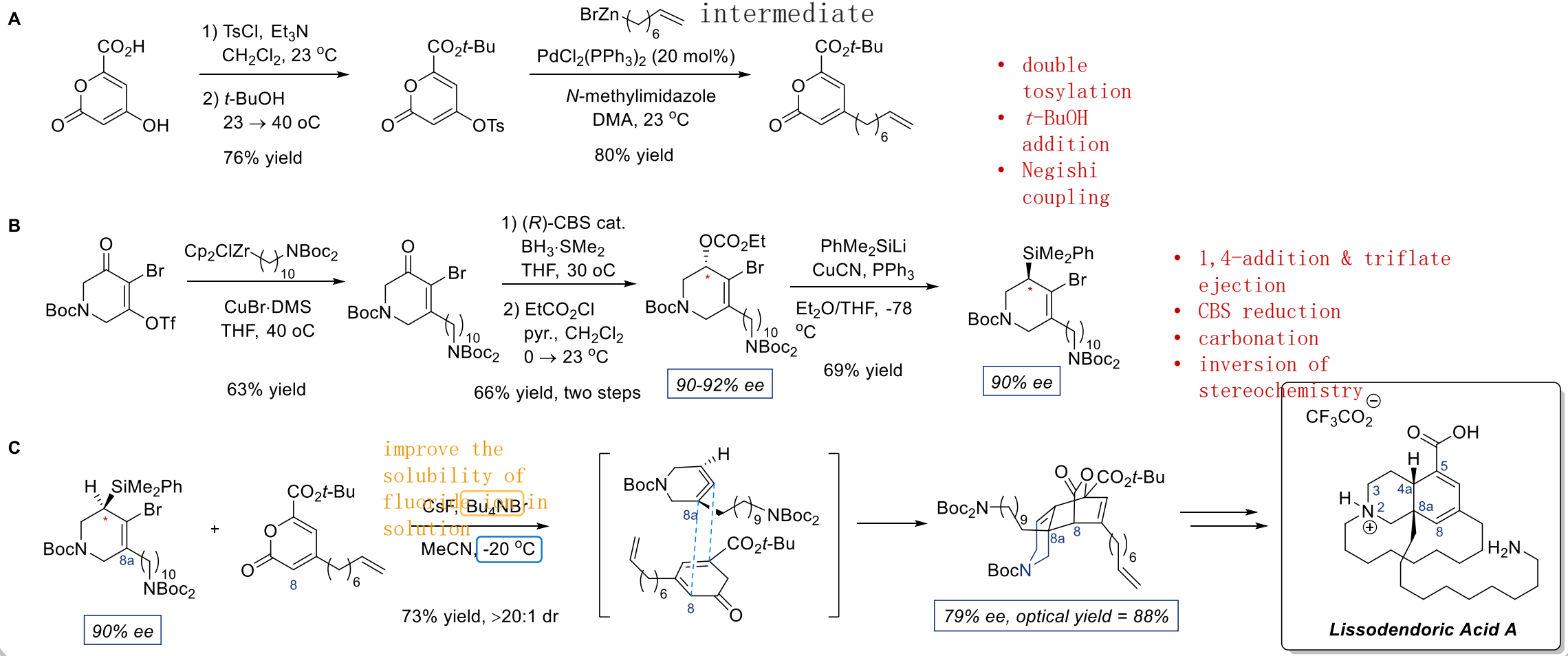
- through an inverse electron-demand Diels-Alder process
- the carbonyl group conjugated with the diene provides the dominant electronic action

Neil K. Garg, *Science*, **2023**, 379, 261-265.

Recent studies of strained cyclic allenes in total synthesis

Assembly of the Azadecalin Core

a regioselective, diastereoselective, and stereospecific trapping reaction of a cyclic allene intermediate



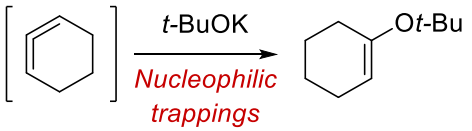
strain-driven cycloaddition is favorable over facile enantiomerization (~14 kcal/mol)

Neil K. Garg, *Science*, **2023**, 379, 261-265.

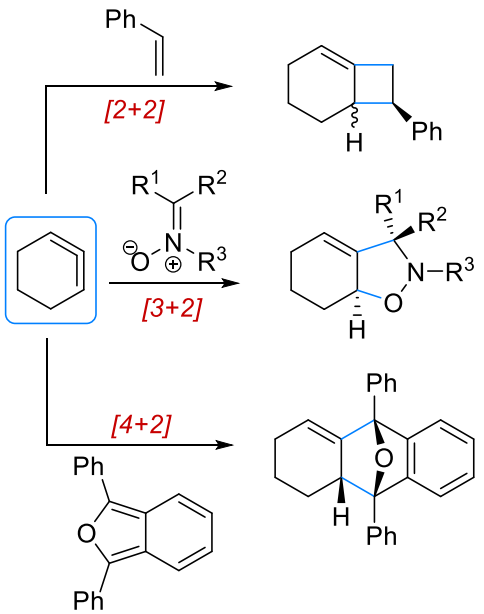
Recent studies of strained cyclic allenes

Frequently Studied

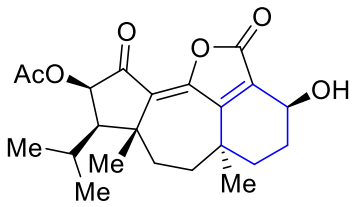
Nucleophilic trappings



Cycloaddition reactions

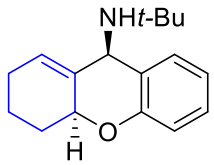


Synthesis

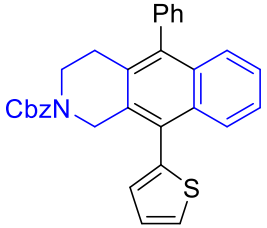


Guanacastepene N

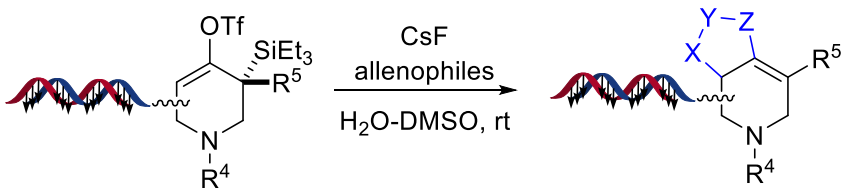
Natural Product Synthesis



Heterocycle Synthesis



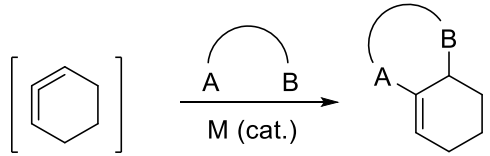
Materials Chemistry



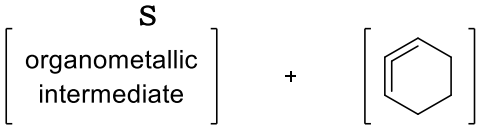
DNA-encoded Library Synthesis

Rarely Studied

Metal catalyzed reactions



Challenges



Catalytically generated ***Fleeting intermediate***

- *Requires reaction between two species generated in situ at low concentrations*
- *Control of stereochemistry*

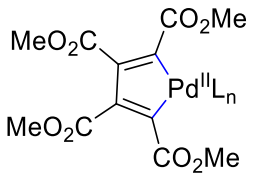
1) Neil. K. Garg, *J. Am. Chem. Soc.* **2021**, 143, 9338−9342; 2) Neil. K. Garg, *Science* **2023**, 379, 261−265; 3) S. L. Schreiber, *J. Am. Chem. Soc.* **2020**, 142, 7776−7782; 4) Neil. K. Garg, *Org. Lett.* **2020**, 22, 4500−4504; 5) Neil. K. Garg, *J. Am. Chem. Soc.* **2023**, 145, 10491−10496.

Metal-catalyzed reactions of strained cyclic allenes

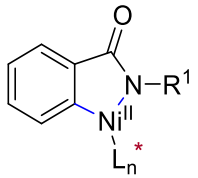
Organometallic Intermediate

σ-Bound Metal Species

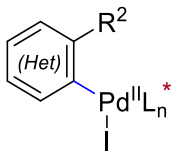
Palladacycle 2009



Nickelacycle 2020

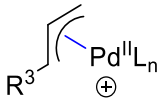


Arylpalladium 2021



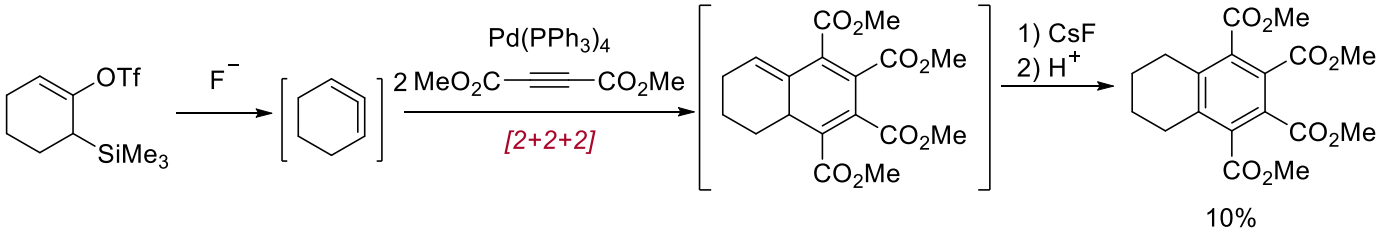
π-Bound Metal Species

π-Allylpalladium 2023

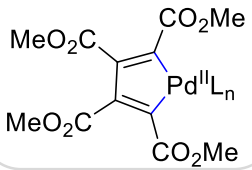


Guitián, 2009

Pd-catalyzed [2+2+2] cycloaddition



Palladacycle



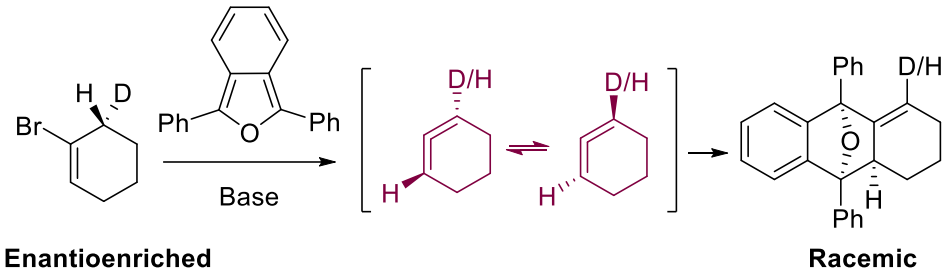
1) E. Guitián, *Eur. J. Org. Chem.* **2009**, 2009, 5519−5524; 2) Neil K. Garg, *Nature*, **2020**, 586, 242-247. 3) Neil K. Garg, *J. Am. Chem. Soc*. **2021**, 143, 9338−9342; 4) Neil K. Garg, *J. Am. Chem. Soc*. **2023**, 145, 10491−10496.

Properties of Cyclohexadiene

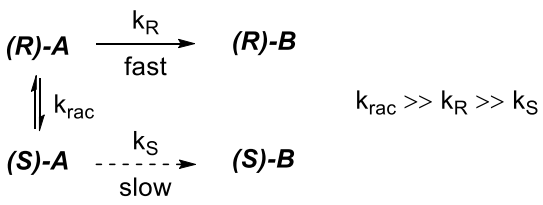
Dynamic Kinetic Resolution (DKR)

Balci & Jones , 1980

Racemization: an enantioenriched cyclic allene precursor is converted to a racemic cycloadduct

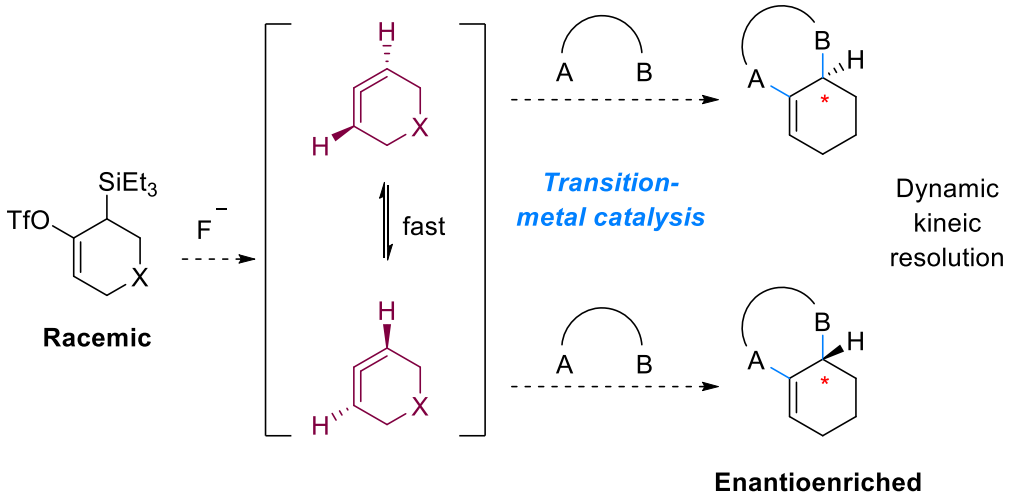


DKRs



$k_{rac} >> k_R >> k_S$

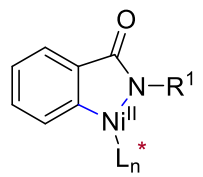
Envisioned reaction pathway



1) M. Balci, W. M. Jones, *J. Am. Chem. Soc.*,**1980**, 02, 7607–7608; 2) Neil K. Garg, *Nature*, **2020**, 586, 242-247.

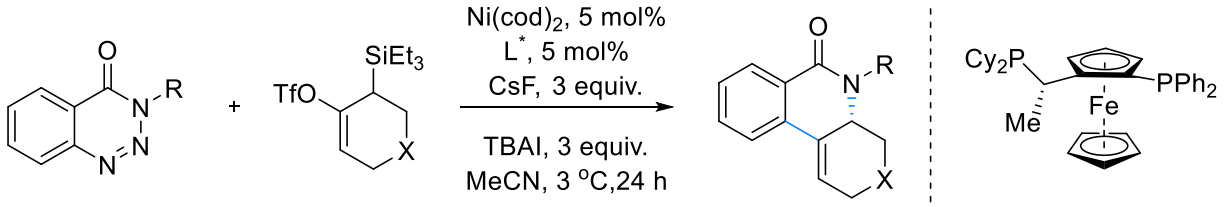
Metal-catalyzed reactions of strained cyclic allenes

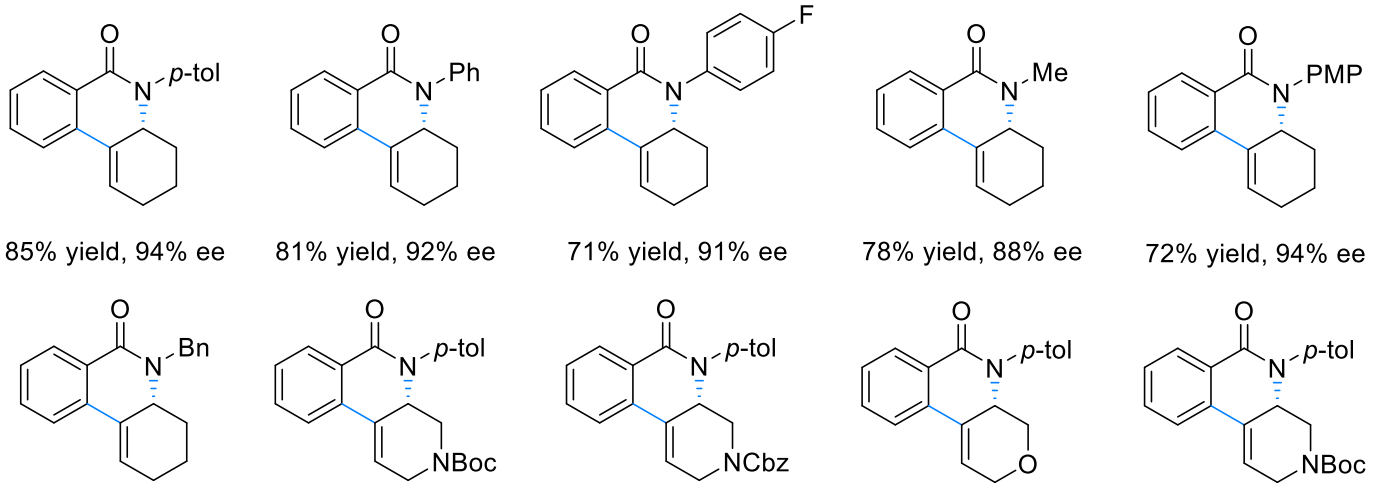
Nickelacycle 2020



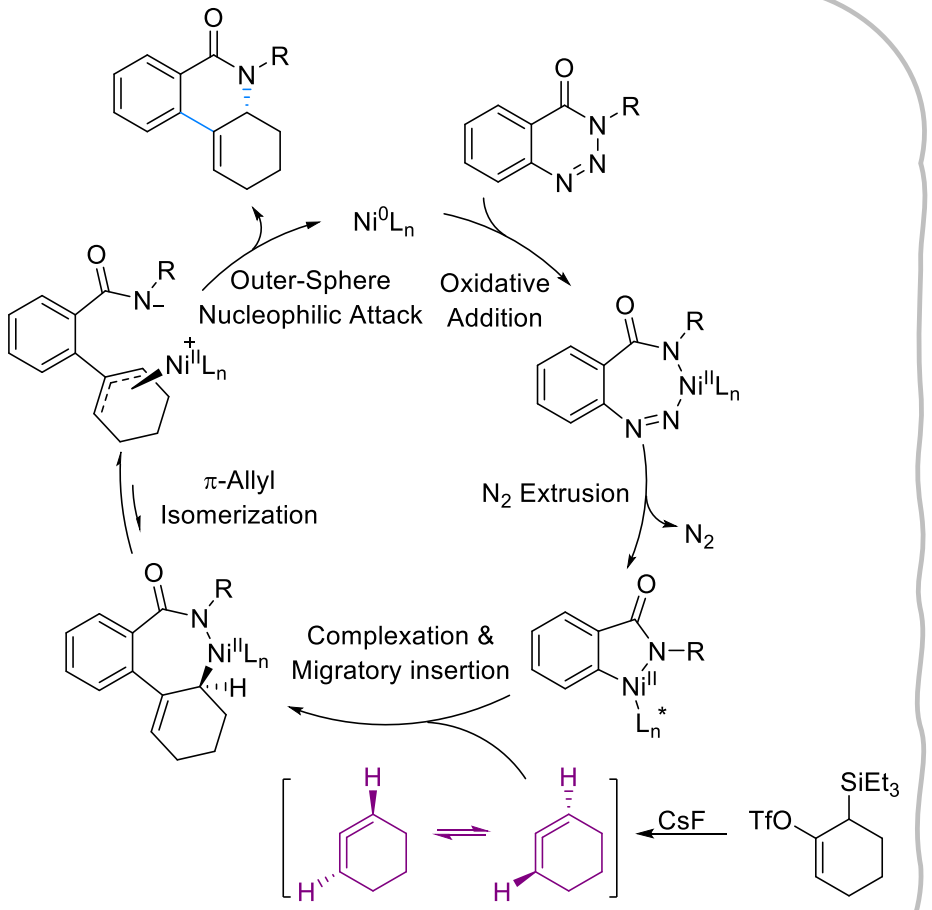
Garg, 2020

Ni-catalyzed dynamic kinetic resolution





Isolated yield. *a* Reaction was performed with 10 mol.% Ni(cod)$_2$ and 10 mol.% of L* in the absence of TBAI. *b* Reaction was performed with 10 mol.% Ni(cod)$_2$ and 10 mol.% of L* in the absence of TBAI at 23 °C.



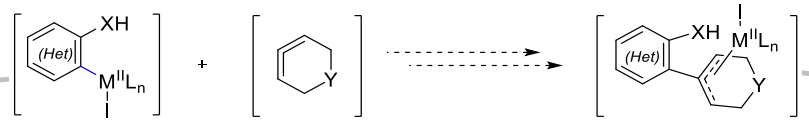
racemic cyclic allene precursor converted to an enantioeriched annulated product via the DKR

Neil K. Garg, *Nature*, **2020**, 586, 242-247.

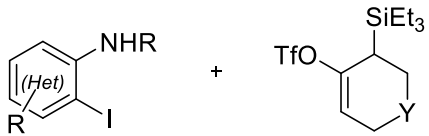
Metal-catalyzed reactions of strained cyclic allenes

Garg, 2021

Pd-Catalyzed Annulations



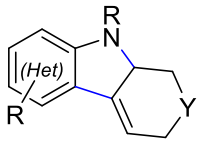
Readily available annulation partners

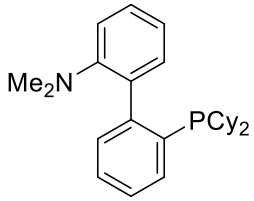


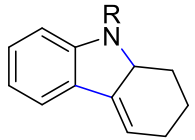
$Pd(OAc)_2$, 10 mol%
Davephos, 20 mol%

CsF, 10 equiv.
Bu_4NOTf, 5 equiv.
Na_2CO_3, 3 equiv.
DMF, 80 °C, 1 h

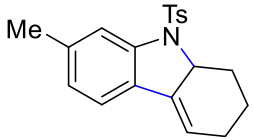
Polycyclic product



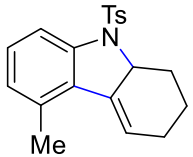




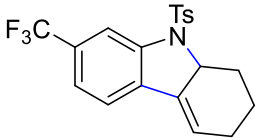
R = Ts, 90% yield
R = Boc, 45% yield
R = Ac, 22% yield



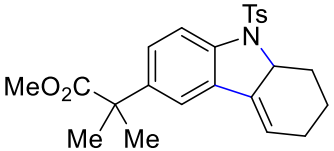
88% yield



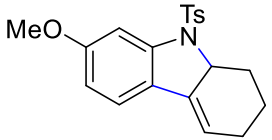
52% yield



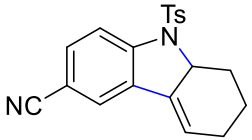
63% yield



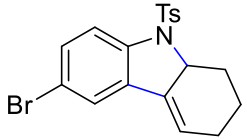
89% yield



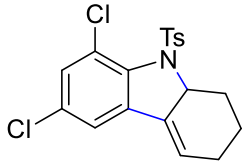
63% yield



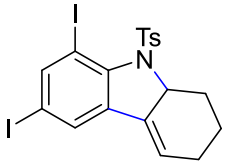
56% yield



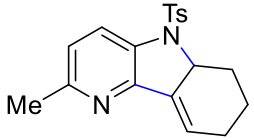
62% yield[a]



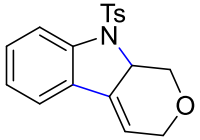
50% yield



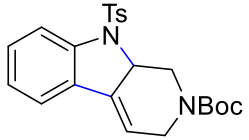
56% yield



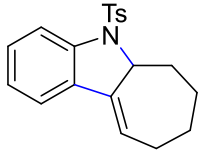
99% yield (from ArI)
78% yield (from ArBr)[b]



60% yield[c]



72% yield[c]



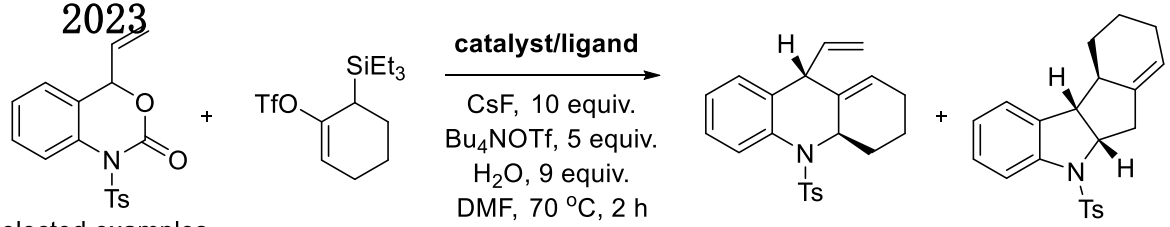
73% yield[d]

a Reaction was performed using 2-(N,N-dimethylaminomethyl)- 1-diphenylphosphanylferrocene as ligand in MeCN at 60 °C for 3 h. *b* ArX = 2-halo-6-methyl-3-N-tosylaminopyridine. c Reaction was performed using 2-(N,N dimethylaminomethyl)-1-diphenylphosphanylferrocene as ligand with CsF (2.5 equiv) in MeCN at 60 °C for 24 h; performed in the absence of Bu_4NOTf. *d* A silyl tosylate was used as the allene precursor.

Neil K. Garg, *J. Am. Chem. Soc.* **2021**, 143, 9338−9342.

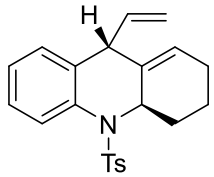
Metal-catalyzed reactions of strained cyclic allene

Garg, 2023

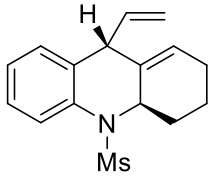


Selected examples

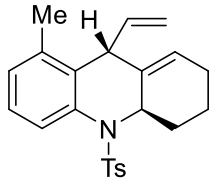
Pd(PPh$_3$)$_4$



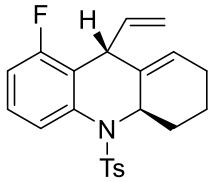
60% yield, 9.4:1 dr



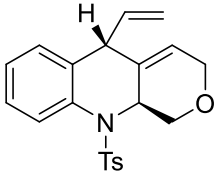
60% yield, >20:1 dr



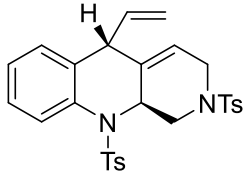
65% yield, >20:1 dr



56% yield, >20:1 dr

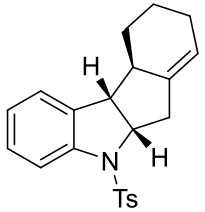


64% yield, 1.8:1 dr

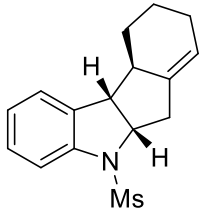


69% yield, 1.3:1 dr

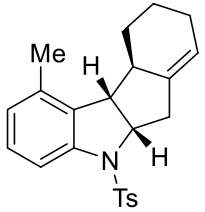
dppf Pd G$_3$



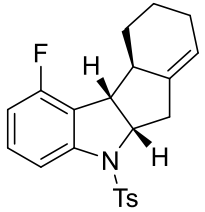
70% yield



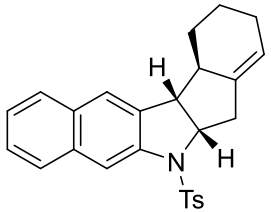
53% yield



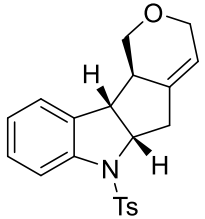
42% yield



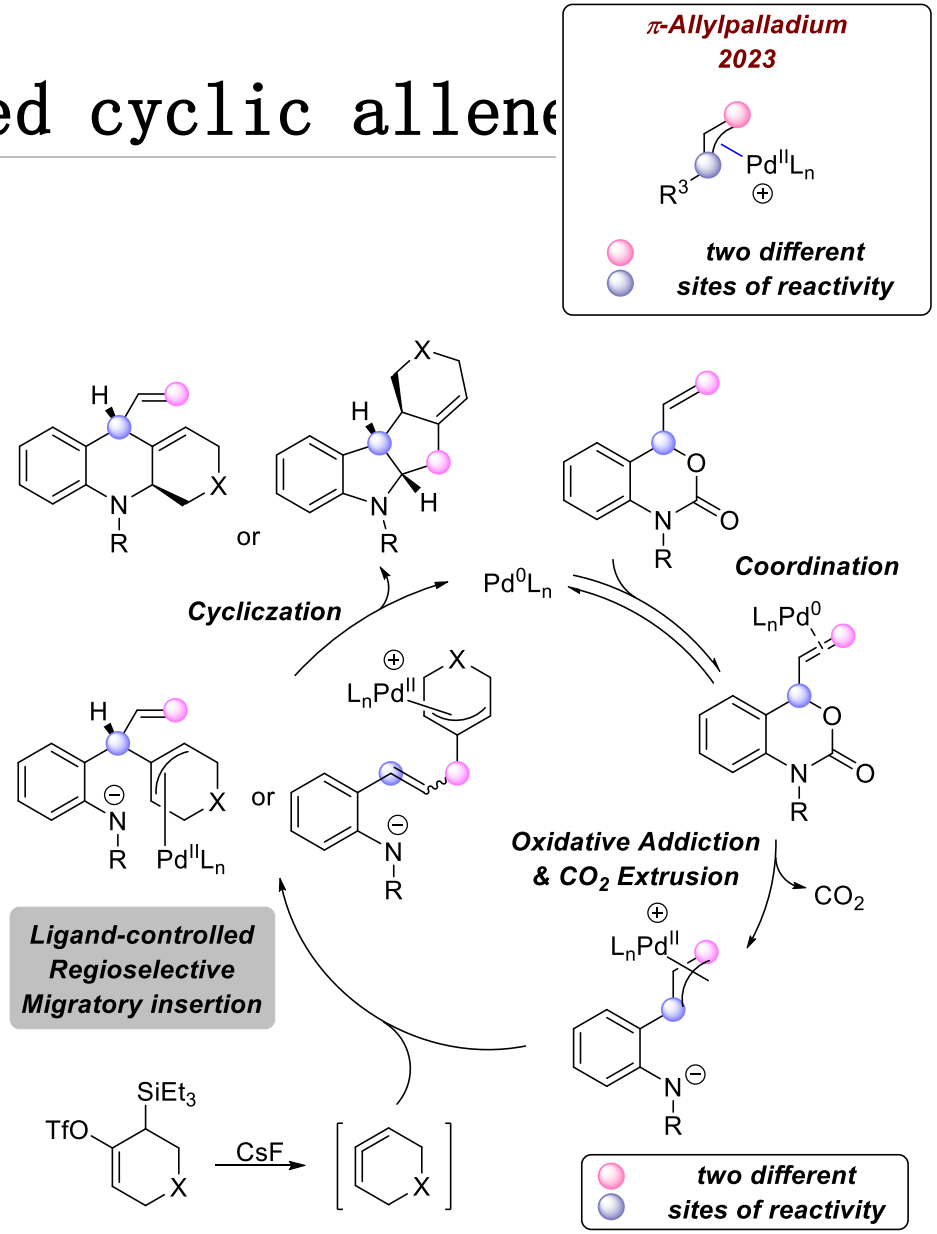
45% yield



59% yield



45% yield

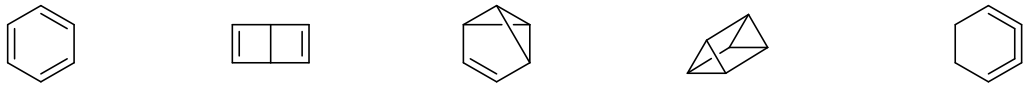


Neil K. Garg, *J. Am. Chem. Soc.* **2023**, 145, 10491−10496

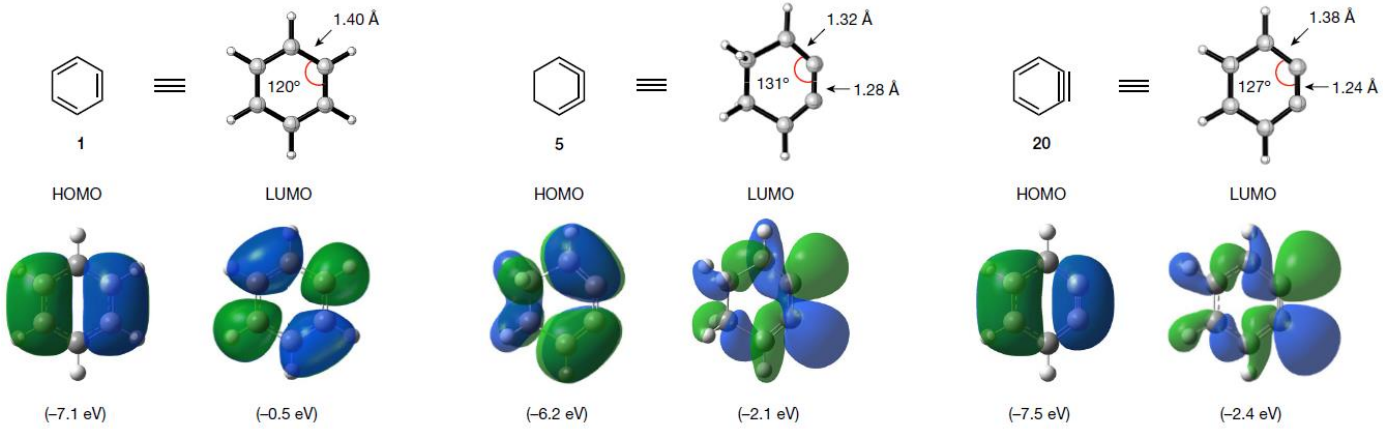
/03

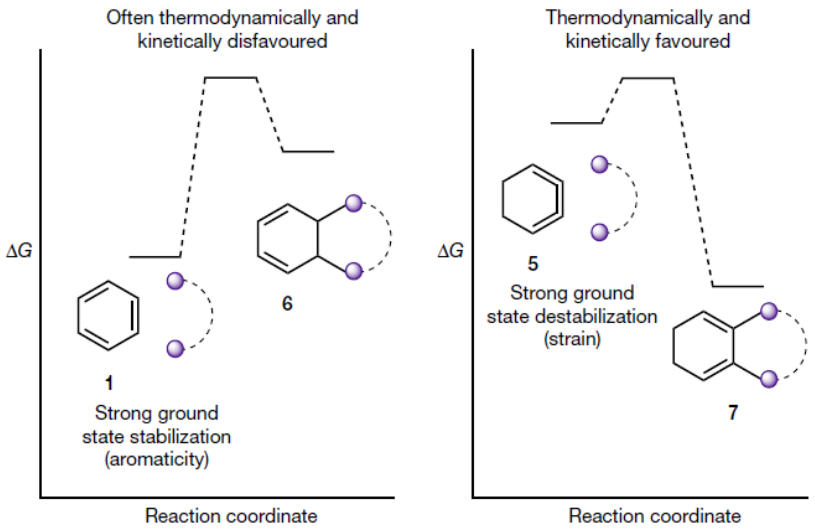
Cyclohexatriene

Comparison of reaction coordinate diagrams



Benzene	Dewar benzene	Benzvalene	Prismane	1,2,3-Cyclo-hexatriene
1825	1963	1966	1973	1990
ΔG_{rel} = 0 kcal mol^{-1}	83 kcal mol^{-1}	81 kcal mol^{-1}	123 kcal mol^{-1}	101 kcal mol^{-1}



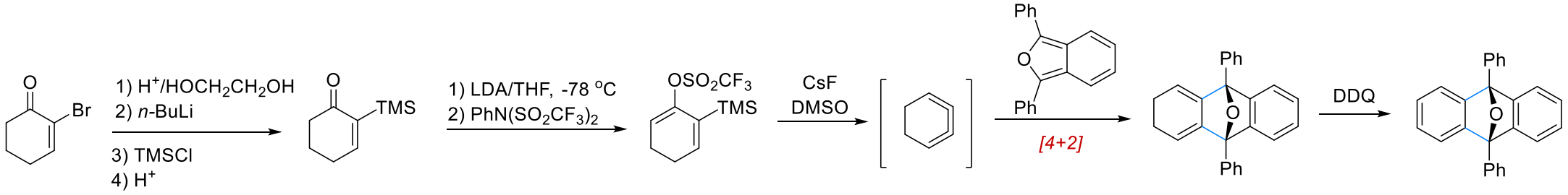


reactions of 1,2,3-cyclohexatriene should be kinetically and thermodynamically favoured because of the considerable strain release

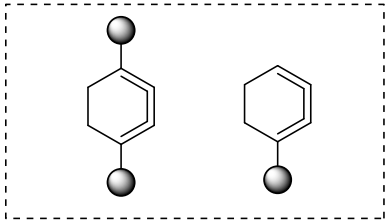
Neil K. Garg, *Nature*, **2023**, 618, 748-754.

1,2,3-cyclohexatriene

1990, Johnson: validated the intermediacy of 1,2,3-cyclohexatriene



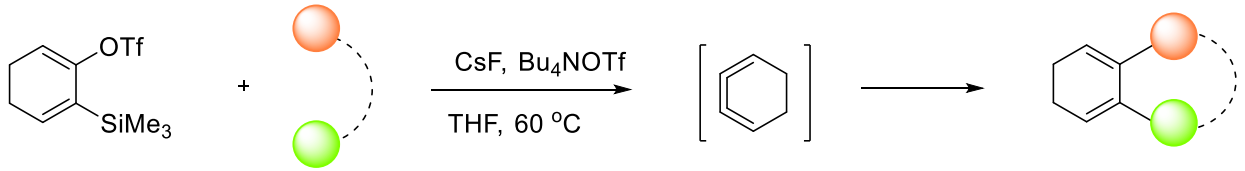
Only **four** experimental studies pertaining to 1,2,3-cyclohexatriene are available in the literature.

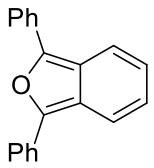
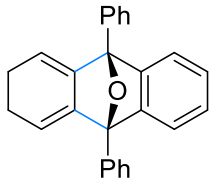
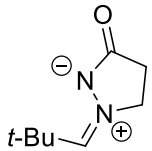
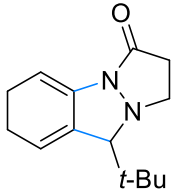
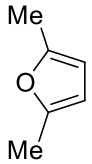
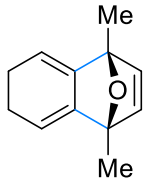
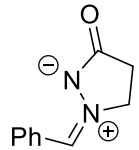
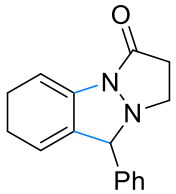
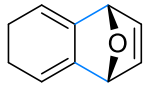
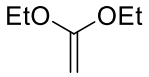
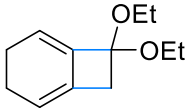
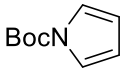
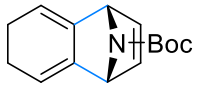
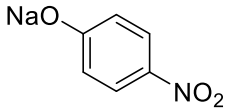
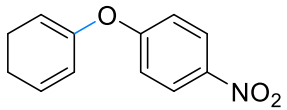


No reports

1) R. P. Johnson, *J. Am. Chem. Soc.* **1990**, 112, 8578–8579; 2) L. A. Paquette, *Tetrahedron Lett*. **1994**, 35, 2309–2312; 3) L. A. Paquette, *J. Am. Chem. Soc.* **1995**, 117, 163–176;3) R. P. Johnson, *J. Am. Chem. Soc.* **1996**, 118, 4218–4219.

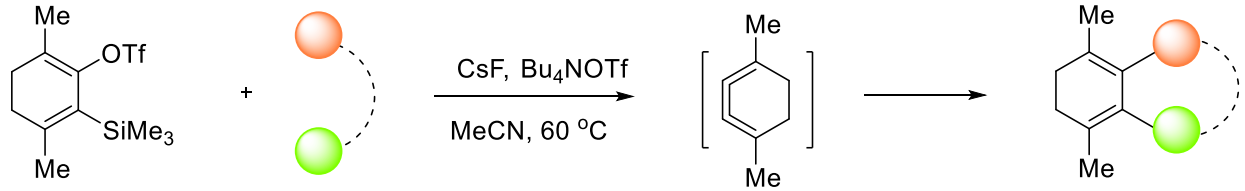
Trapping reactions of 1,2,3-cyclohexatriene

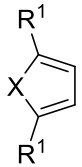
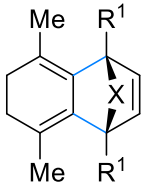
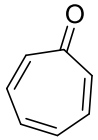
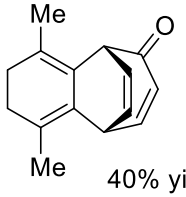
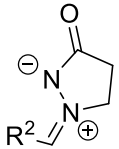
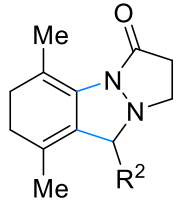


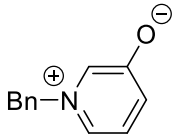
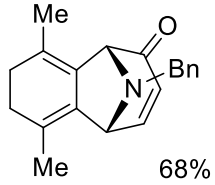
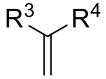
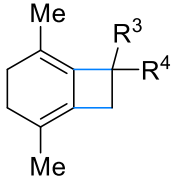
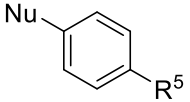
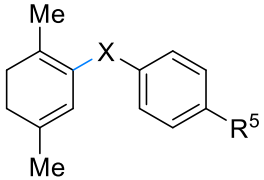
Entry	Trapping agent	Product	Yield	Entry	Trapping agent	Product	Yield
1			65%	5			59%
2			62%	6			51%
3			72%	7			44%
4			61%	8			51%

Neil K. Garg, *Nature*, **2023**, 618, 748-754.

Trapping reactions of a disubstituted cyclic triene precursor



Entry	Trapping agent	Product and yield
Selected examples		
1 2	 X = O, R^1 = Me X = NBoc, R^1 = H	 X = O, R^1 = Me, 80% yield X = NBoc, R^1 = H, 82% yield
3		 40% yield
4 5	 R^2 = *t*-Bu R^2 = Ph	 R^2 = *t*-Bu, 86% R^2 = Ph, 87%

Entry	Trapping agent	Product and yield
6		 68% yield
7 8	 R^3 = R^4 = OEt R^3 = $NBoc_2$, R^4 = CO_2Me	 R^3 = R^4 = OEt, 47% yield R^3 = $NBoc_2$, R^4 = CO_2Me, 48% yield
9 10	 Nu = NaO, R^5 = NO_2 Nu = SH, R^5 = H	 Nu = NaO, R^5 = NO_2, 83% yield Nu = SH, R^5 = H, 81% yield

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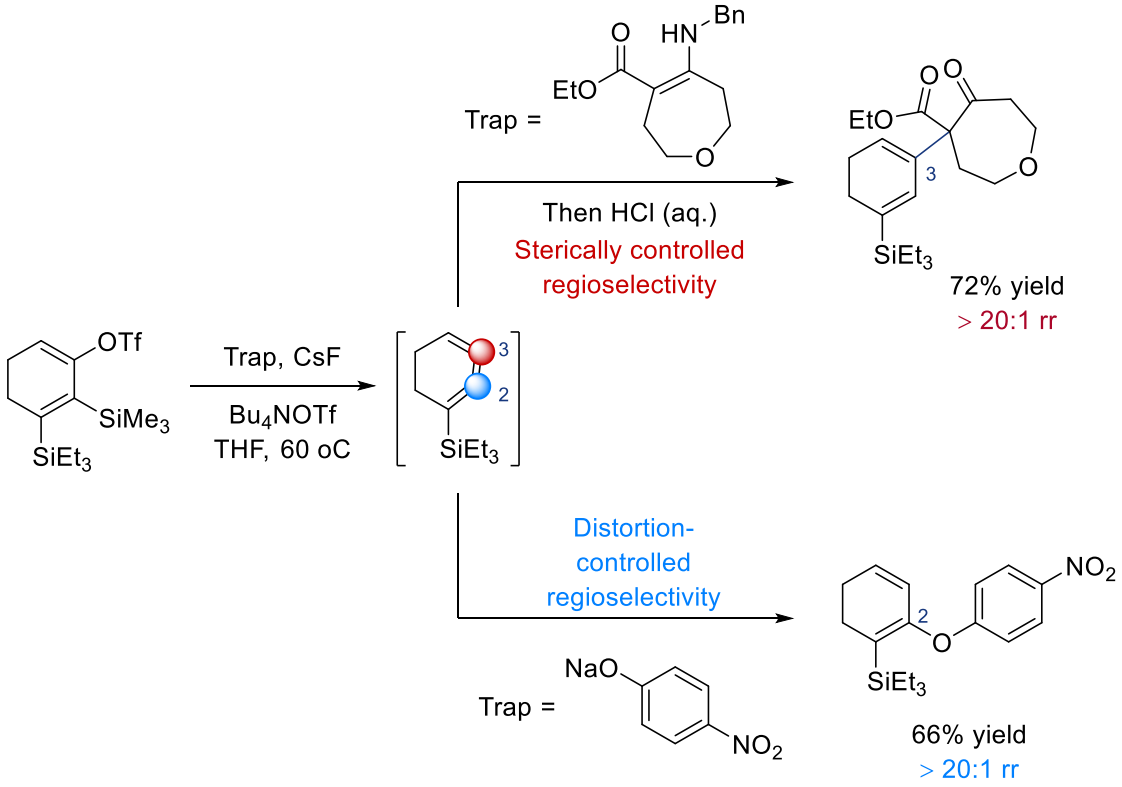
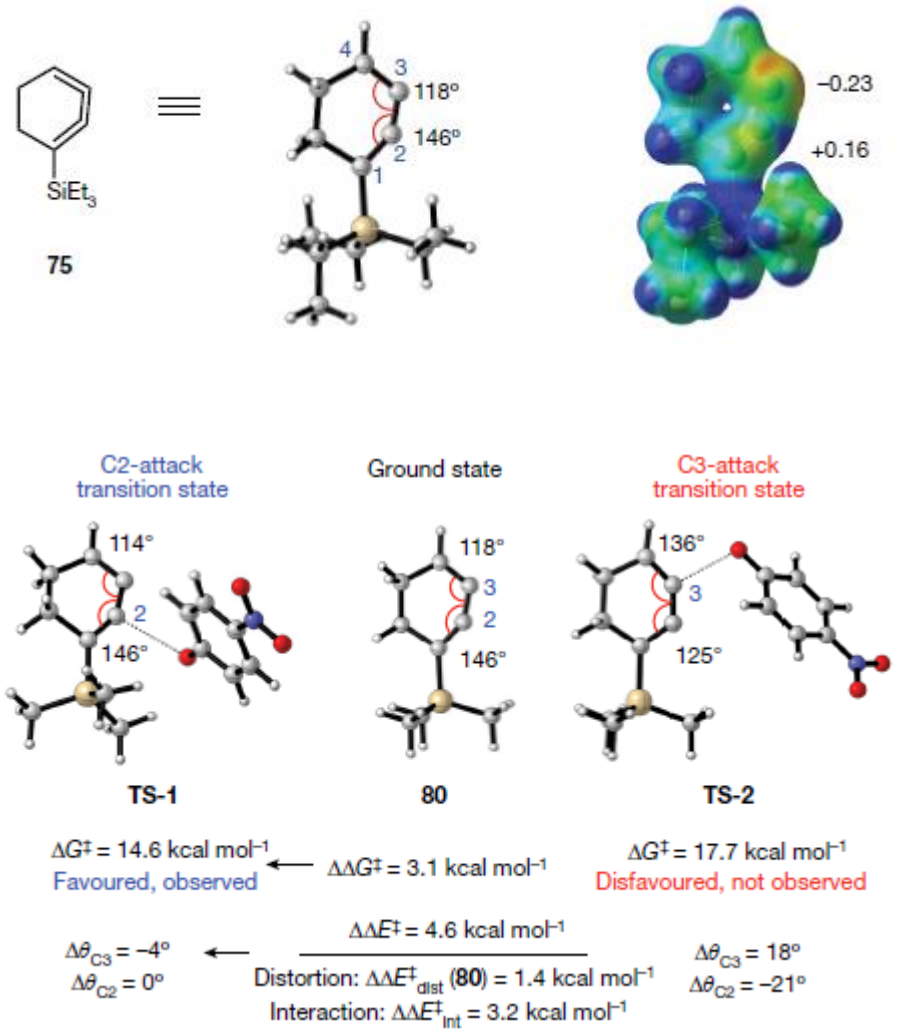
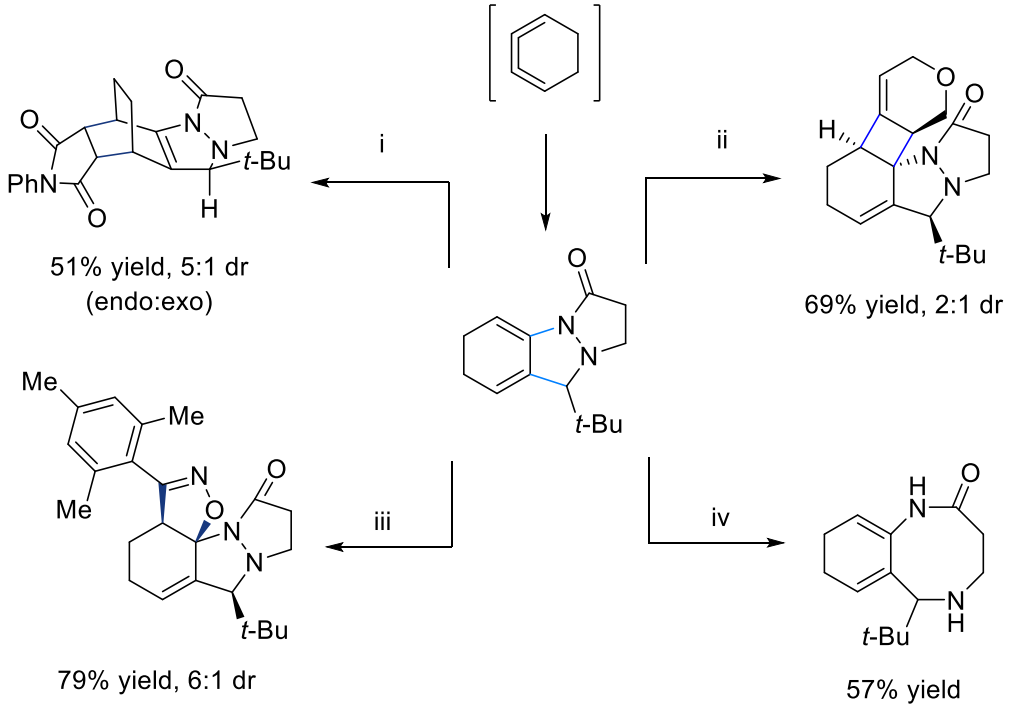
Structure and regioselective reactions of monosubstituted cyclic trienes



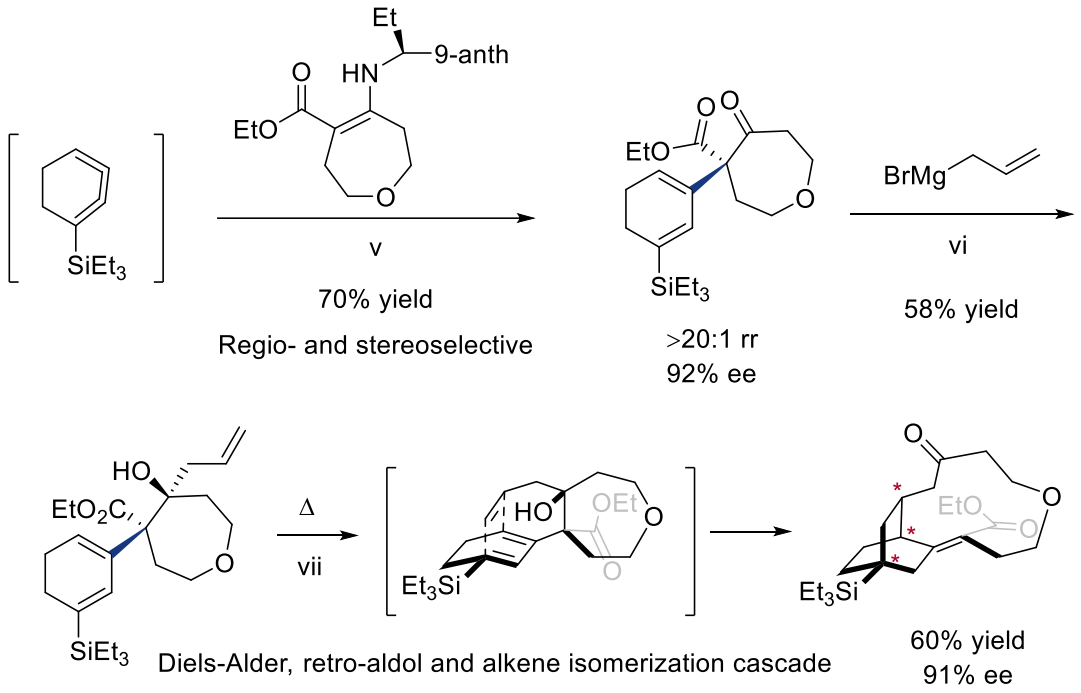


Neil K. Garg, *Nature*, **2023**, 618, 748-754.

Strained 1,2,3-cyclohexatrienes in multistep synthesis



i, *N*-Ph maleimide (2.5 equiv.), benzene, 80 °C, 51% yield, 5:1 dr. ii, Oxacyclic allene precursor (1.5 equiv.), CsF (5 equiv.), MeCN, 23 °C, 69% yield, 2:1 dr at the stereocentre indicated by an asterisk. iii, Mesitylene nitrile oxide (1.5 equiv.), CH_2Cl_2, 0 °C to 40 °C, 79% yield, 6:1 dr. iv, Sodium naphthalenide (3 equiv.), THF, 0 °C, 57% yield.



v, enamine (5 equiv.), CsF (10 equiv.), Bu_4NOTf (2 equiv.), THF, 60 °C, then HCl (1 M), 23 °C, 70% yield, >20:1 rr, 92% ee. vi, AllylMgBr (2 equiv.), THF, −78 °C, 58% yield, >20:1 dr. vii, Hexadecane, 220 °C, 60% yield.

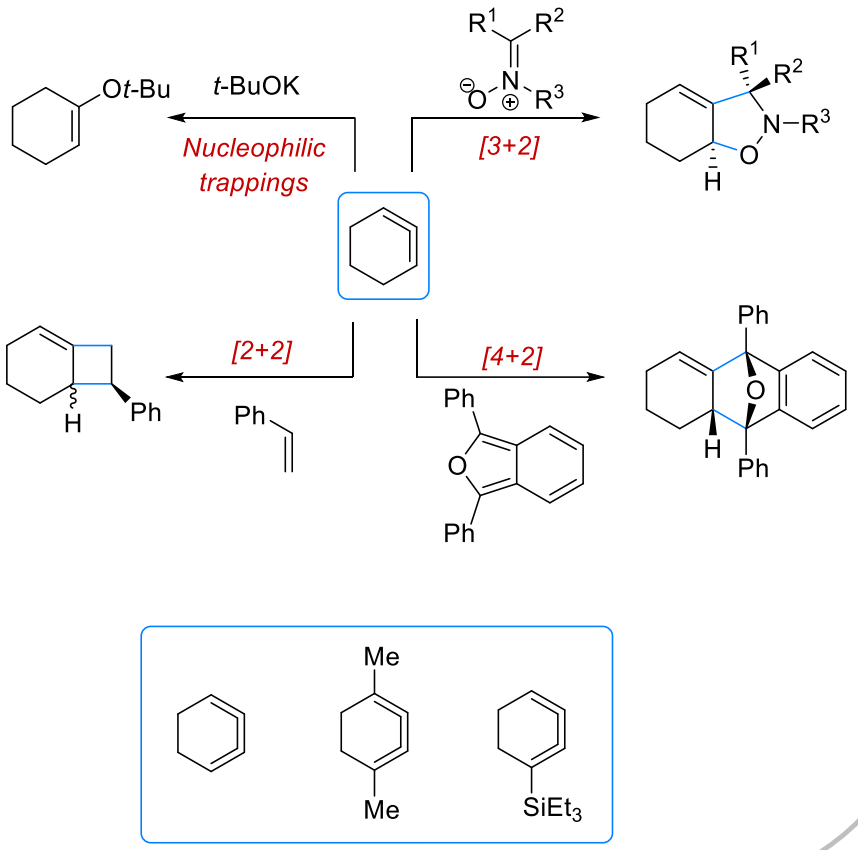
Neil K. Garg, *Nature*, **2023**, 618, 748-754.

/04

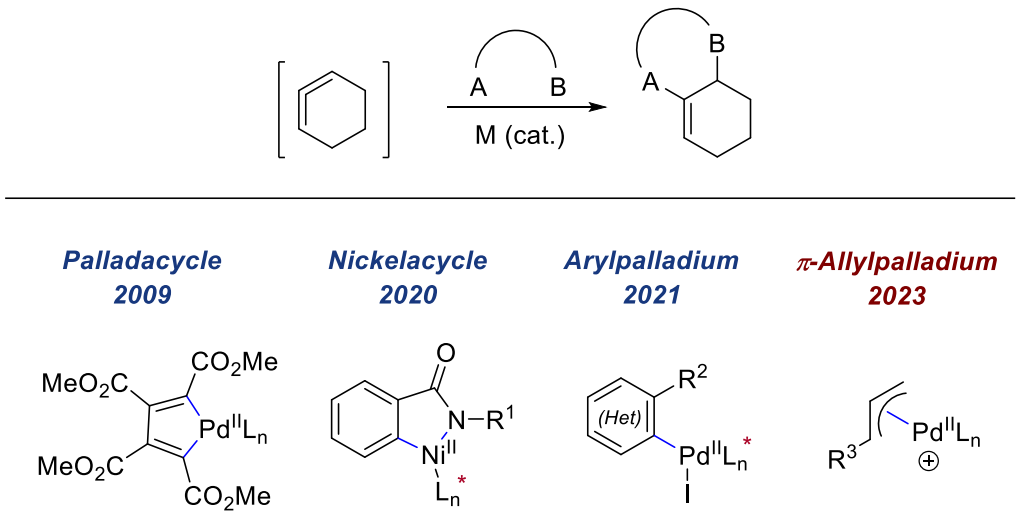
Summary and outlook

Summary and outlook

Trapping reactions



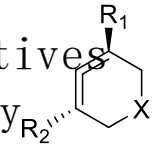
Metal-catalyzed reactions



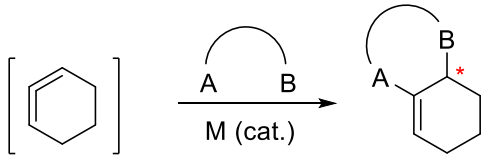
Summary and outlook

cyclohexadiene

- Stabilized cyclohexene derivatives
  full use of axial chirality

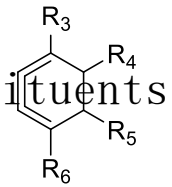


- More metal catalytic systems: Pd, Ni, Cu etc.



cyclohexatriene

- Cyclohexatriene precursors with more abundant substituents



- cyclic reactions, nucleophilic addition reactions, and transition metal catalyzed reactions

THANKS