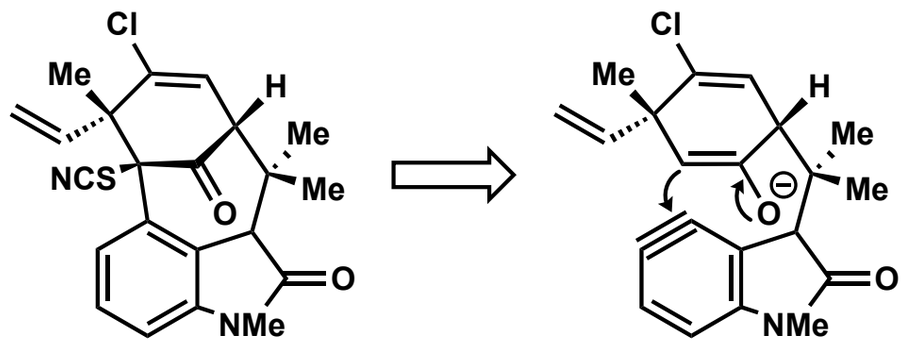
Strain-Promoted Reactions of 1,2,3-Cyclohexatriene and Its Derivatives

Nature **2023**, *618*, 748-754

Samuel Tandang Kasmali G1

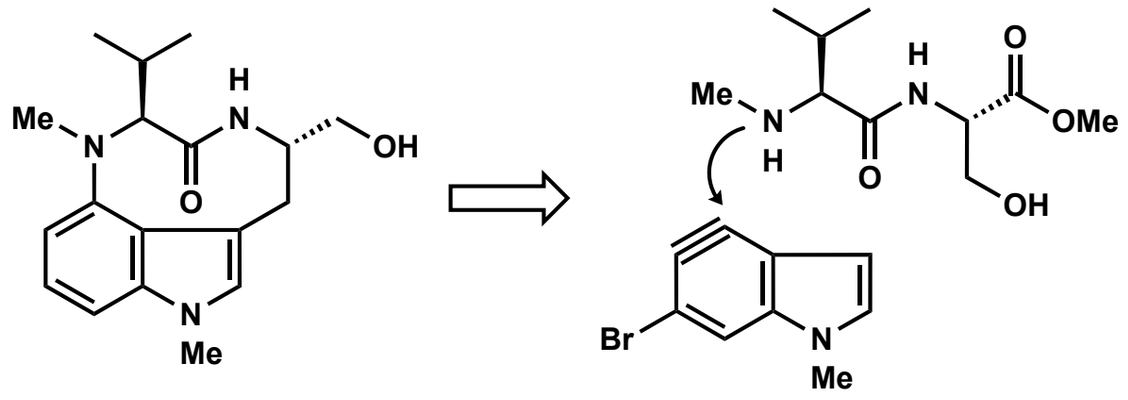
A Career in Strained Intermediates

GARG LAB



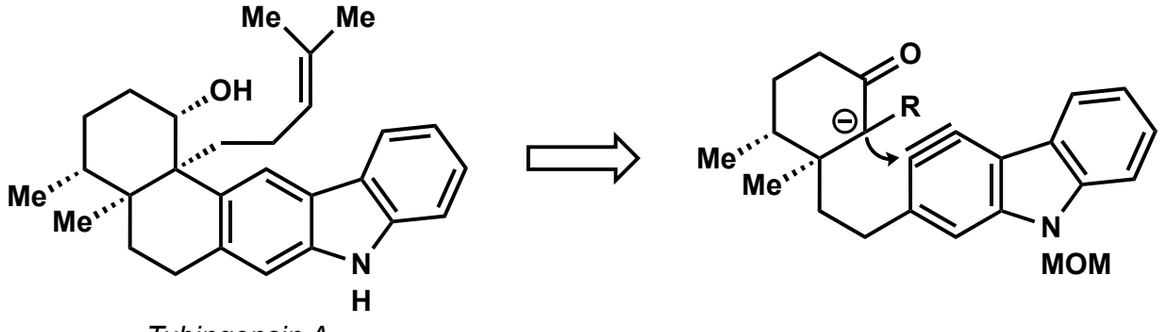
N-Methylwelwitindolinone C Isothiocvanate

OL **2009**, *11*, 2349–2351
JACS **2011**, *133*, 15797-15799
JACS **2012**, *134*, 1396–1399
ACIE **2012**, *51*, 3758
ACIE **2013**, *52*, 12422-12425
JACS **2014**, *136*, 14710-14713



Indolactam V

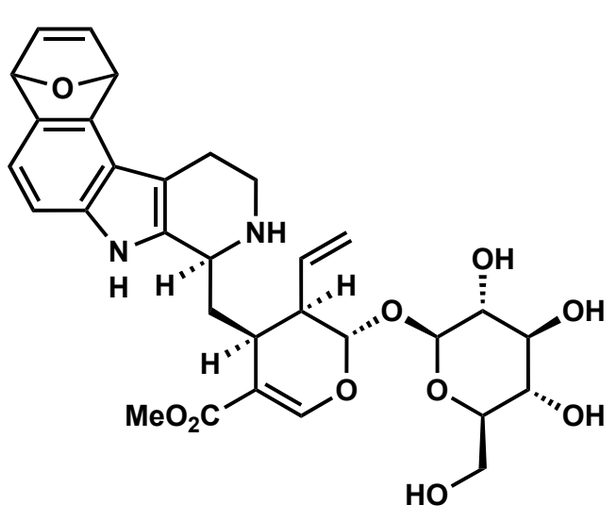
JACS **2011**, *133*, 3832–3835
Synlett **2011**, *18*, 2599-2604

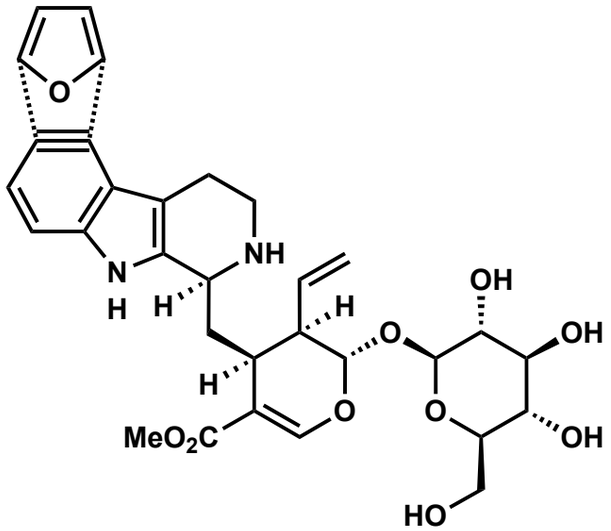


Tubingensin A

JACS **2014**, 136, 3036-3039

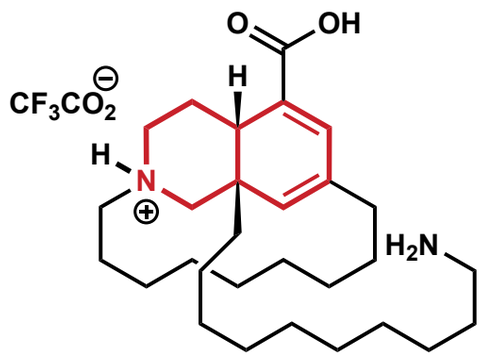
A Career in Strained Intermediates



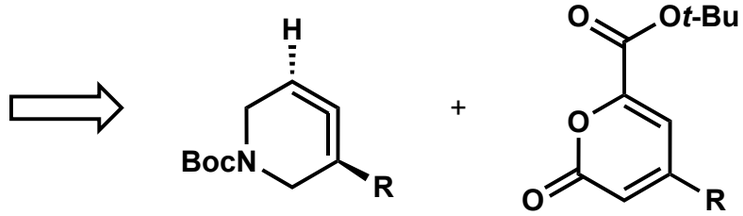


JACS **2021**, *143*, 7471–7479

Strictosidine "strictosidyne"

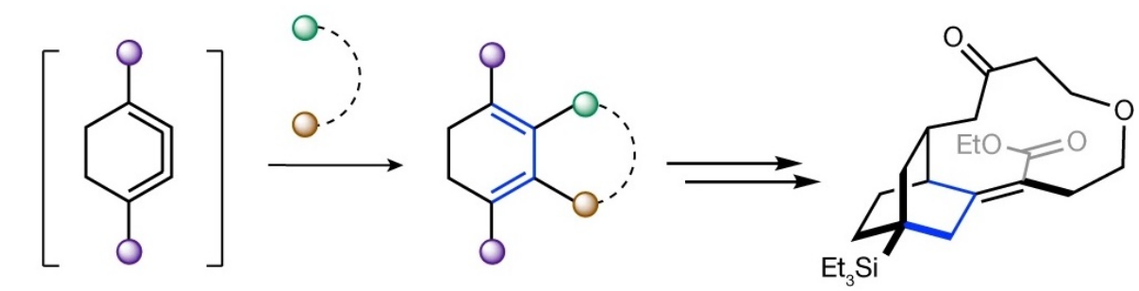


Lissodendoric Acid A



Science **2023**, *379*, 261–265

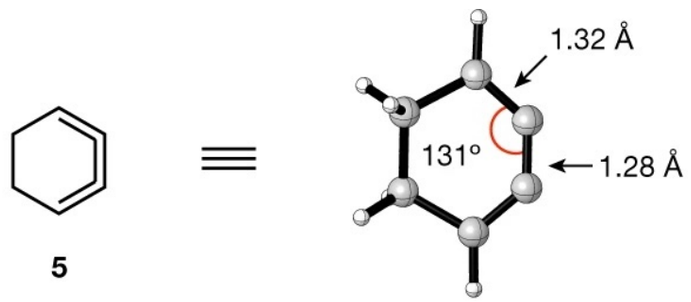
[This work]



From readily accesible precursors under mild conditions

Diverse highly functionalized 1,3-dienes

Unconventional entryway to complex scaffolds



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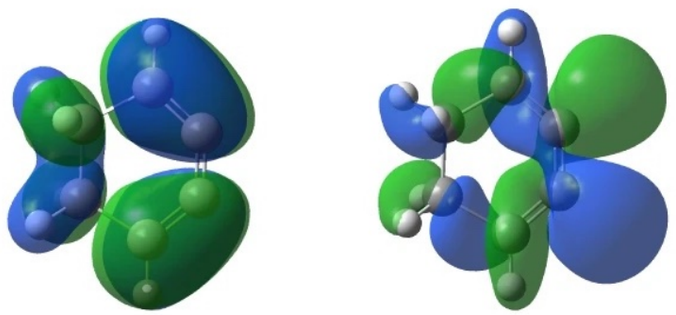


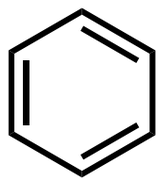
HOMO (–6.2 eV)

LUMO (–2.1 eV)

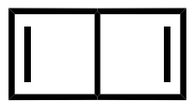
The Story of C_6H_6

1825 — Faraday Isolation of C_6H_6

1865 — Kekulé's Benzene

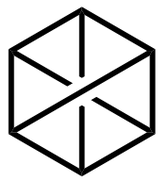


1867 — Dewar's Benzene

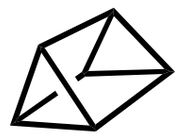


[1962]

1867 — Claus Benzene

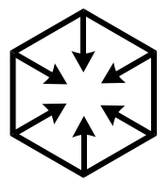


1869 — Prismane

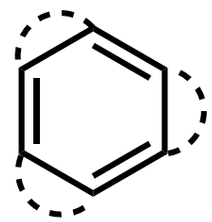


[1973]

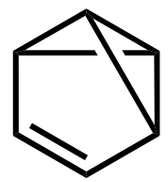
1877 — Armstrong-Baeyer's Benzene



1899 — Thiele's Benzene



1937 — Hückel's Benzvalene

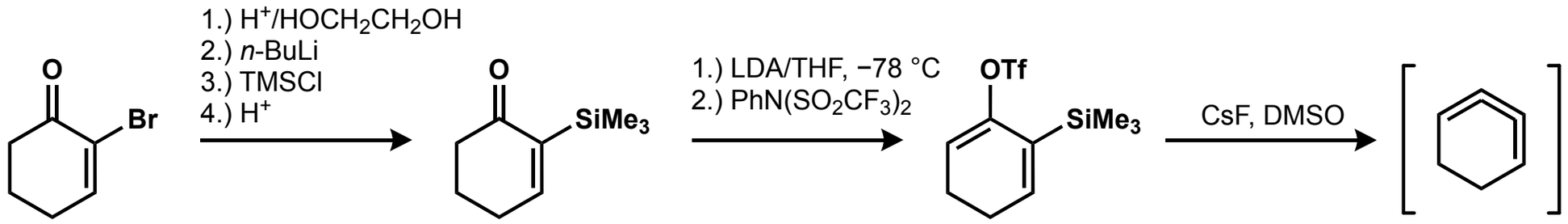


[1971]

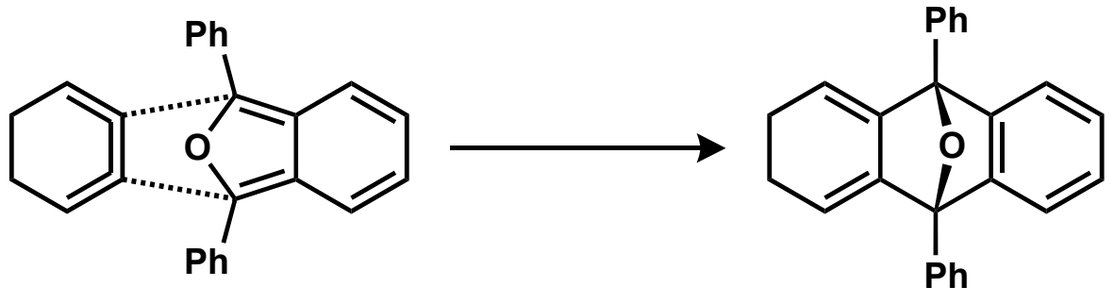
[1990]

Johnson, R. P. *et al*. *JACS* **1990**, *112*, 8578-8579
Review: *Chem. Rev.* **1989**, *89*(5)

1,2,3-Cyclohexatriene Seminal Methods



Kobayashi silyl triflate

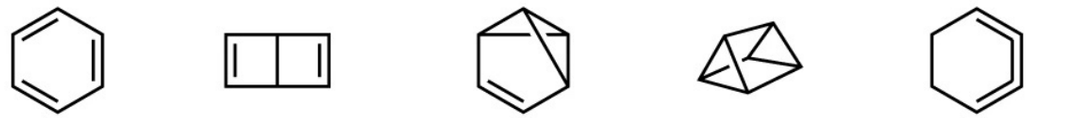


The most distinct advantage of this generation method is not because it CAN generate aryne but the way how it maintains a low-level concentration of aryne species under arynophile-friendly conditions. The combination of CsF and acetonitrile solvent, sometimes with toluene as cosolvent, is a magic recipe in Kobayashi's protocol. An explanation for this is that CsF has low solubility in acetonitrile, which in turn would only activate a small portion of *o*-silylaryl triflate at any reaction stage.[69] In addition, DFT calculations on the fluoride-induced benzyne generation process of *o*-silylphenyl triflate revealed that the removal of the TMS group by fluoride is through a pseudo-S_N2 mechanism with the formation of a pentacoordinated silicon ate complex as the rate-determining step.[70] Therefore, this system could provide a constant supply of a suitably low concentration of aryne intermediate. As a consequence of Kobayashi's method, the reaction efficiency can be generally enhanced with high functional group tolerance, which could also accommodate different aryne reaction modes.

Johnson, R. P. *et al*. *JACS* **1990**, *112*, 8578-8579
Kobayashi, H. et al. *Chem. Lett.* **1983**, *12*, 1211– 1214
Review: *Chem. Rev.* **2021**, *121*, 3892–4044

Computational Studies

LOT B3LYP-D3/6-311+G(d,p)



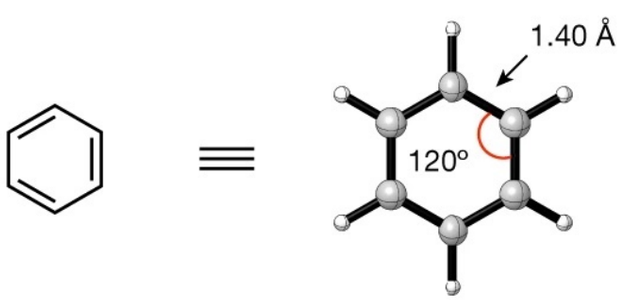
1 Benzene (1825) ΔG_{rel} = 0 kcal mol^{-1}

2 Dewar benzene (1963) 83 kcal mol^{-1}

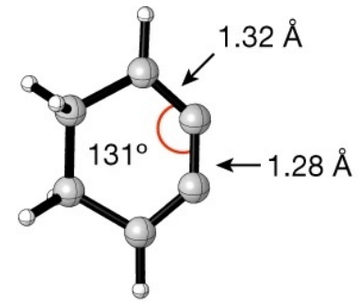
3 Benzvalene (1966) 81 kcal mol^{-1}

4 Prismane (1973) 123 kcal mol^{-1}

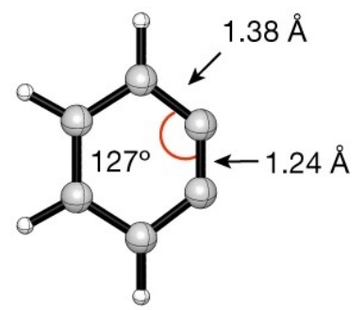
5 1,2,3-Cyclo-hexatriene (1990) 101 kcal mol^{-1}



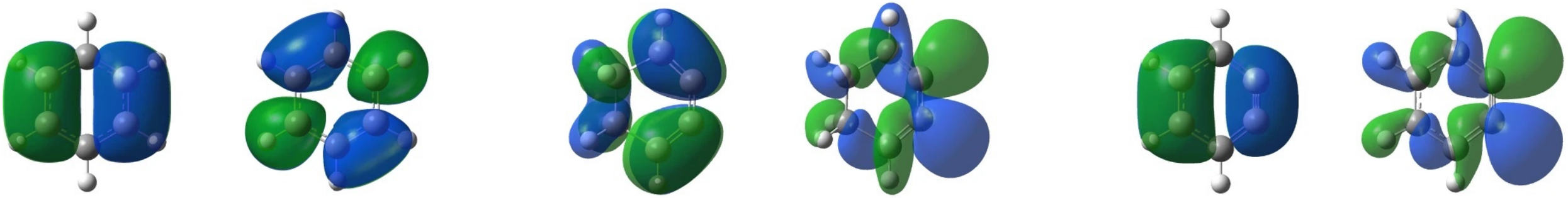
HOMO LUMO



HOMO LUMO

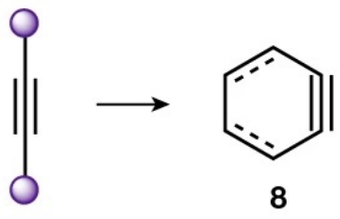


HOMO LUMO



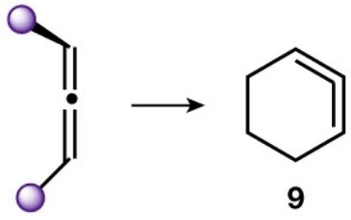
(–7.1 eV) (–0.5 eV) (–6.2 eV) (–2.1 eV) (–7.5 eV) (–2.4 eV)

Arynes and cyclic alkynes



8 40–50 kcal mol^{-1}

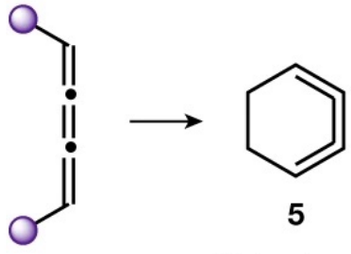
Cyclic allenes



9 30 kcal mol^{-1}

Underexplored strained intermediates

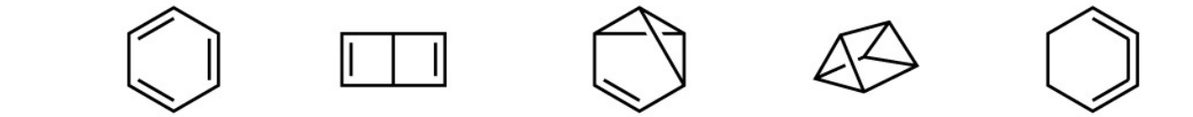
1,2,3-Cyclohexatrienes



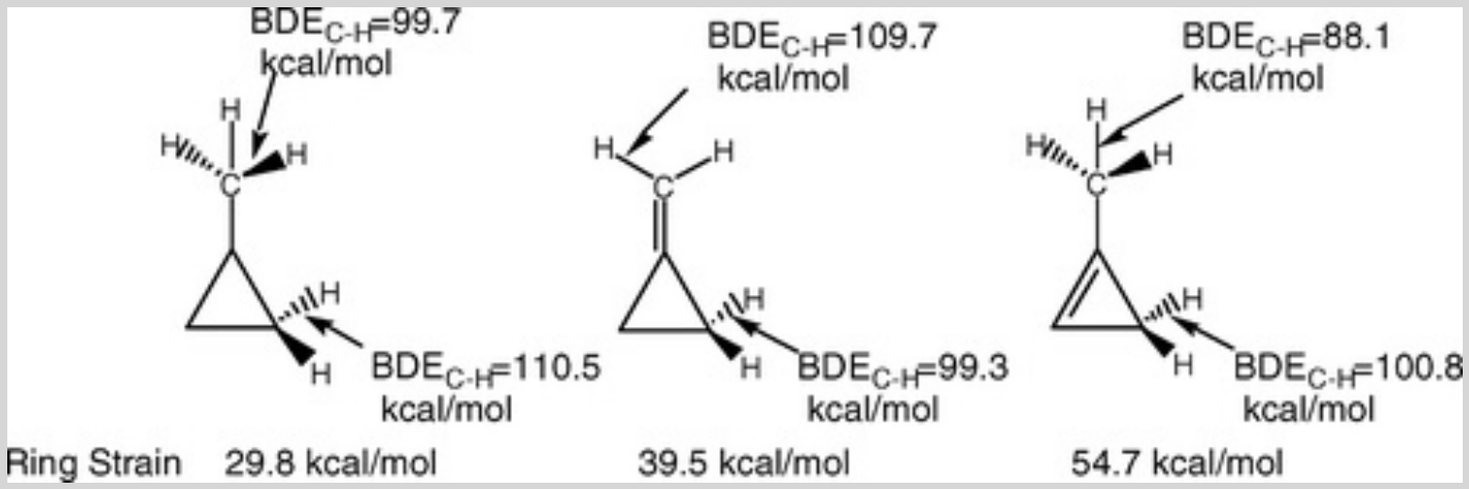
5 50 kcal mol^{-1}

Computational Studies

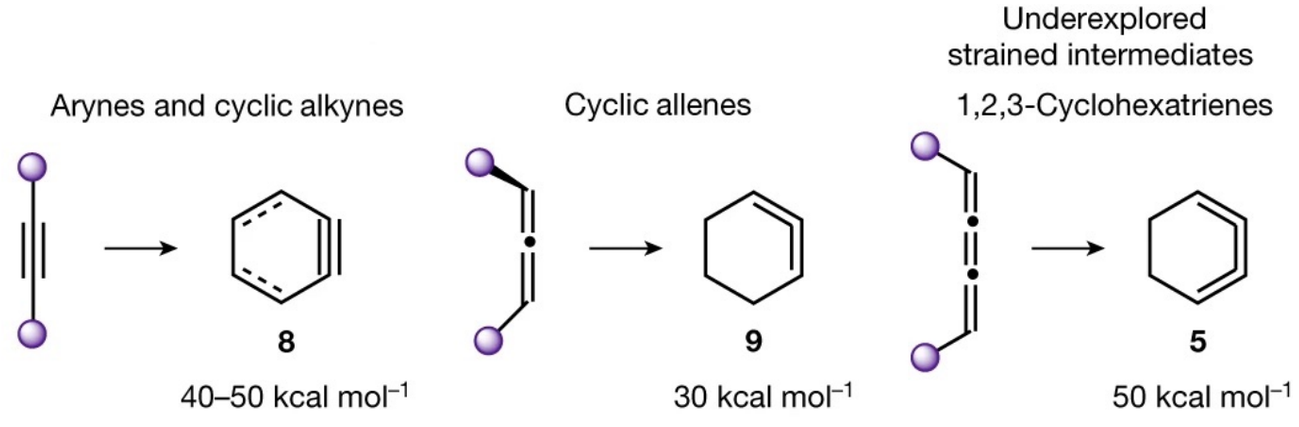
LOT B3LYP-D3/6-311+G(d,p)



1 Benzene	**2** Dewar benzene	**3** Benzvalene	**4** Prismane	**5** 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}



JACS **2004**, *126* 4444–4452



Computational Studies

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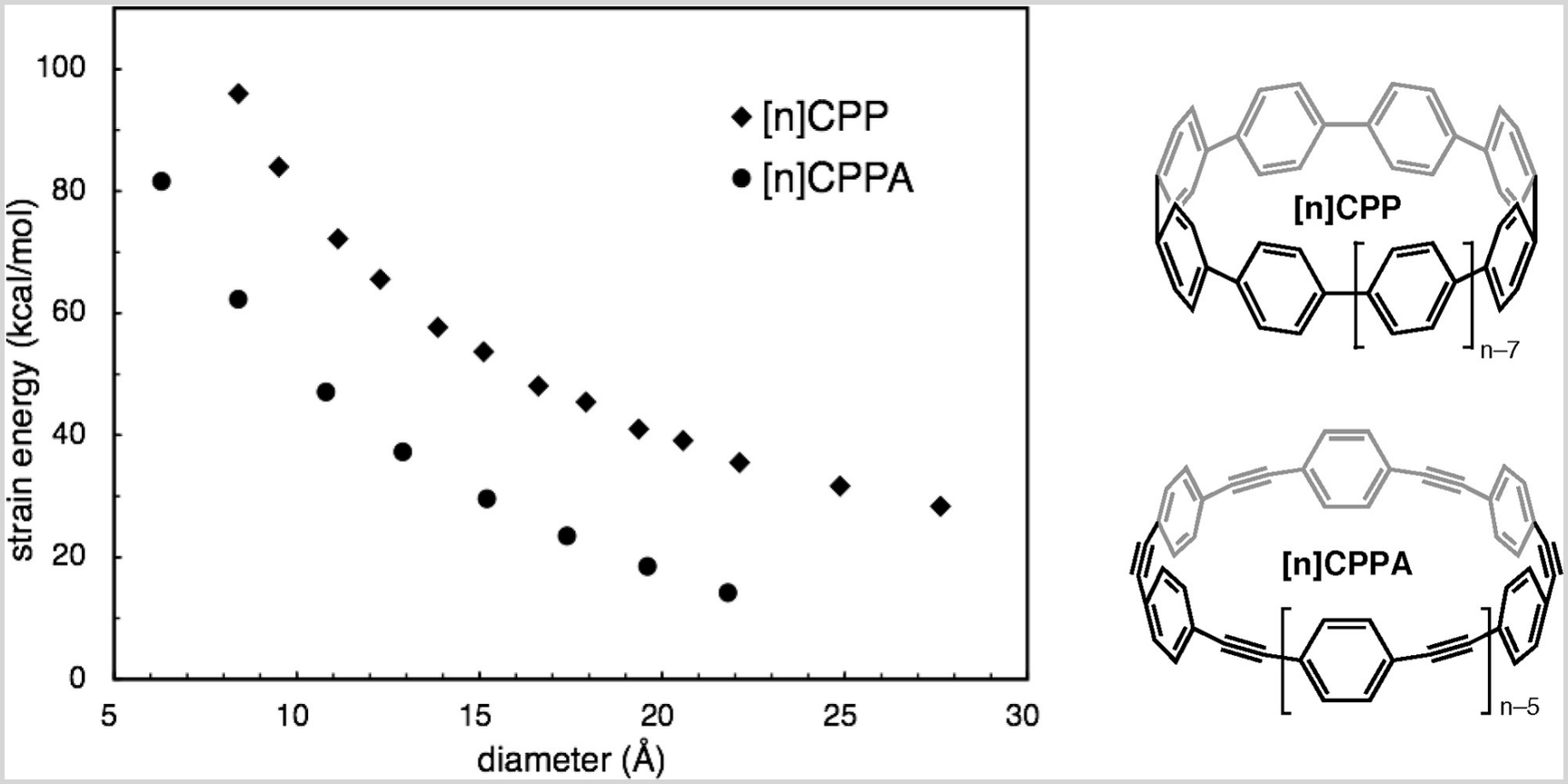
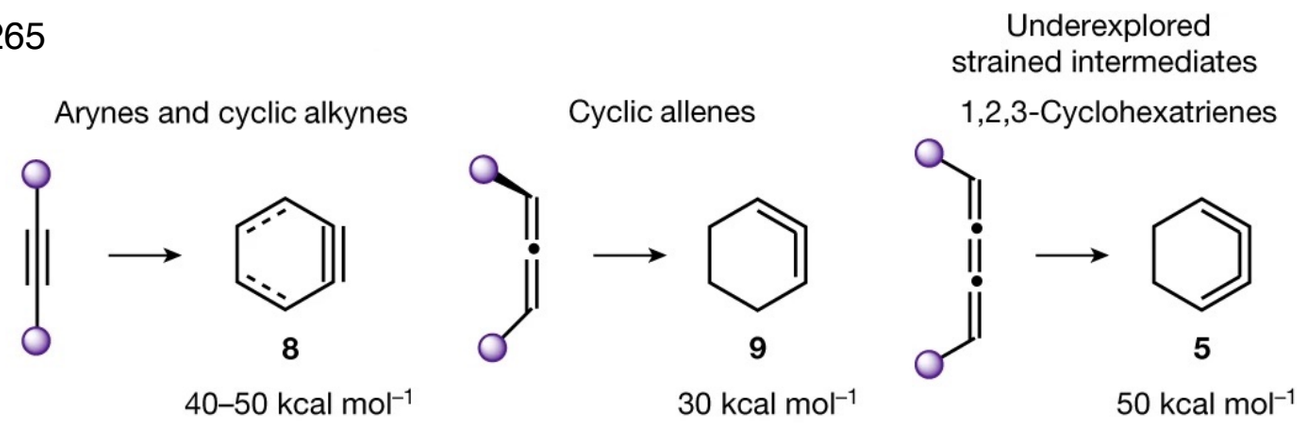
ΔG_{rel} = 0 kcal mol^{-1}	83 kcal mol^{-1}	81 kcal mol^{-1}	123 kcal mol^{-1}	101 kcal mol^{-1}

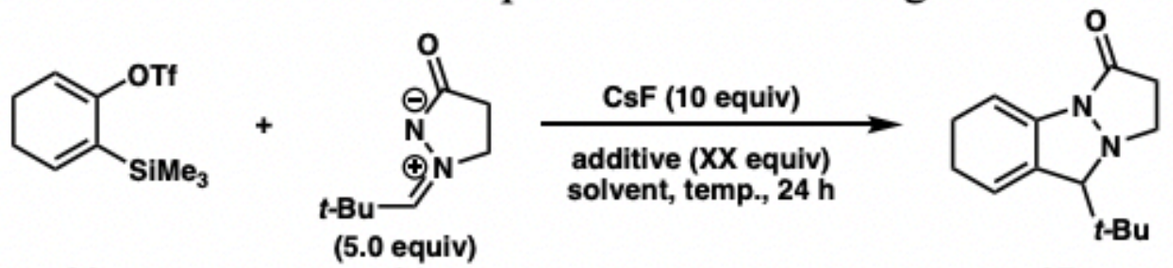


Itami, K. *et al*. *OL* **2010**, 12, 2262–2265



1,2,3-Cyclohexatriene

Table S1. Selected Optimization Screening Results

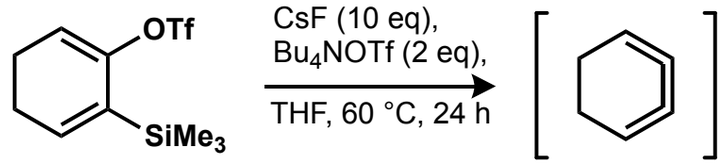


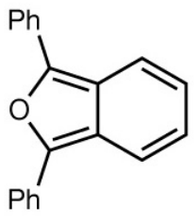
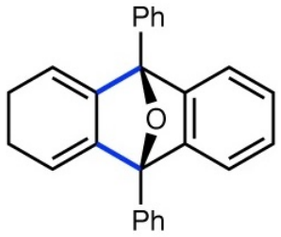
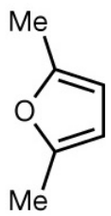
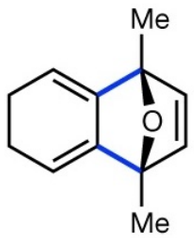
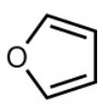
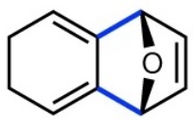
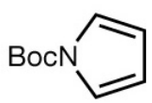
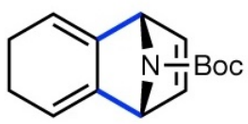
21 *31* *35*

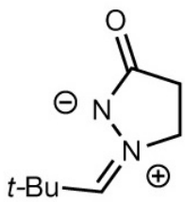
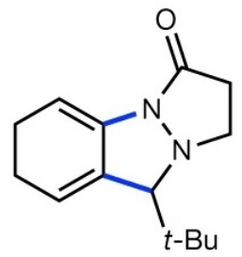
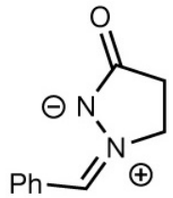
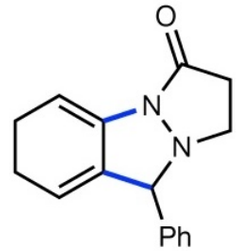
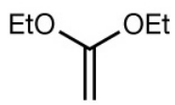
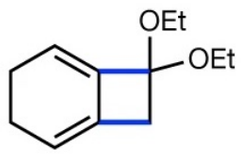
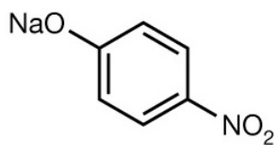
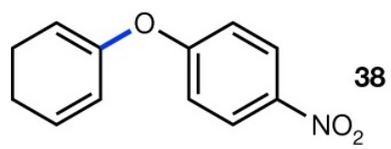
Entry	Conditions	^{1}H NMR Yield[a]	Yield BRSM
1	DMSO, 23 °C	26%	26%
2	MeCN, 23 °C	2%	100%
3	Bu_4NI (1.0 equiv), MeCN, 60 °C	24%	32%
	Solvent Screen		
4	Bu_4NI (1.0 equiv), DMSO, 60 °C	24%	24%
5	Bu_4NI (1.0 equiv), DMF, 60 °C	28%	28%
6	Bu_4NI (1.0 equiv), PhCN, 60 °C	19%	23%
7	Bu_4NI (1.0 equiv), Dioxane, 60 °C	14%	61%
8	Bu_4NI (1.0 equiv), DME, 60 °C	13%	25%
9	Bu_4NI (1.0 equiv), PhH, 60 °C	12%	40%
10	Bu_4NI (1.0 equiv), DCE, 60 °C	0%	N/A
11	Bu_4NI (1.0 equiv), THF, 60 °C	38%	42%
	Fluoride Source Screen		
12	–CsF, +TBAF (5.0 equiv), THF, 23 °C	9%	17%
13	–CsF, +TASF (5.0 equiv), THF, 23 °C	16%	16%
14	CsF (5 equiv), Bu_4NOTf (2.0 equiv), THF, 23 °C	44%	46%
	Additive Loading Screen		
15	Bu_4NOTf (1.0 equiv), THF, 60 °C	42%	76%
16	Bu_4NOTf (2.0 equiv), THF, 60 °C	54%	54%
17[b]	Bu_4NOTf (2.0 equiv), THF, 60 °C	36%[c]	40%

Glovebox required

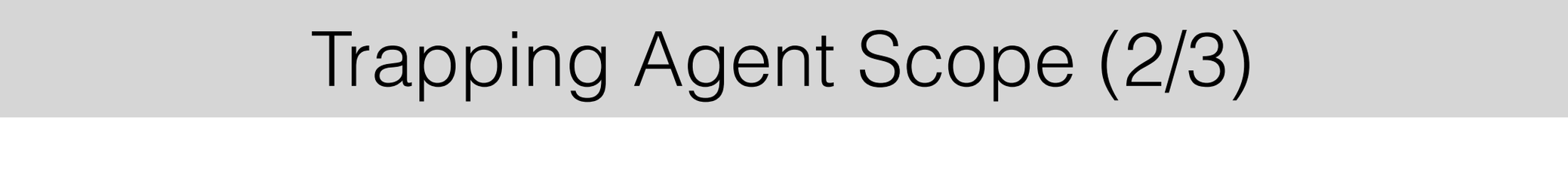
Trapping Agent Scope (1/2)



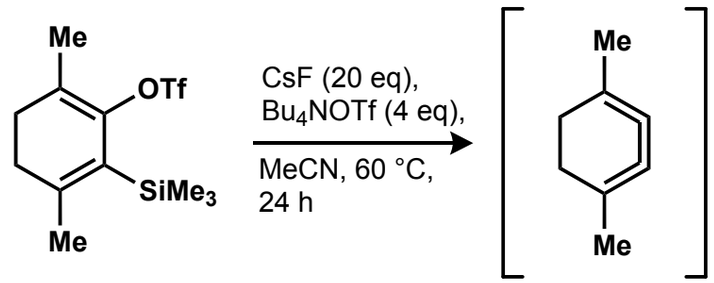
Entry	Trapping agent		Product		Yield
1		**23**		**27**	65%
2		**24**		**28**	62%
3		**25**		**29**	72%
4		**26**		**30**	61%

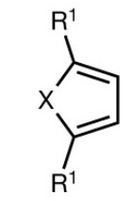
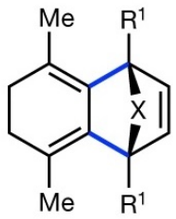
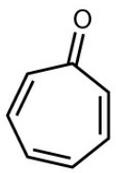
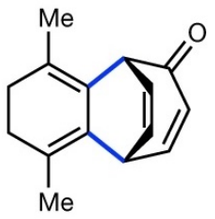
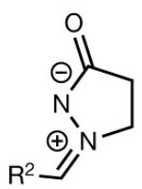
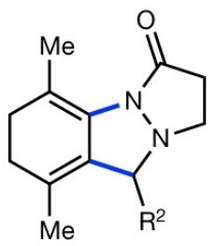
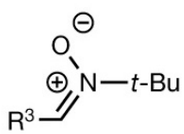
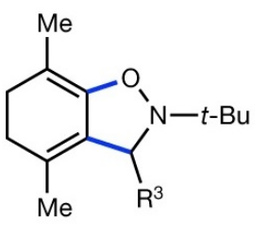
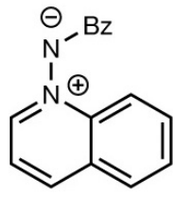
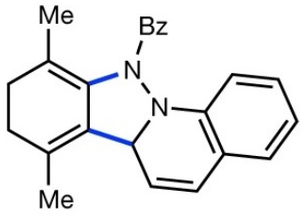
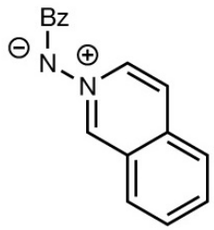
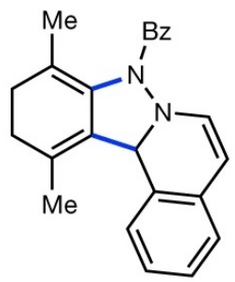
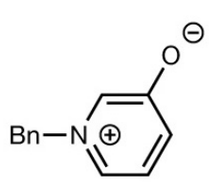
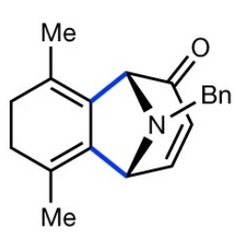
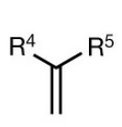
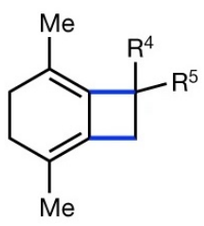
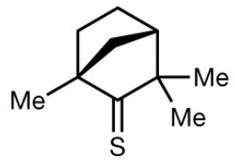
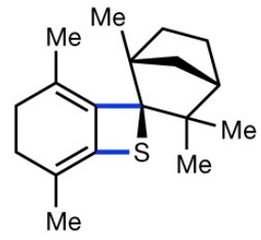
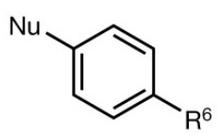
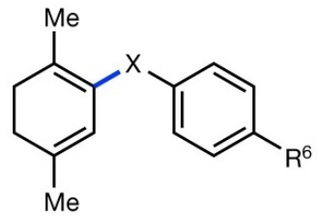
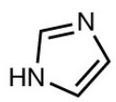
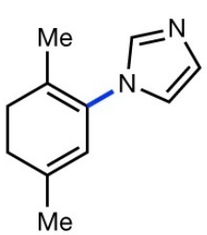
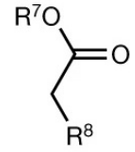
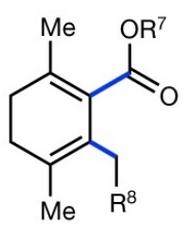
Entry	Trapping agent		Product		Yield
5		**31**		**35**	59%
6		**32**		**36**	51%
7		**33**		**37**	44%
8*		**34**		**38**	51%

Trapping Agent Scope (2/3)

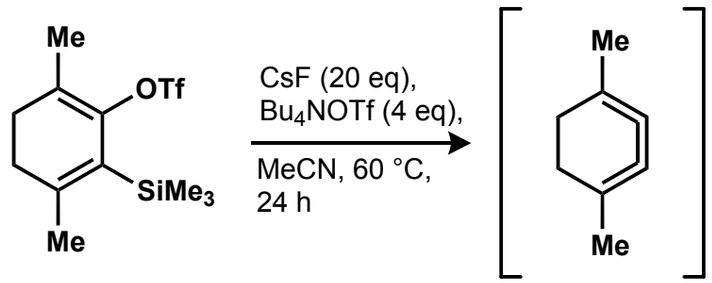


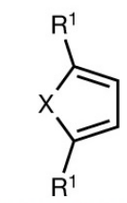
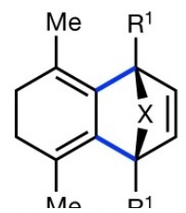
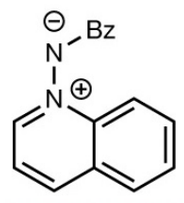
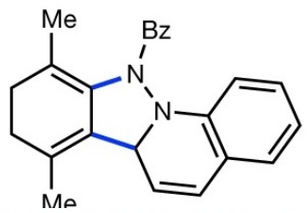
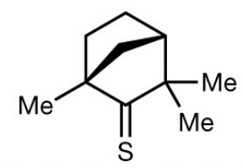
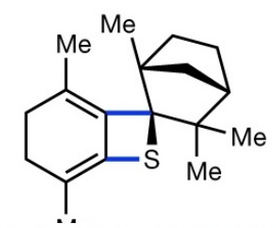
Trapping Agent Scope (3/3)



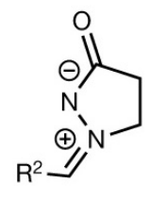
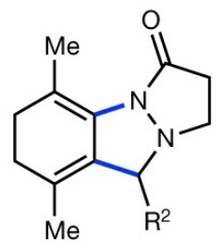
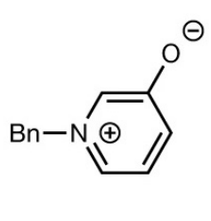
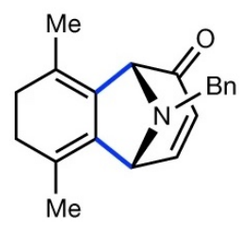
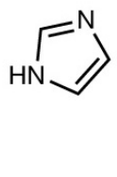
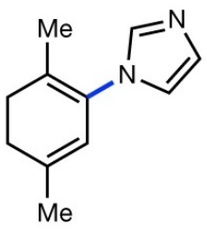
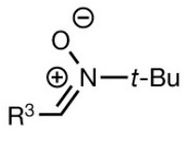
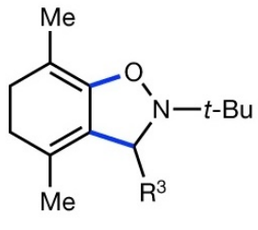
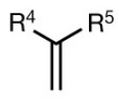
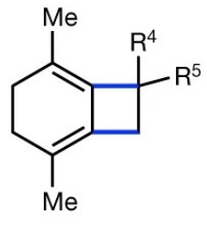
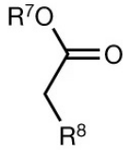
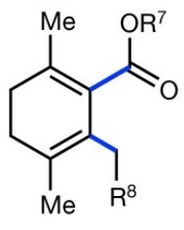
Entry	Trapping agent	Product and yield
1 2		 X = O, R^1 = Me, **50**, 80% X = NBoc, R^1 = H, **51**, 82%
3		 **52**, 40%
4 5		 R^2 = *t*-Bu, **53**, 86% R^2 = Ph, **54**, 87%
6 7		 R^3 = Ph, **55**, 74% R^3 = *t*-Bu, **56**, 75%
8		 **57**, 79%
9		 **58**, 51%
10		 **66**, 68%
11* 12*		 R^4 = R^5 = OEt, **67**, 47% R^4 = $NBoc_2$, R^5 = CO_2Me, **68**, 48%
13		 **69**, 77% (2.7:1 dr)
14 15		 Nu = NaO, R^6 = NO_2, **34** Nu = SH, R^6 = H, **62** X = O, R^6 = NO_2, **70**, 83% X = S, R^6 = H, **71**, 81%
16		 **63** **72**, 58%
17 18		 R^7 = Et, R^8 = CN, **64** R^7 = Me, R^8 = CO_2Me, **65** R^7 = Et, R^8 = CN, **73**, 47% R^7 = Me, R^8 = CO_2Me, **74**, 82%

Trapping Agent Scope (3/3)



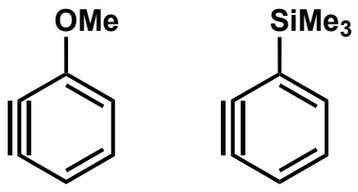
Entry	Trapping agent	Product and yield
1 2		
8		
13		

switching the solvent to acetonitrile and increasing the loading of Bu_4NOTf facilitated full conversion and good yields in trappings of **43**. More generally, we observed that trappings of disubstituted triene **43** proceeded in higher yields and with broader scope compared with trappings of the parent compound, 1,2,3-cyclohexatriene (**5**), despite **43** bearing an increased steric profile. The results indicate the engagement of disubstituted triene **43** in (a) (4 + 2)

Entry	Trapping agent	Product and yield
4 5		
	R^2 = *t*-Bu, **31** R^2 = Ph, **32**	R^2 = *t*-Bu, **53**, 86% R^2 = Ph, **54**, 87%
10		
	59	**66**, 68%
16		
	63	**72**, 58%
6 7		
	R^3 = Ph, **46** R^3 = *t*-Bu, **47**	R^3 = Ph, **55**, 74% R^3 = *t*-Bu, **56**, 75%
11* 12*		
	R^4 = R^5 = OEt, **33** R^4 = $NBoc_2$, R^5 = CO_2Me, **60**	R^4 = R^5 = OEt, **67**, 47% R^4 = $NBoc_2$, R^5 = CO_2Me, **68**, 48%
17 18		
	R^7 = Et, R^8 = CN, **64** R^7 = Me, R^8 = CO_2Me, **65**	R^7 = Et, R^8 = CN, **73**, 47% R^7 = Me, R^8 = CO_2Me, **74**, 82%

Monosubstituted Triene Case Study

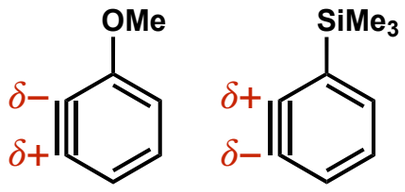
Selectivity of Aryne Chemistry: an Analogy



Methoxy aryne Stoltz, B. *et al*. *OL* **2010**, *12*(6), 1224–1227
Distortion model Garg, N. *et al*. *JACS* **2012**, 134(34), 13966–13969; Garg, N.; Houk, K. N. et al. *JACS* **2010**, *132*(4), 1267–1269

Monosubstituted Triene Case Study

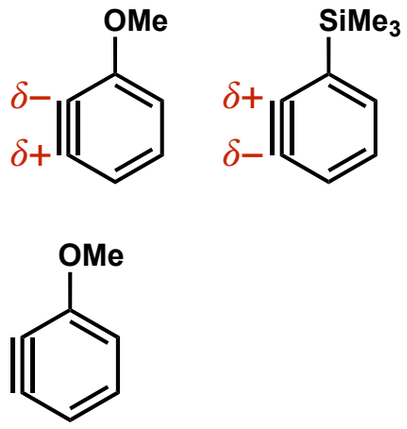
Selectivity of Aryne Chemistry: an Analogy



Methoxy aryne Stoltz, B. *et al*. *OL* **2010**, *12*(6), 1224–1227
Distortion model Garg, N. *et al*. *JACS* **2012**, 134(34), 13966–13969; Garg, N.; Houk, K. N. et al. *JACS* **2010**, *132*(4), 1267–1269

Monosubstituted Triene Case Study

Selectivity of Aryne Chemistry: an Analogy



Methoxy aryne Stoltz, B. *et al*. *OL* **2010**, *12*(6), 1224–1227
Distortion model Garg, N. *et al*. *JACS* **2012**, 134(34), 13966–13969; Garg, N.; Houk, K. N. et al. *JACS* **2010**, *132*(4), 1267–1269

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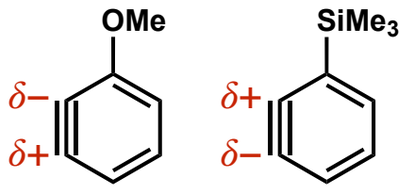

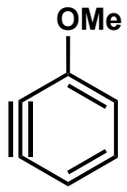

meta selective (electronics)

Methoxy aryne Stoltz, B. *et al*. *OL* **2010**, *12*(6), 1224–1227
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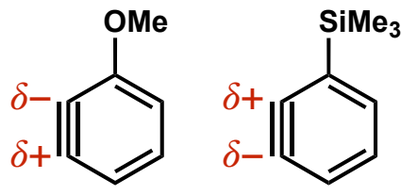
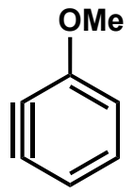
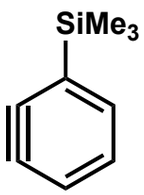




meta selective (electronics)

But how about?



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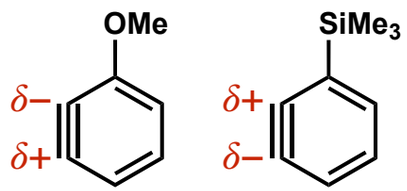
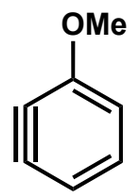
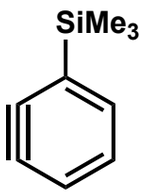
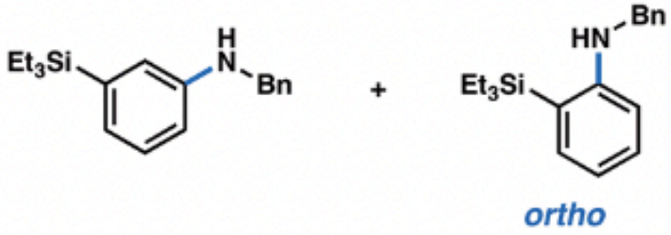
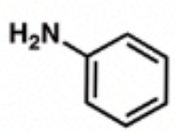
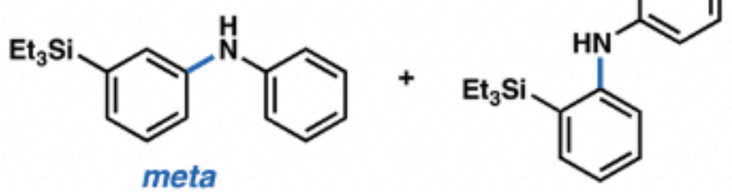
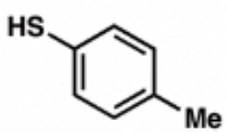
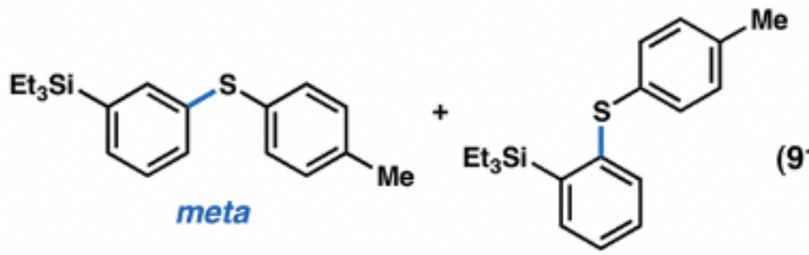
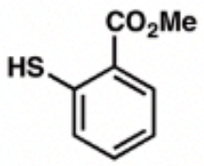
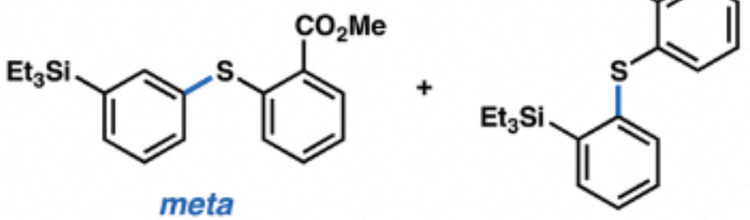
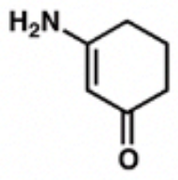
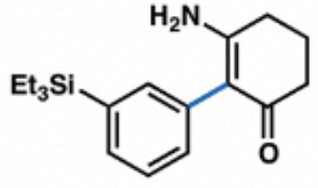
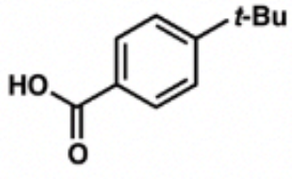
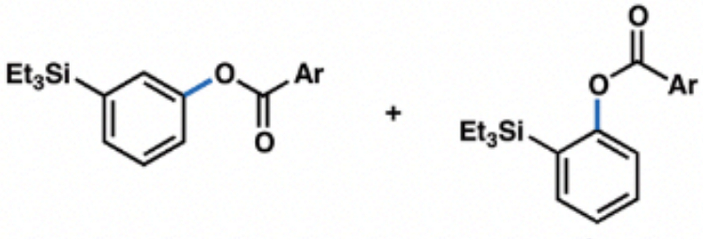




meta selective (electronics)

But how about?



entry	trapping agent	product(s)	ratio (yield[b])
1	H_2N–Bn		*1:2* (81% yield)
2			*2:1* (99% yield)
3			*4:1* (91% yield)
4			*10:1* (77% yield)
5			(52% yield)
6			*1:3* (53% yield)

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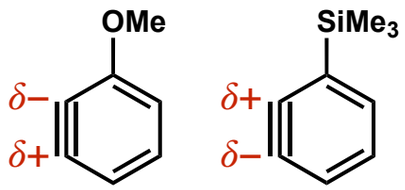
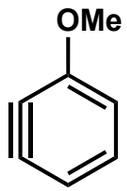
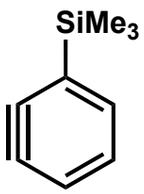




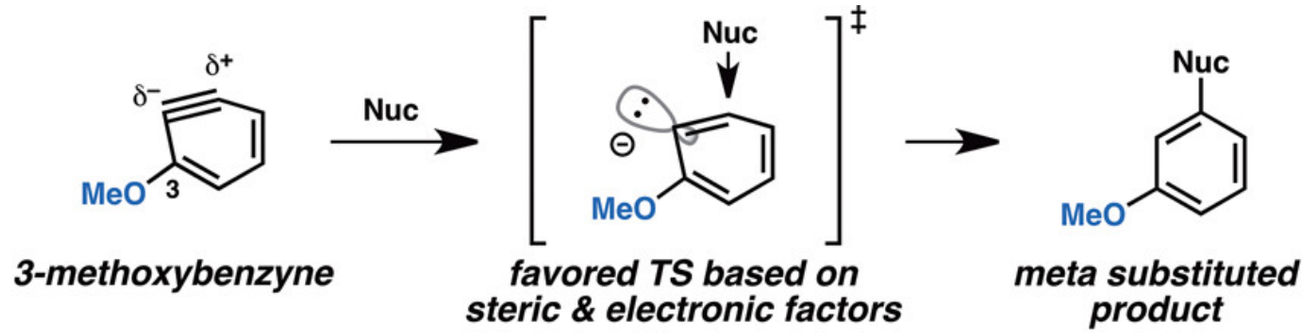
meta selective (electronics)

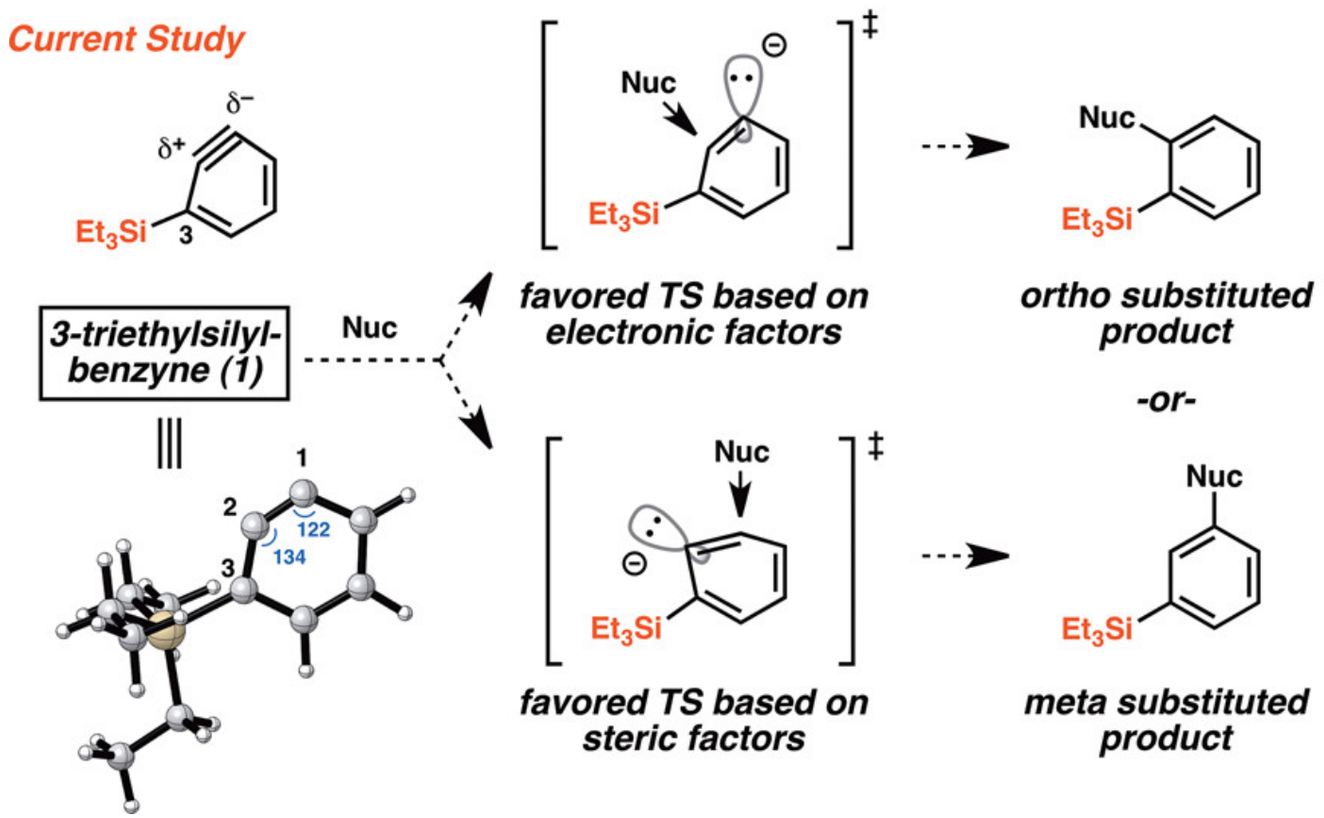
But how about?



Introducing…

The aryne distortion model





LOT B3LYP/6-311+G(d,p)

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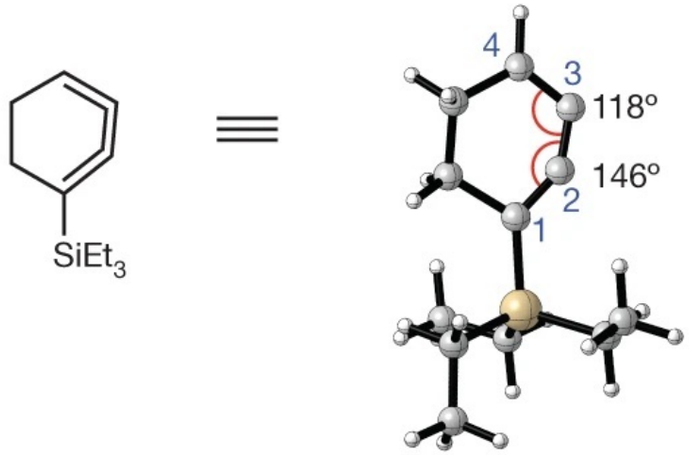
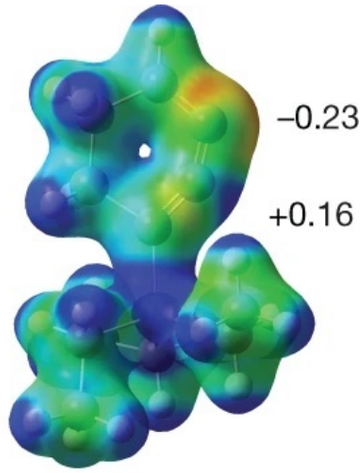
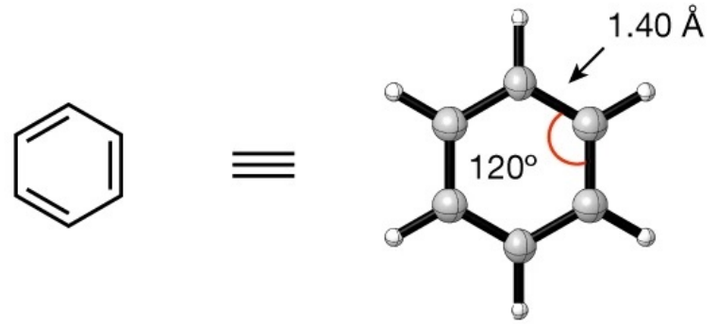
Monosubstituted Triene Case Study

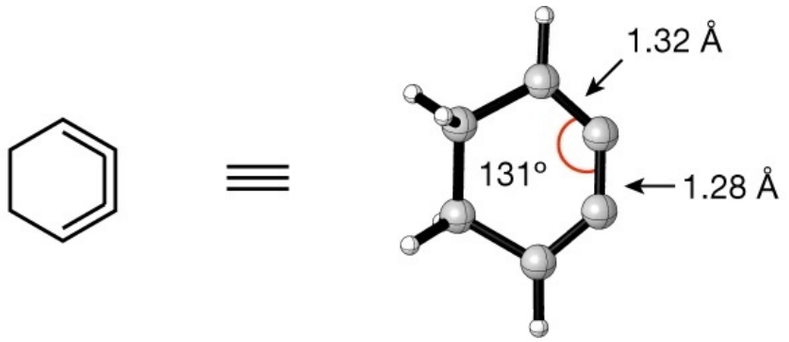
LOT B3LYP-D3/6-311+G(d,p)



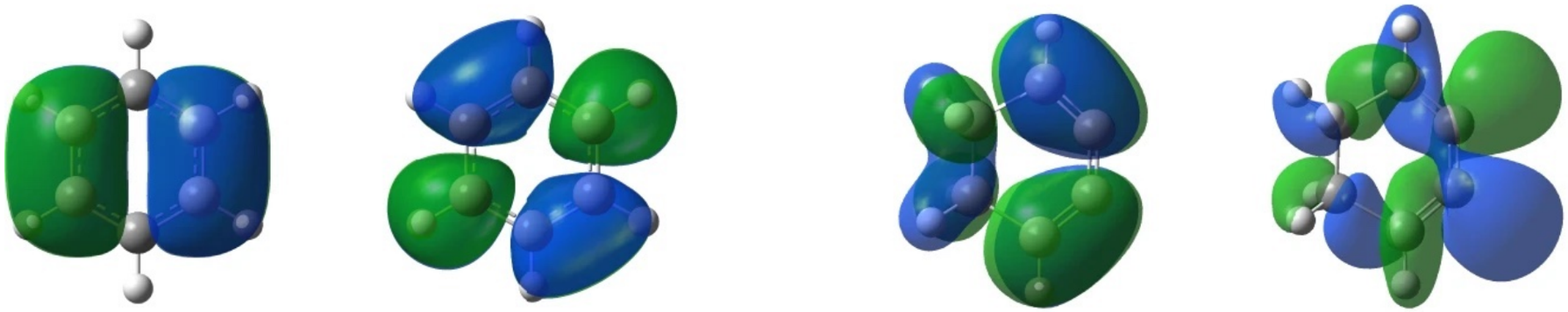


Comparison…





HOMO LUMO HOMO LUMO



(−7.1 eV) (−0.5 eV) (−6.2 eV) (−2.1 eV)

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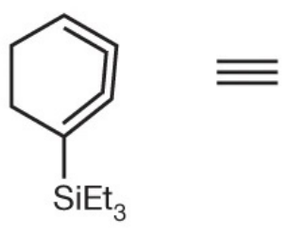
LOT B3LYP-D3/6-311+G(d,p)



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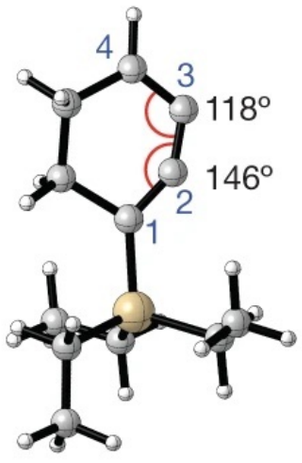
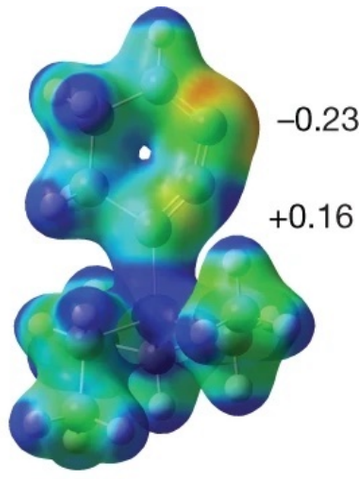
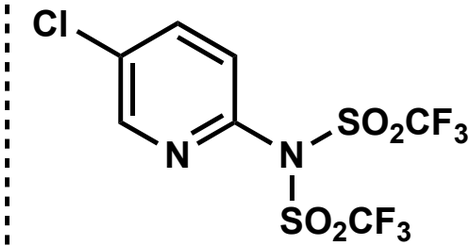
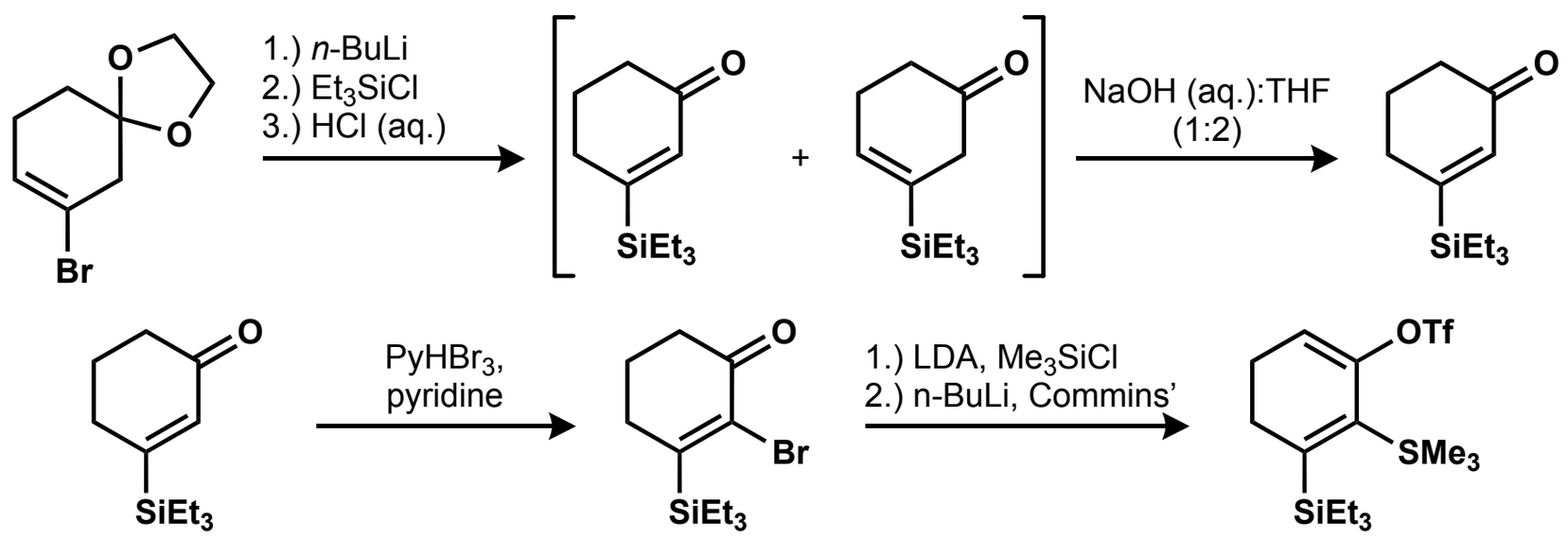






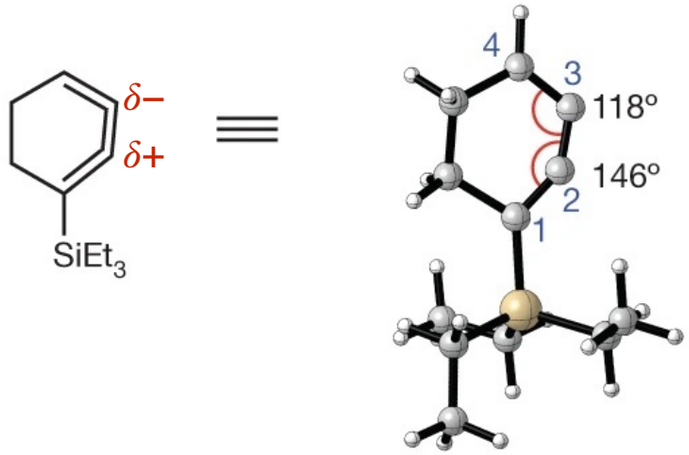
Commins's reagent

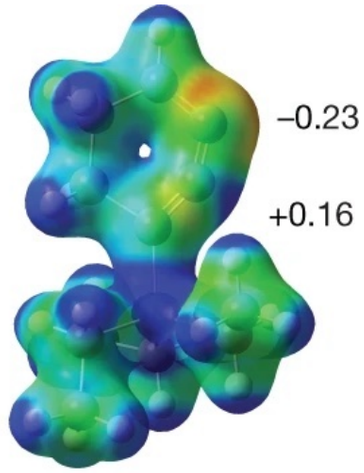


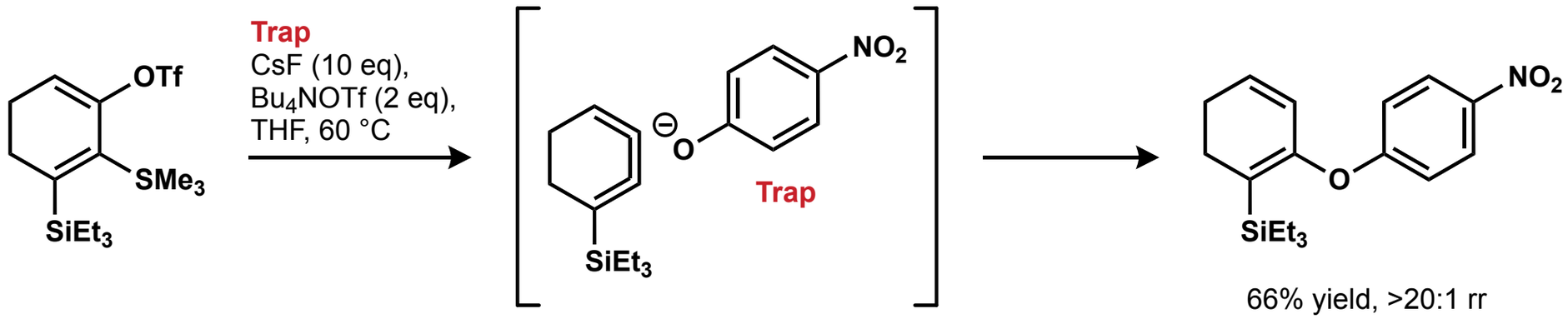
Commin's reagent *TL* **1992**, *33*(42), 6299-6302

Monosubstituted Triene Case Study and Application

LOT B3LYP-D3/6-311+G(d,p)



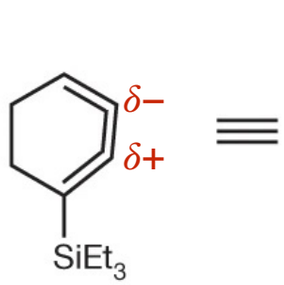




66% yield, >20:1 rr

Monosubstituted Triene Case Study and Application

LOT B3LYP-D3/6-311+G(d,p)



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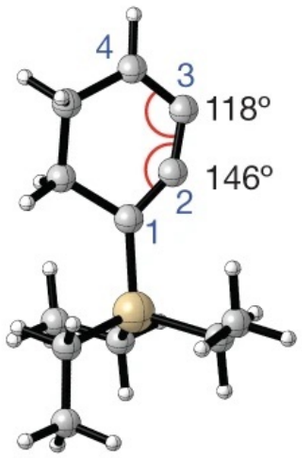
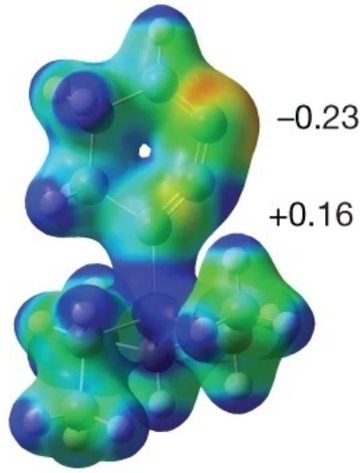
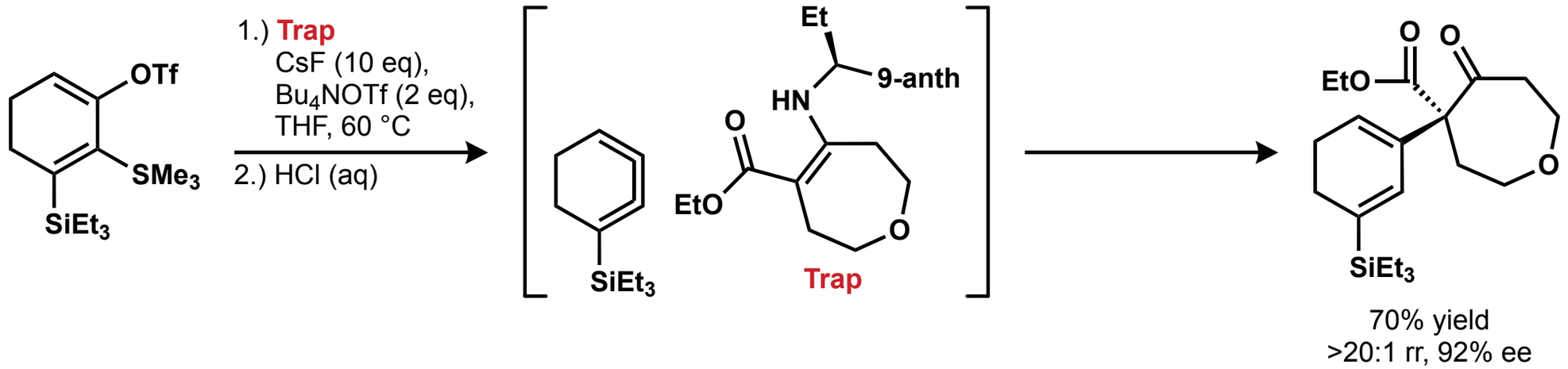




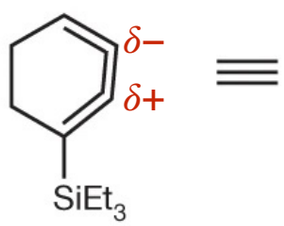


70% yield
>20:1 rr, 92% ee

Chiral auxiliary *beta*-ketoesters Garg, N.; Houk, K. N. *et al*. *JACS* **2018**, *140*(24), 7605–7610
C–C cleavage Stoltz, B. M. et al. *JACS* **2005**, *127*(15), 5340–5341

Monosubstituted Triene Case Study and Application

LOT B3LYP-D3/6-311+G(d,p)



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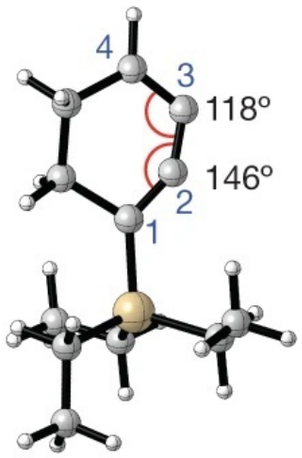
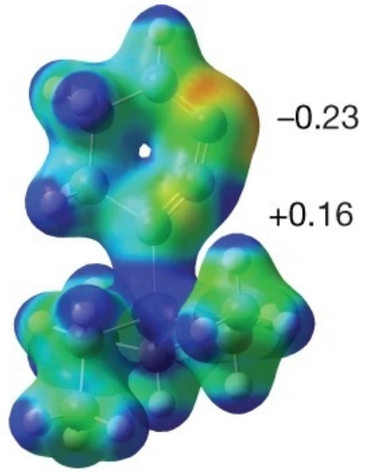
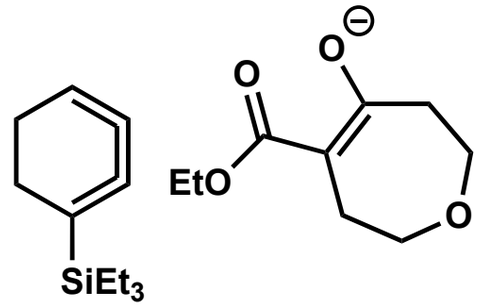
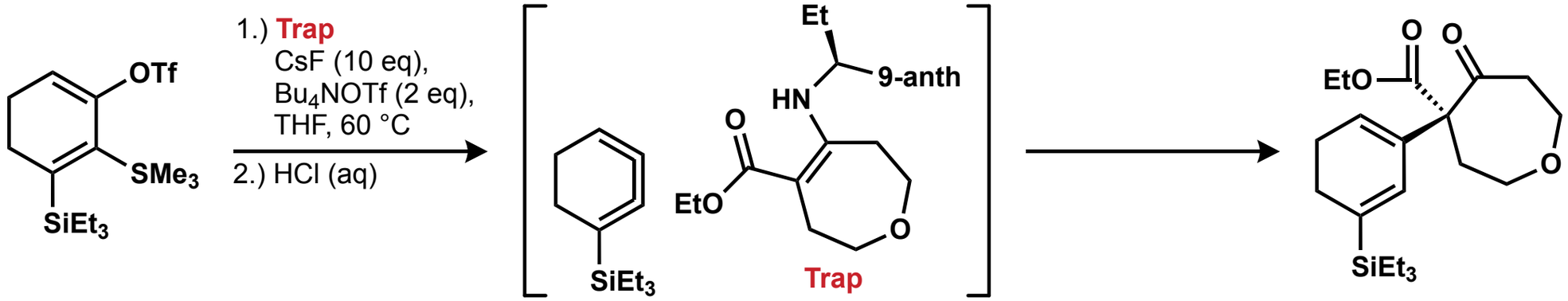






Direct from the ketoester?



70% yield
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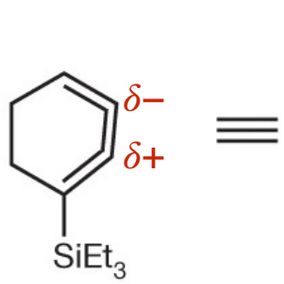
C–C cleavage Stoltz, B. M. et al. *JACS* **2005**, *127*(15), 5340–5341

Monosubstituted Triene Case Study and Application

LOT B3LYP-D3/6-311+G(d,p)



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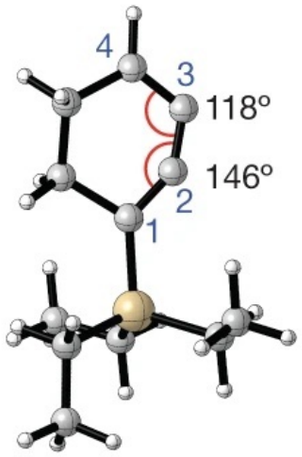

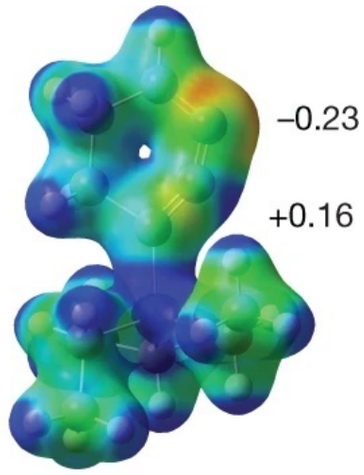

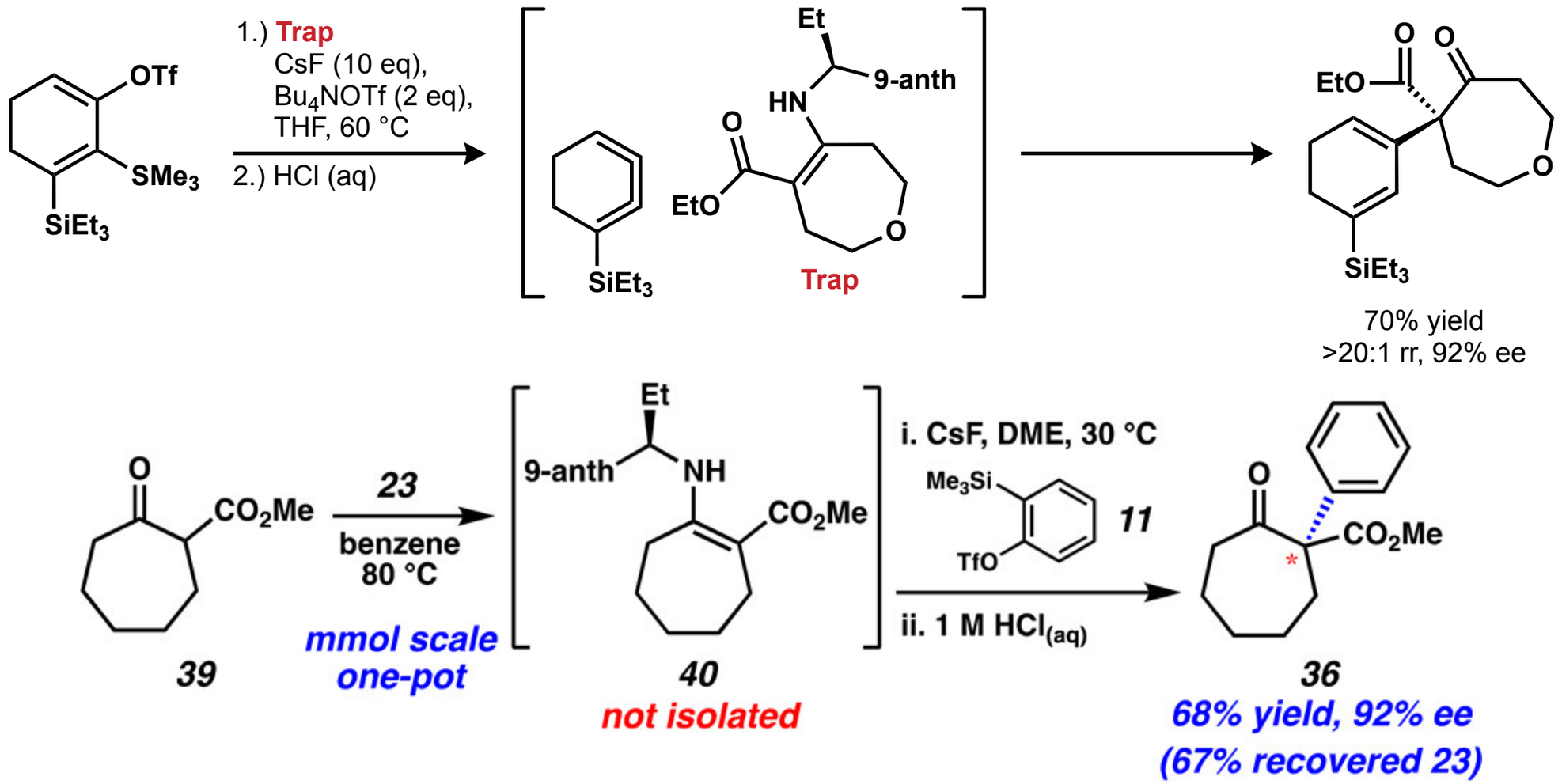

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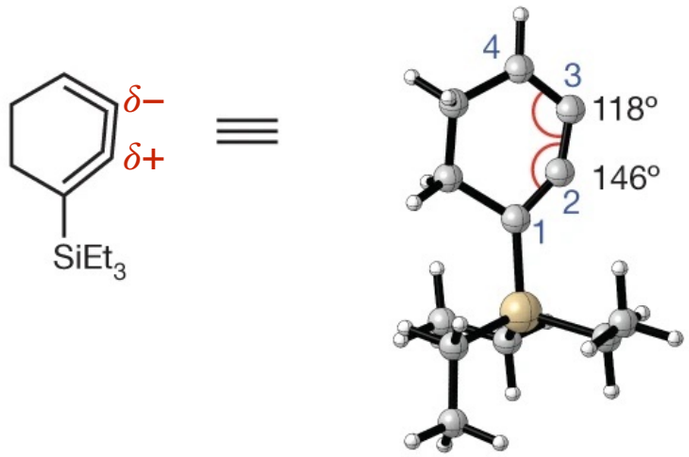
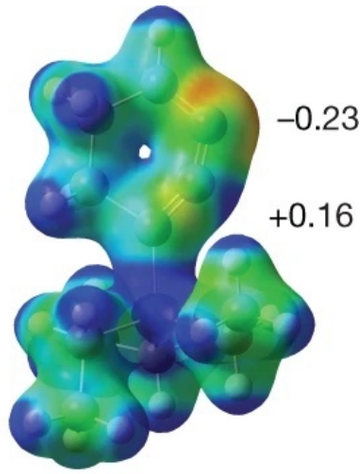
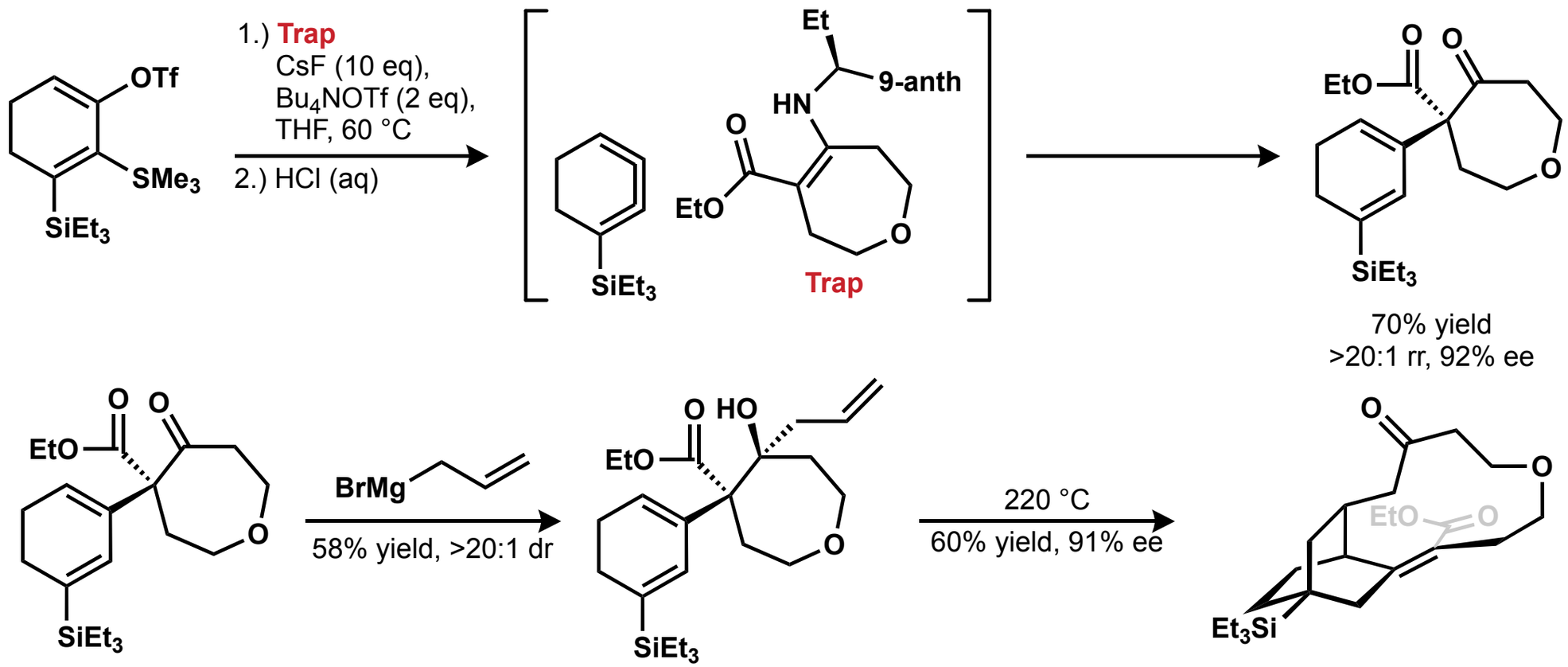


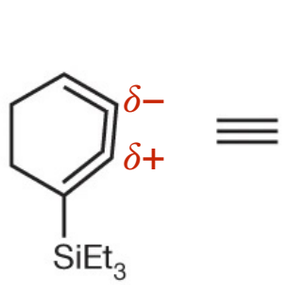


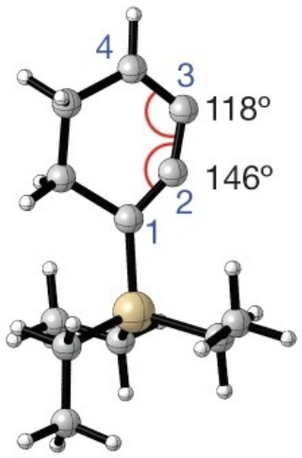


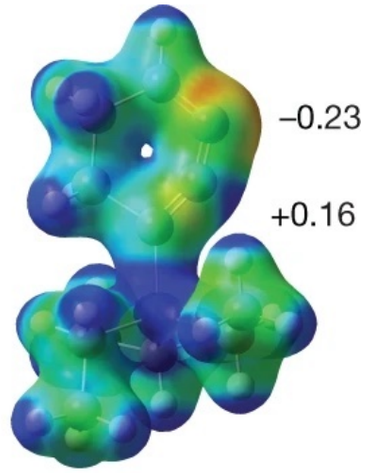
Chiral auxiliary *beta*-ketoesters Garg, N.; Houk, K. N. *et al*. *JACS* **2018**, *140*(24), 7605–7610
C–C cleavage Stoltz, B. M. et al. *JACS* **2005**, *127*(15), 5340–5341

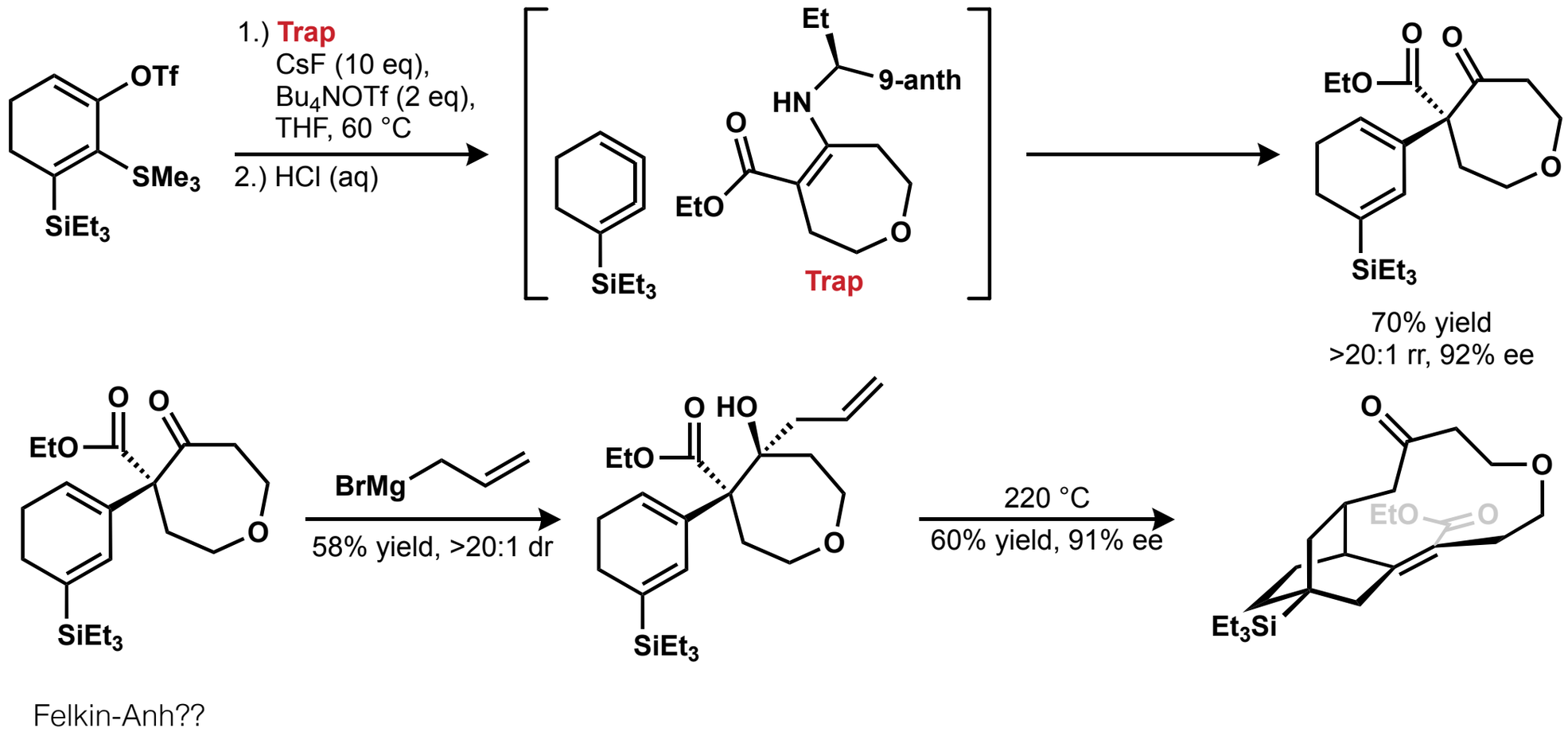
Monosubstituted Triene Case Study and Application

LOT B3LYP-D3/6-311+G(d,p)









Felkin-Anh??

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Monosubstituted Triene Case Study and Application

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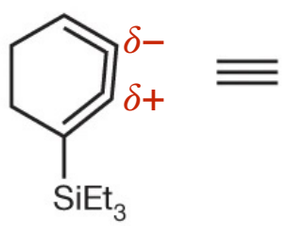

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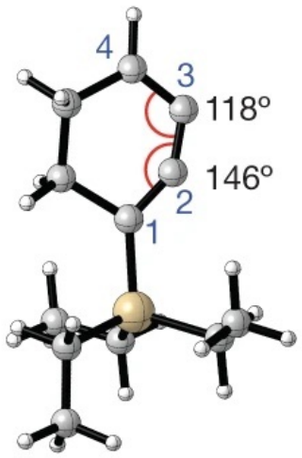
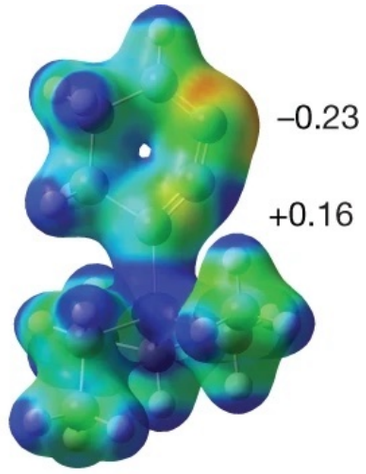
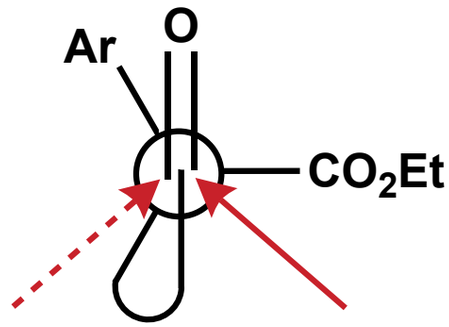
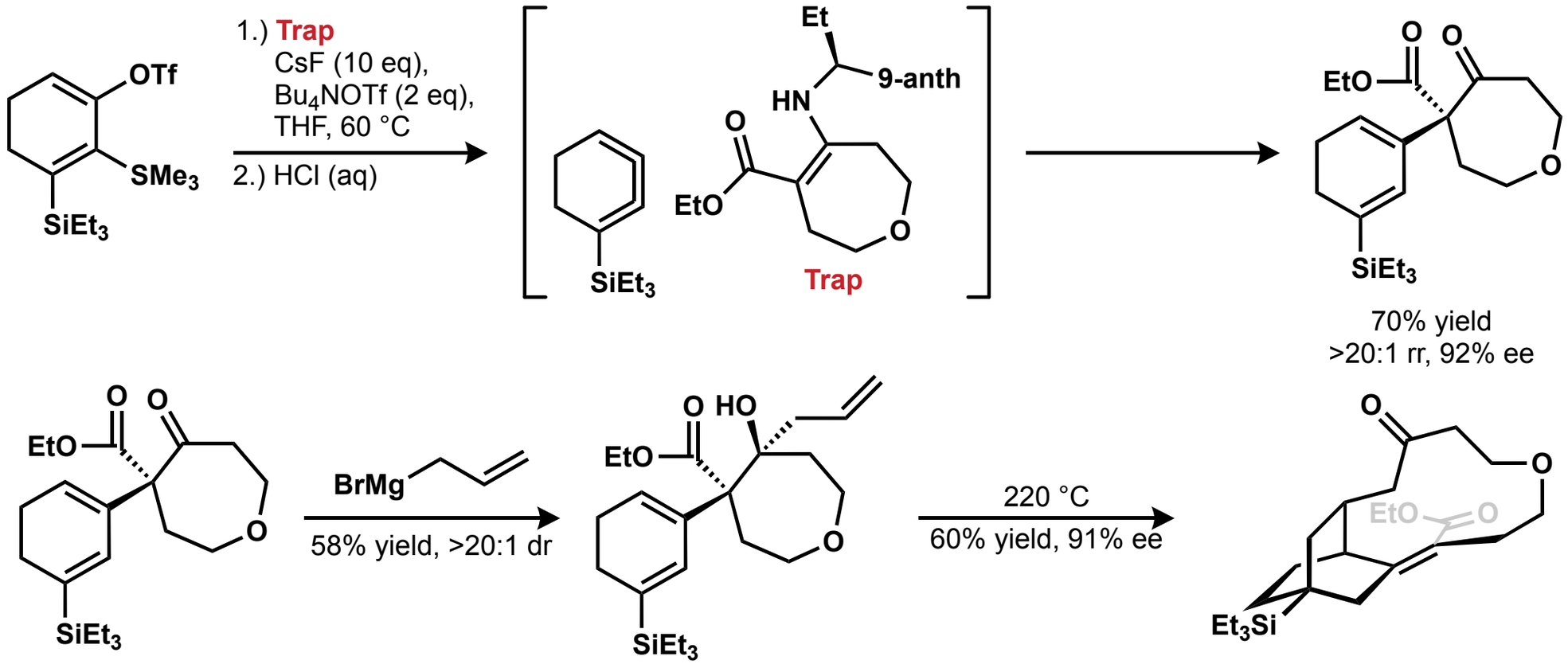






Steric strain Torsional strain



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Monosubstituted Triene Case Study and Application

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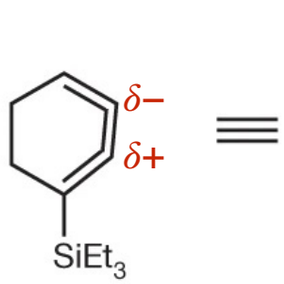

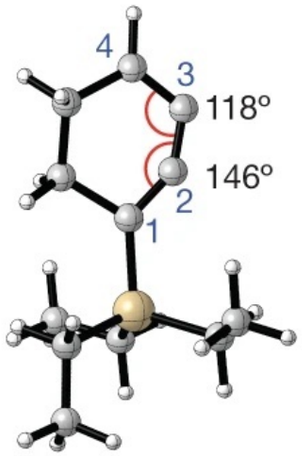

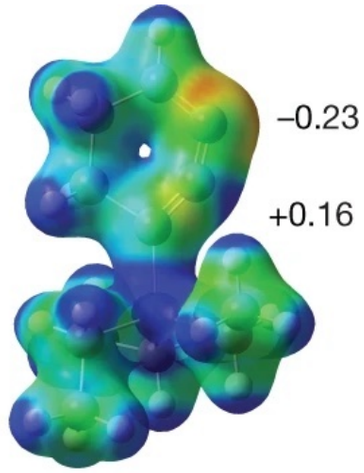

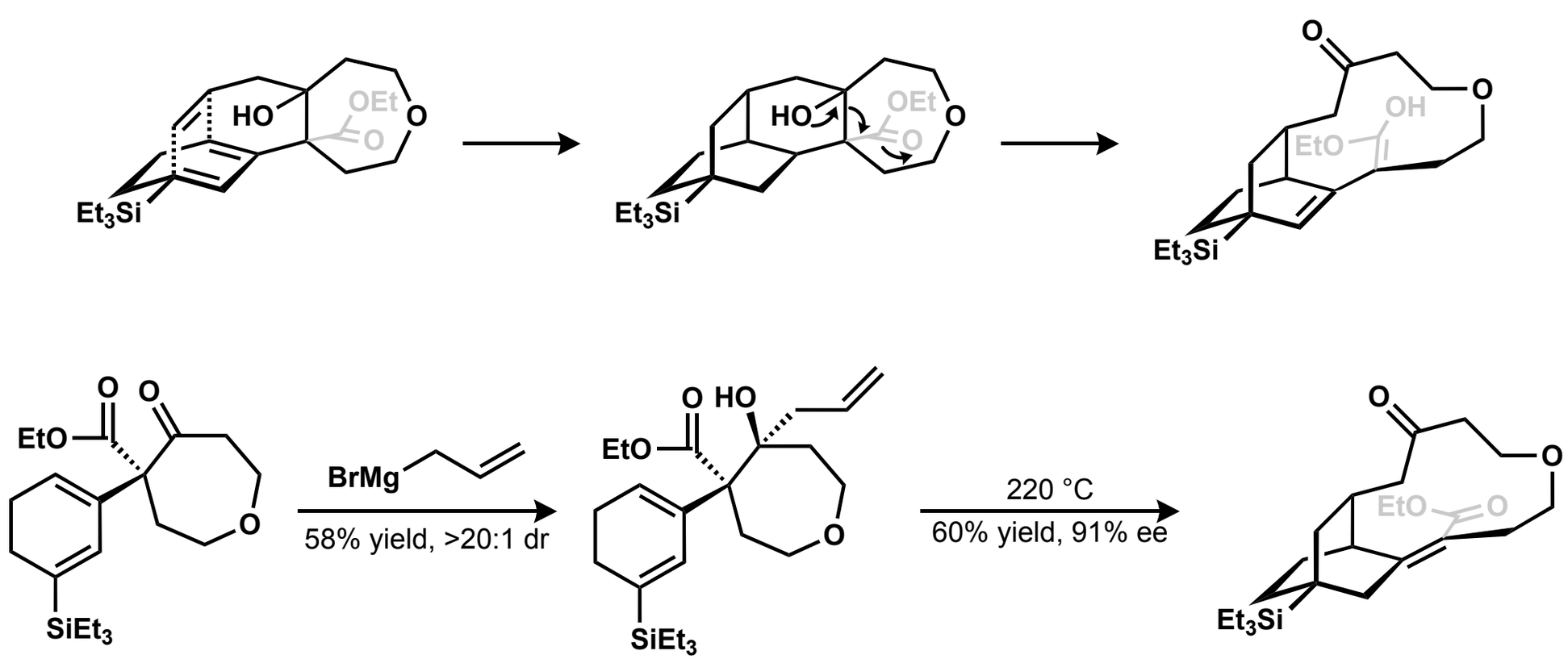

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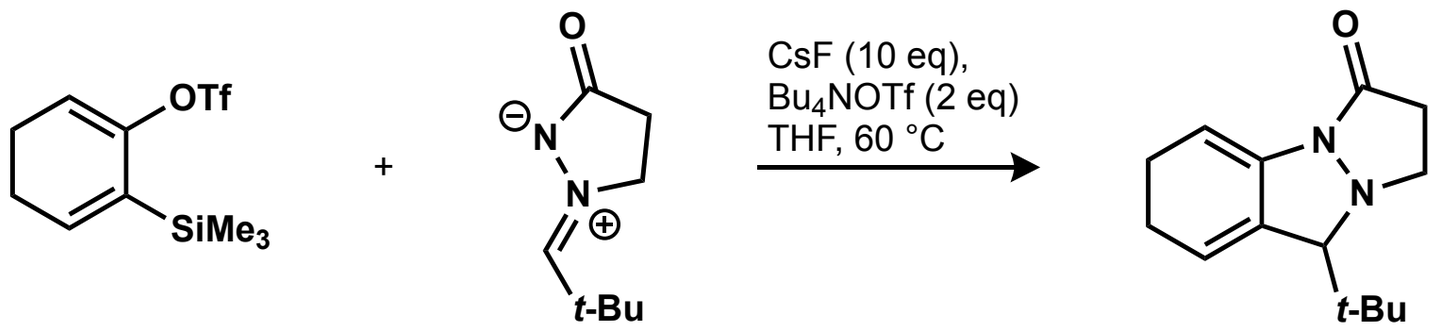
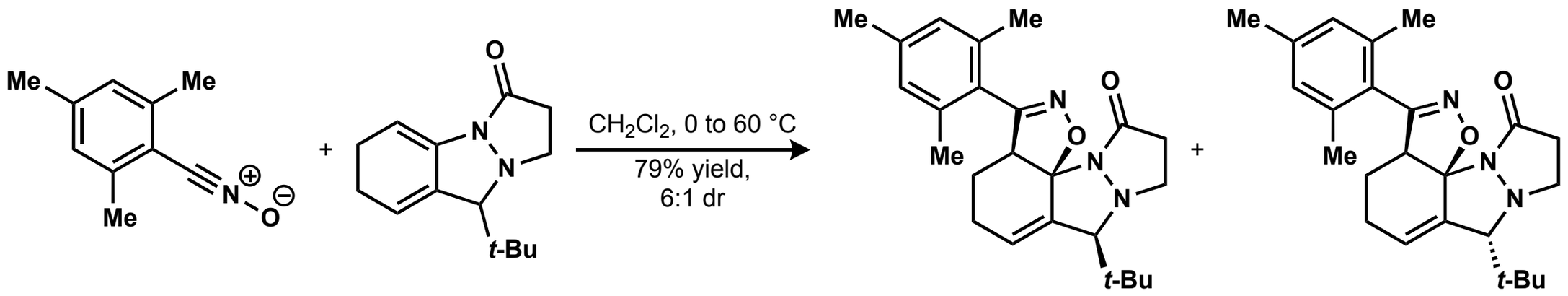
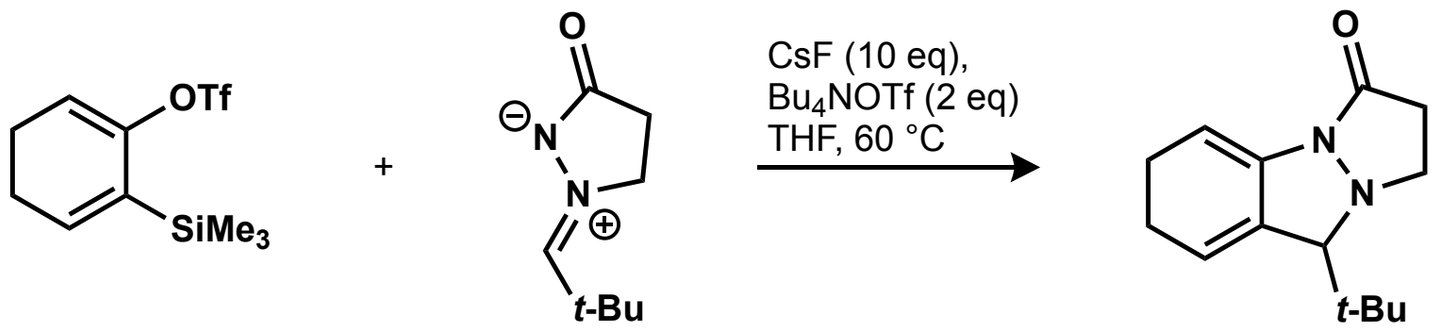
Further Application

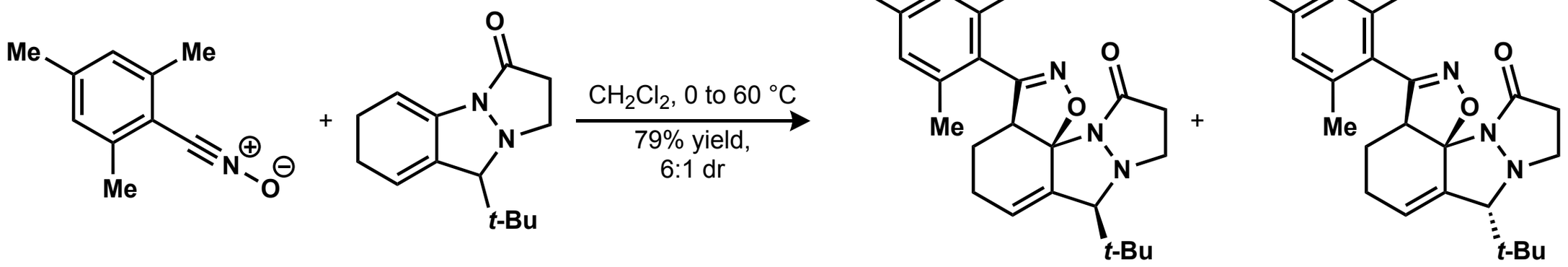




major *minor*

Further Application

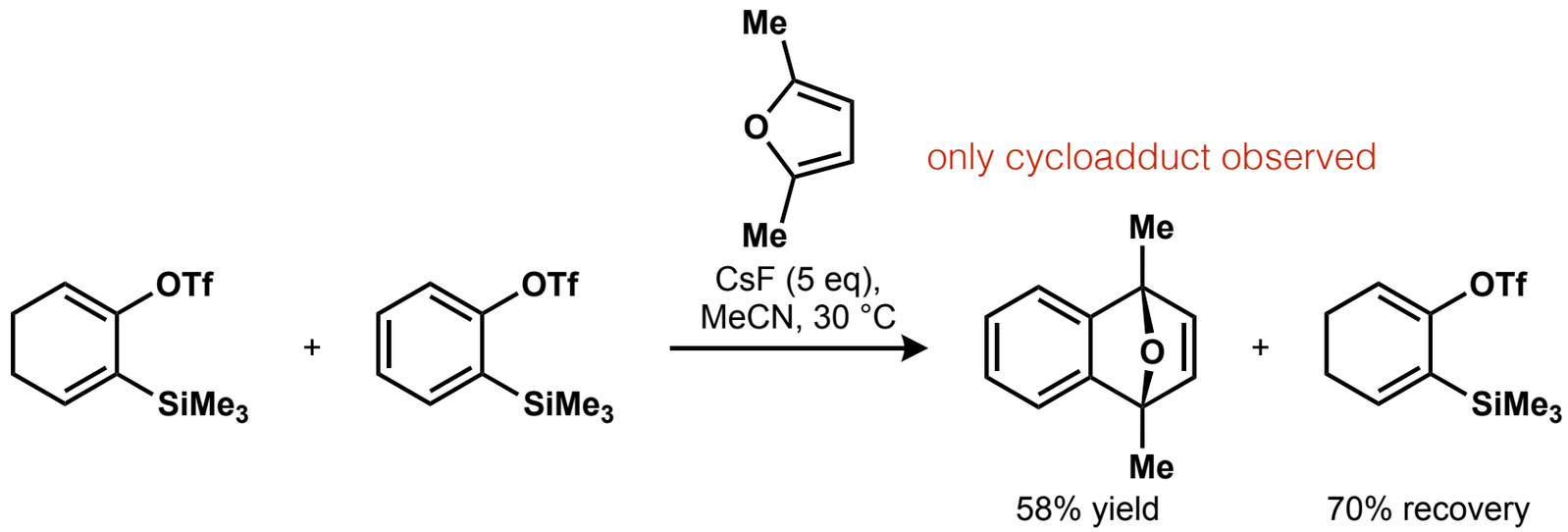


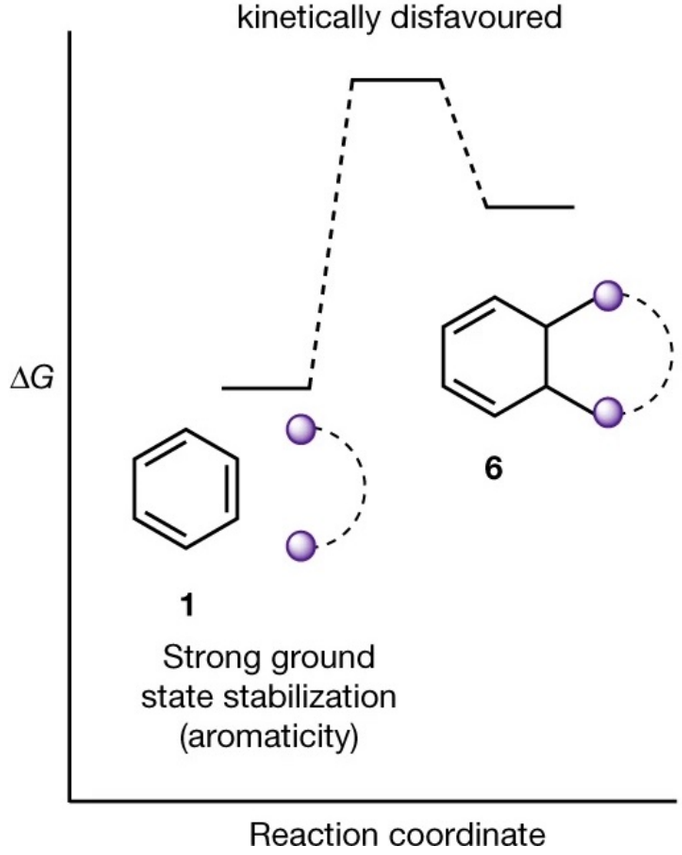


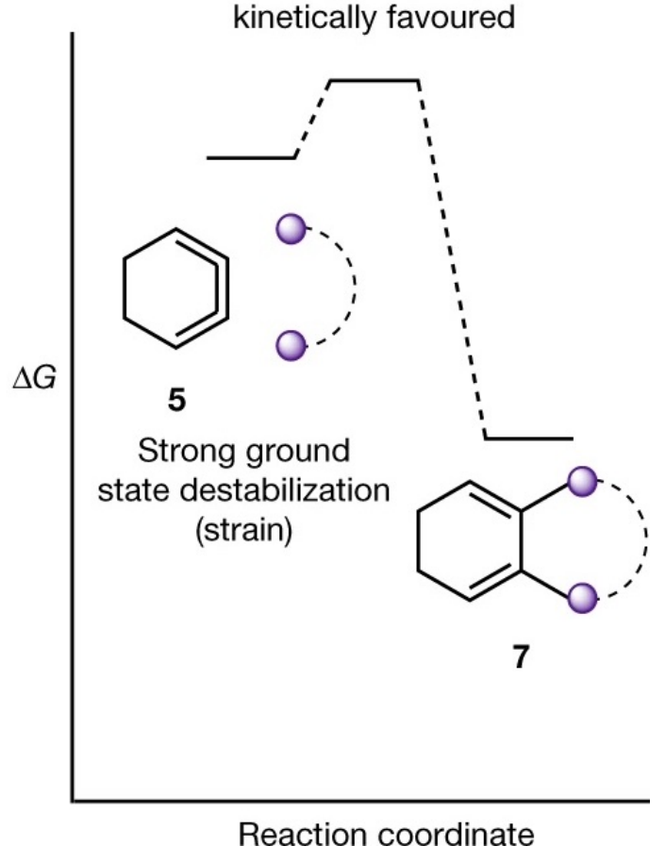
major *minor*

Diastereoselectivity?

Competition Experiment

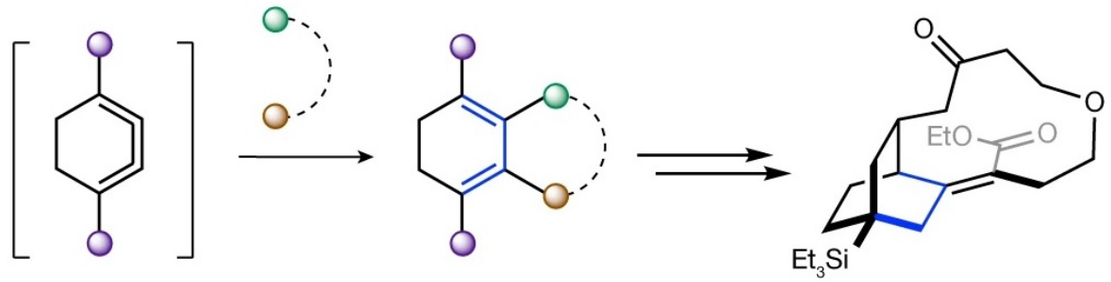






Summary and Evaluation

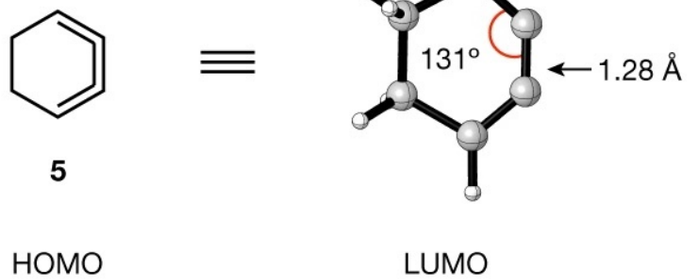
Strain-promoted reactions of 1,2,3-cyclohexatriene and its derivatives



From readily accesible precursors under mild conditions

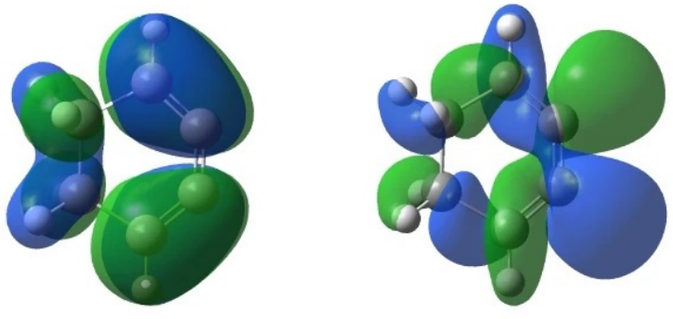
Diverse highly functionalized 1,3-dienes

Unconventional entryway to complex scaffolds



HOMO

LUMO



(–6.2 eV)

(–2.1 eV)

Synthetic elaboration

[4+2] Cycloadditions
[3+2] Cycloadditions
[2+2] Cycloadditions
Nu trapping
symmetrical and unsymmetrical triene