Interrupted Nazarov Cyclizations

Denmark Group Meeting

Jan. 29, 2008

Presenter Matthew T. Burk

Outline

History of the Nazarov cyclization

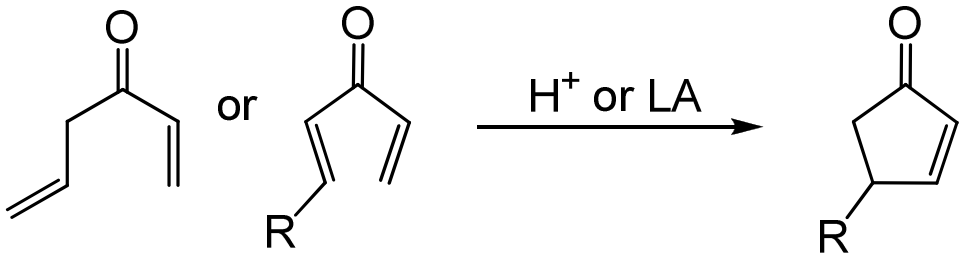
Mechanism

π- Cation Cyclizations

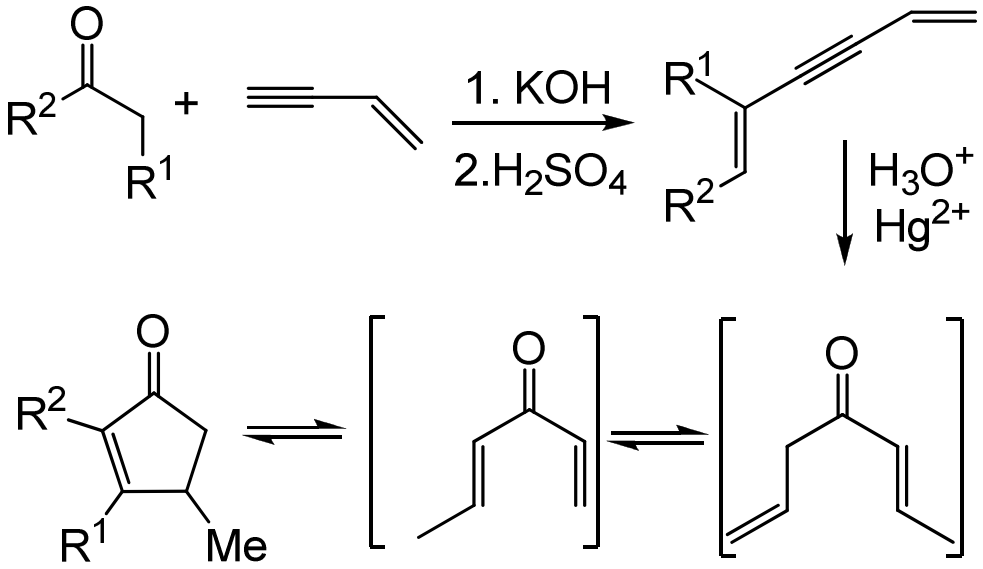
Intermolecular Trapping

Other Precursors

Introduction



Reported in 1941 by I. N. Nazarov

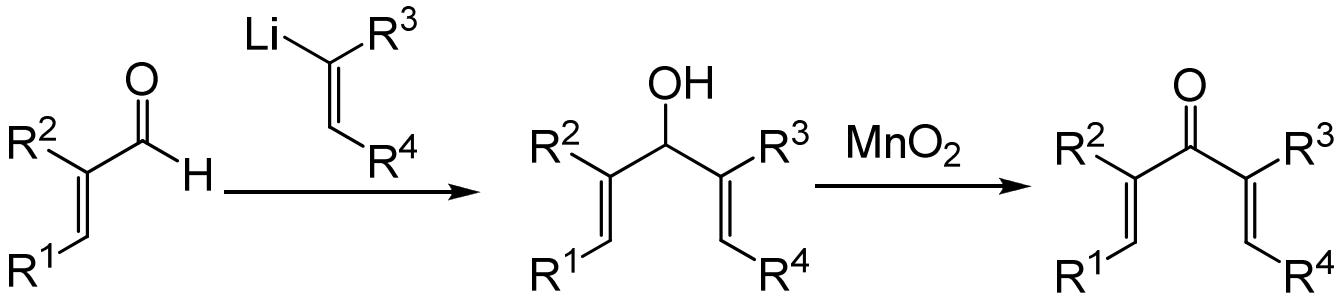


Ivan Nikolaevich Nazarov
(1906-1957)

Russ. Chem. Bull. **1957**, 1177

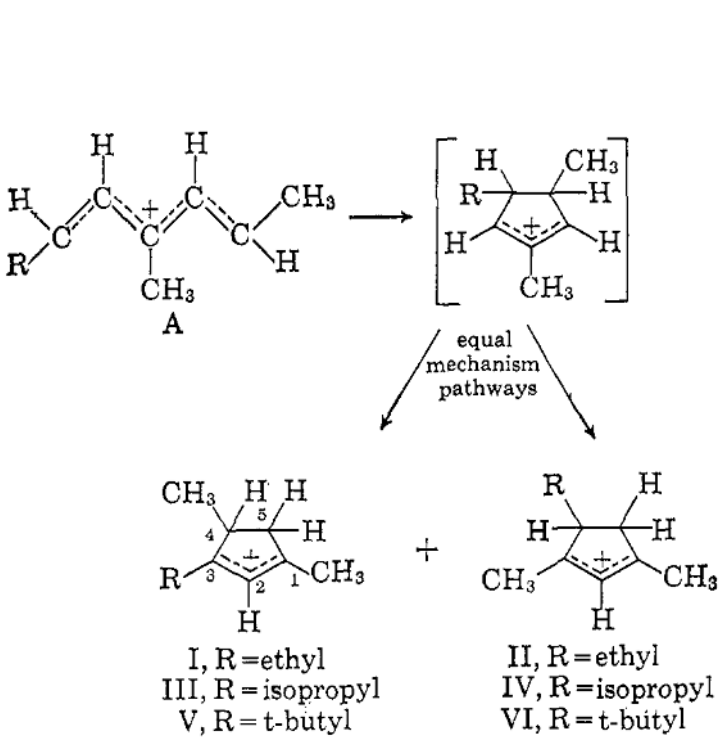
Nazarov, I. N.; Zaretskaya, I. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1941,** 211
Santelli-Rouvier, C.; Santelli, M. *Synthesis,* **1983**, 429

Typical Preparation of Starting Materials



Simple preparation of simple starting materials.

Mechanism: Cationic Intermediates



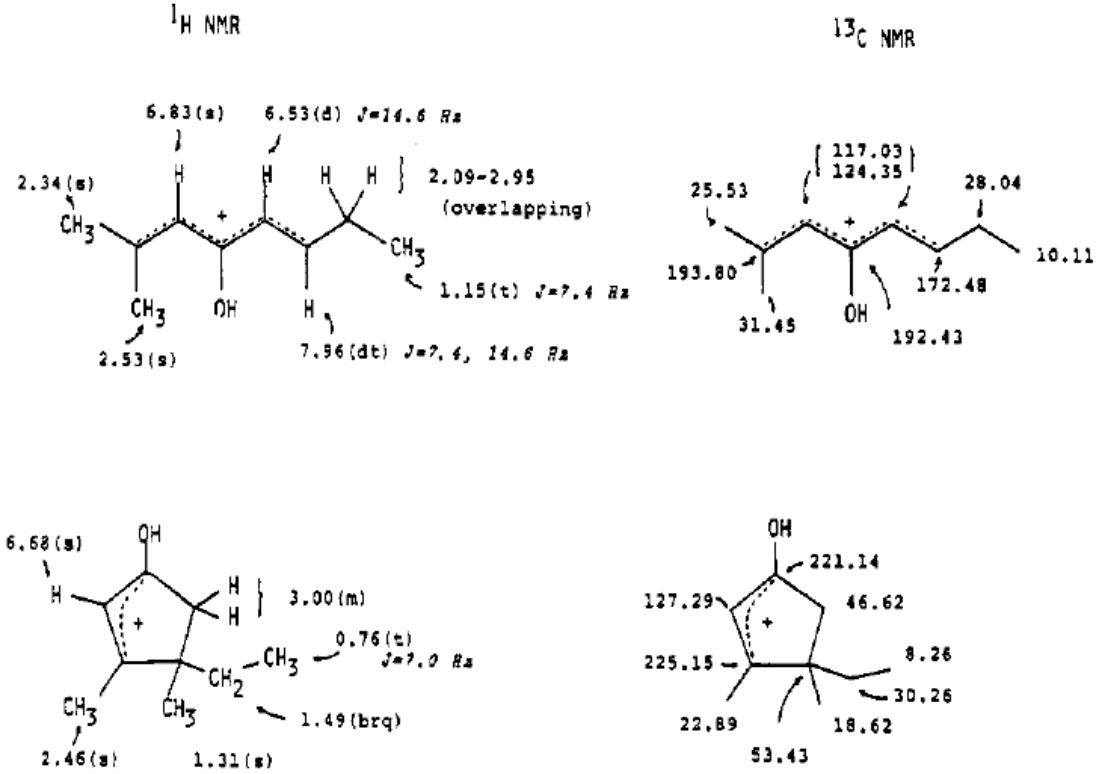
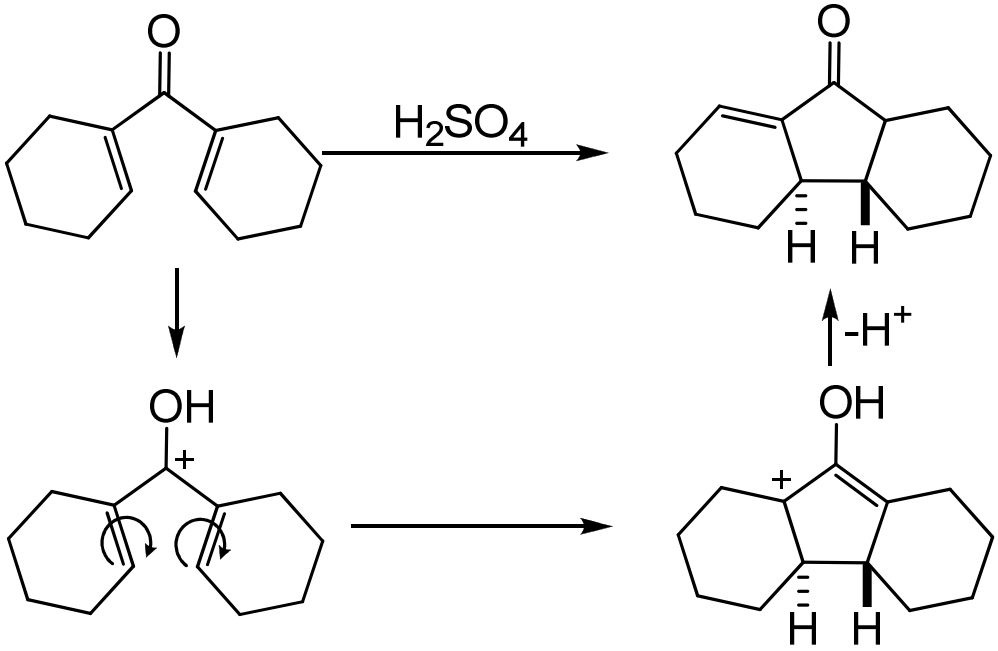


Figure 1. Chemical shifts of carbocation intermediates **2b** → **4b** measured in concentrated H_2SO_4. Me_4Si as an external standard.

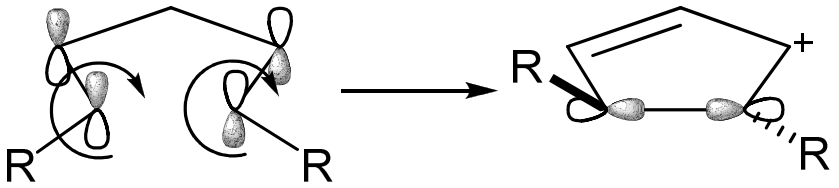
Sorensen, T. S. *J. Am. Chem. Soc.* **1967**, 3782

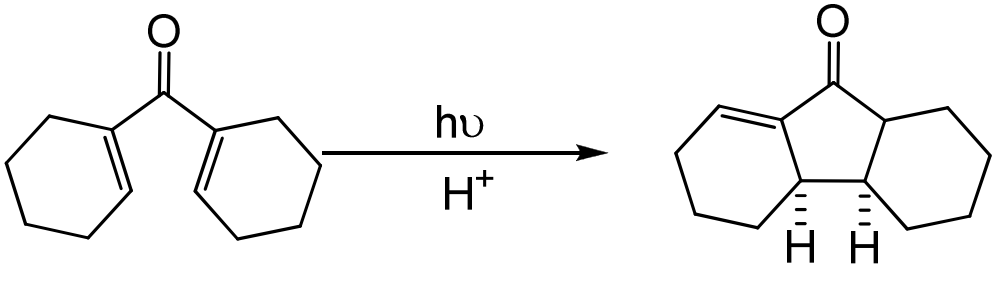
Motoyoshia, J.; Yazaki, T.; Hayashi, S. *J. Org. Chem.* **1991**, 735

Mechanism: Stereochemical Evidence

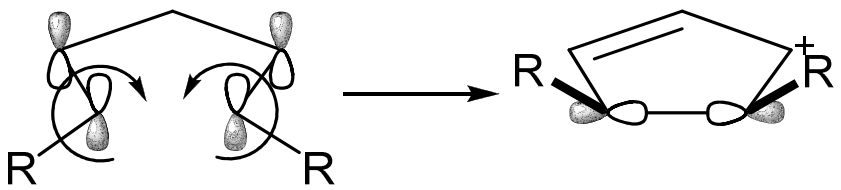


2 π conrotary thermal electrocyclization



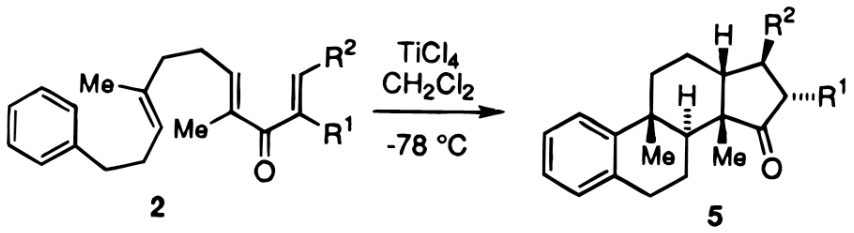


2π disrotary photochemical electrocyclization



Woodward, R. B. *Chem. Soc. Special Publication No. 21*, **1967**, 237.

Nazarov – Initiated π-Cation Cyclizations

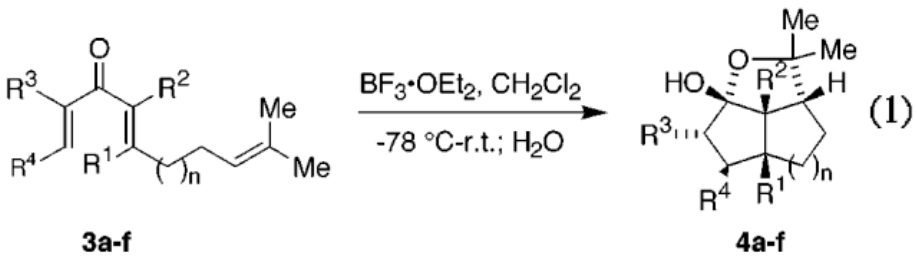


2 **5**

substrate	R^1	R^2	product	yield (%)[b]
2a	H	H	**5a**	—[c]
2b	Me	H	**5b**	99
2c	Me	Et	**5c**	73[d]
2d	$-(CH_2)_4-$		**5d**	98
2e	$-(CH_2)_5-$		**5e**	74[d]

10 steps to make **2**

Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443

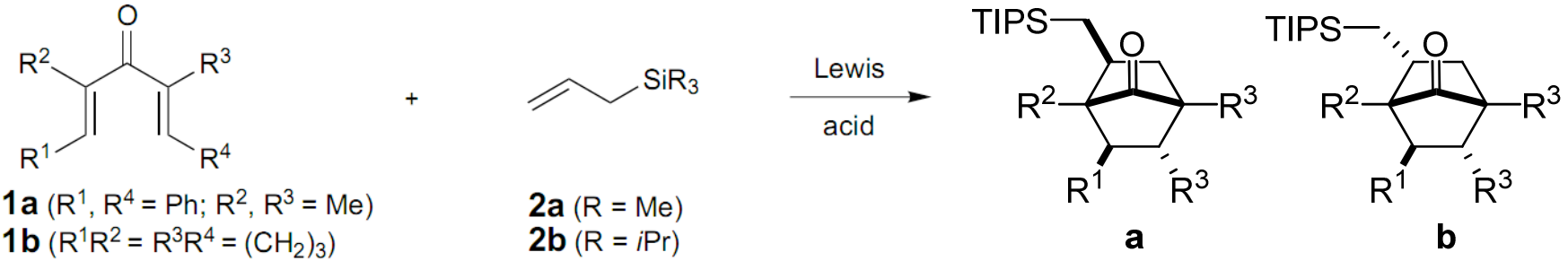


3a-f **4a-f** (1)

entry	dienone	R^1	R^2	R^3	R^4	n	yield of **4**[b] (%)
1	**3a**	H	CH_3	CH_3	H	1	75
2	**3b**	H	CH_3	$C(CH_3)_3$	H	1	89[c]
3	**3c**	H	CH_3	CH_2CH_3	CH_3	1	73
4	**3d**	H	CH_3	$-(CH_2)_4-$		1	62
5	**3e**	H	CH_3	CH_3	H	2	42[d]
6	**3f**	CH_3	H	CH_3	H	1	e

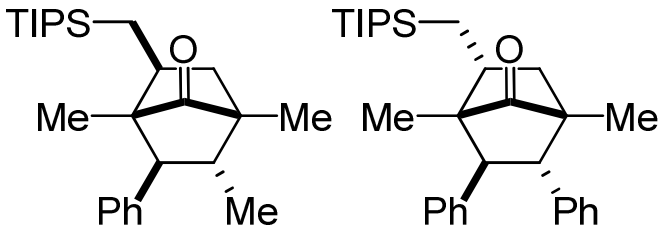
Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, 63, 2430

Allyl Silane Nucleophiles

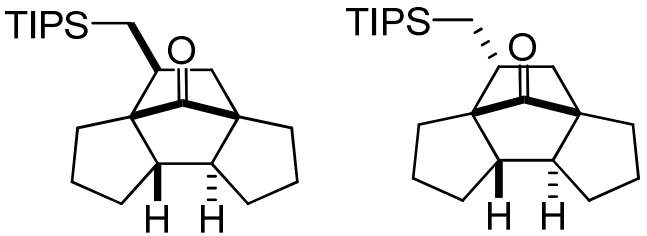


1a (R^1, R^4 = Ph; R^2, R^3 = Me)
1b (R^1R^2 = R^3R^4 = $(CH_2)_3$)
1c (R^1 = Ph; R^2, R^4 = Me; R^3 = H)

2a (R = Me)
2b (R = *i*Pr)



72%(BF_3•OEt_2) 51% ($SnCl_4$)



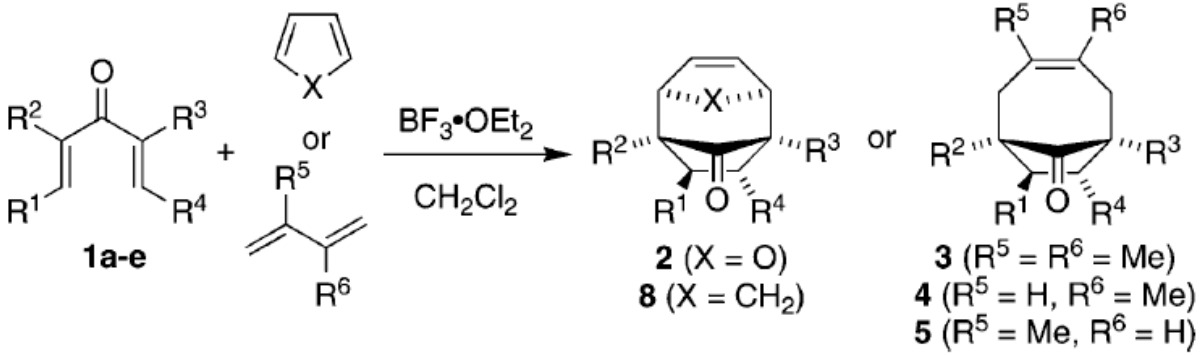
65% (BF_3•OEt_2) 91% ($TiCl_4$)

TMS allyl silane gives mixtures of allylation and cycloaddition

$SnCl_4$ favors **b,** BF_3·OEt_2 favors **a**

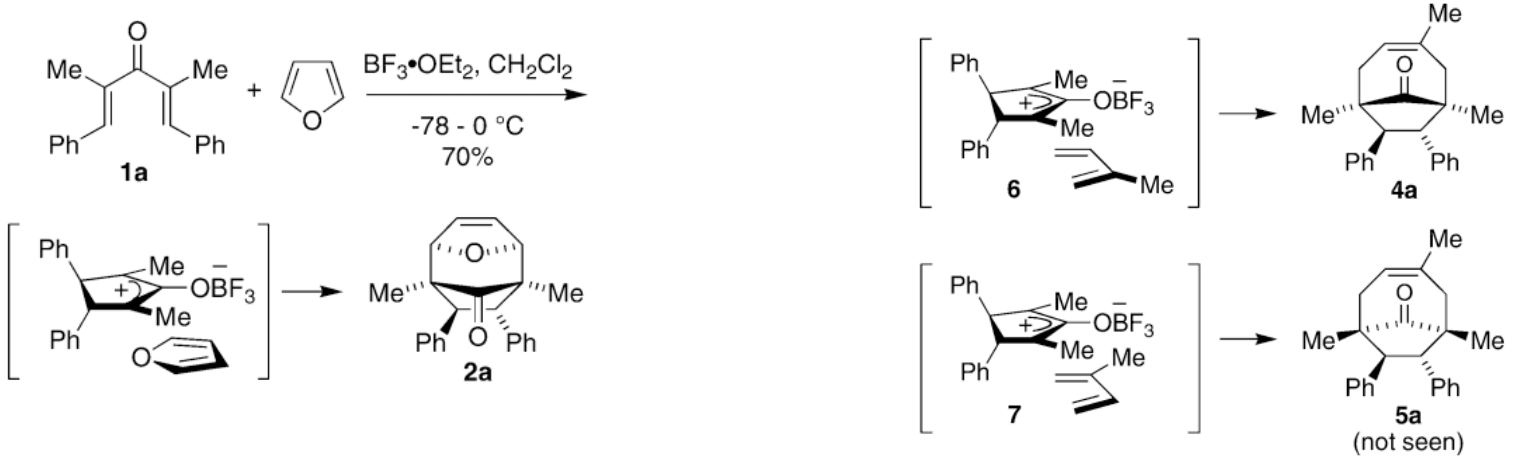
Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem. Int. Ed.* **2000,** 39, 1970

Intermolecular [4+3] Cycloadditions



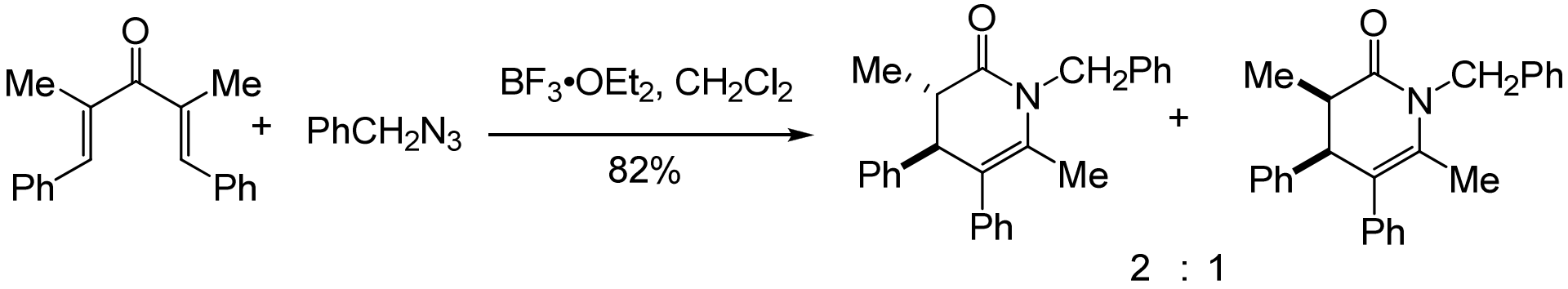
20-93% yield

Unsymmetrical dienes favor **4** mostly >4:1



Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003,** *5*, 2747

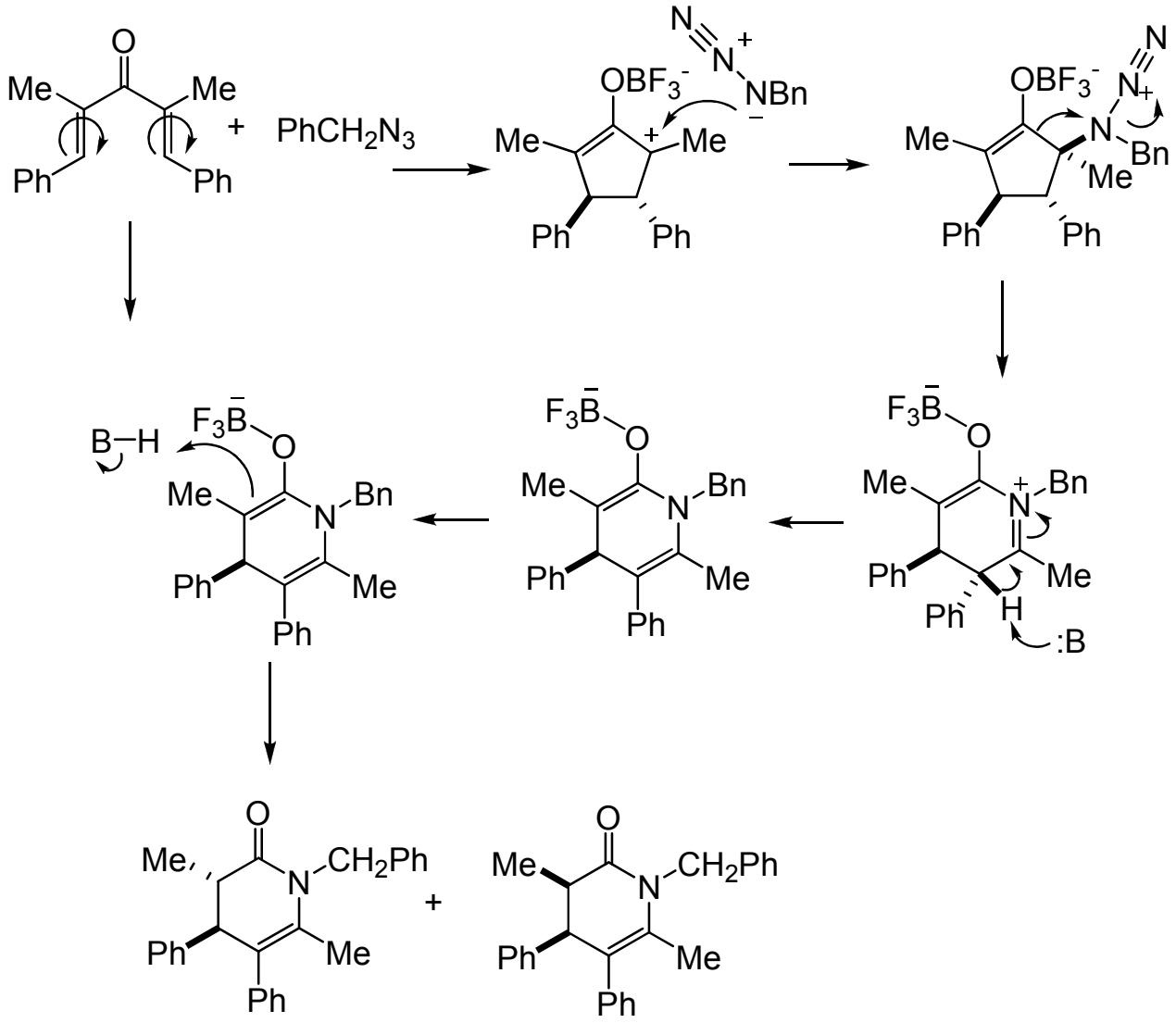
Question



Propose a mechanism for this transformation

Song, D; Rostami, A.; West, F. G. *J. Am. Chem. Soc.* **2007**, *129,* 12019

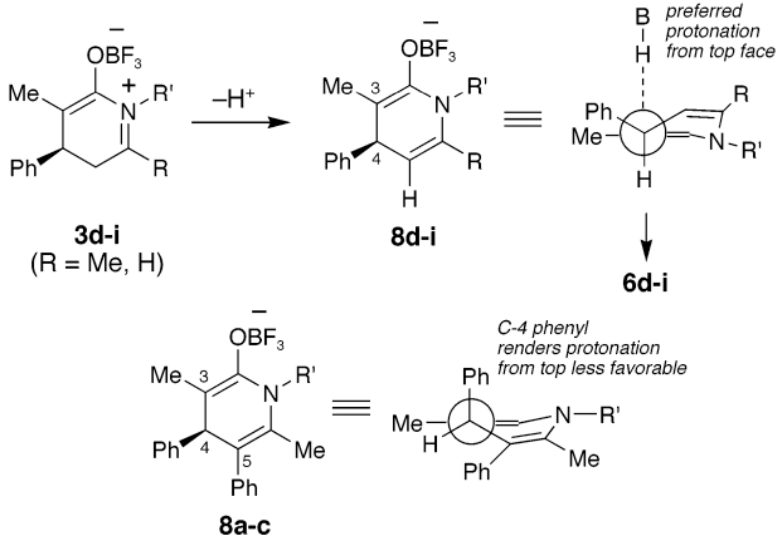
Answer

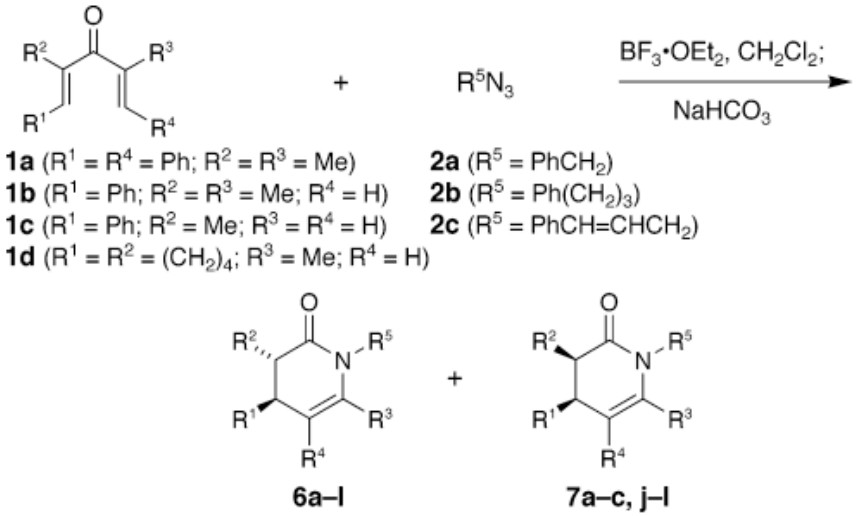


2 : 1

Song, D.; Rostami, A; West, F. G. *J. Am. Chem. Soc.* **2007,** *129,* 12019

Intermolecular Azide Trapping cont'd.



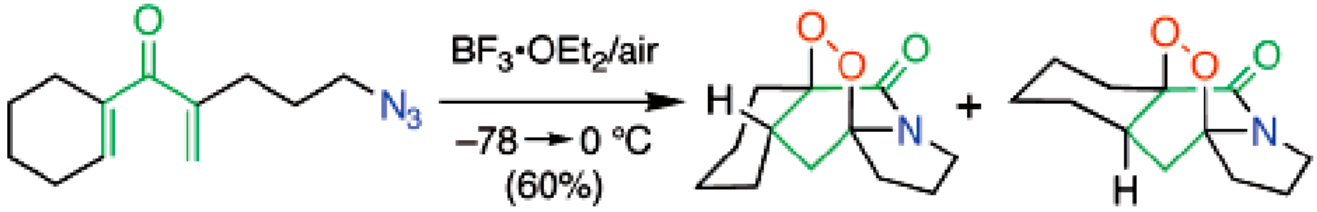


entry	dienone	azide	conditions	products (% yield; ratio)[b]
1	**1a**	**2a**	−78 °C/10 min	**6a** + **7a** (82; 2:1)
2	**1a**	**2b**	−78 °C/10 min	**6b** + **7b** (78; 2.3:1)
3	**1a**	**2c**	−78 °C/10 min	**6c** + **7c** (85; 2:1)
4	**1b**	**2a**	−78 °C/0.5 h	**6d** (75)
5	**1b**	**2b**	−78 °C/0.5 h	**6e** (80)
6	**1b**	**2c**	−78 °C/0.5 h	**6f** (72)
7	**1c**	**2a**	0 °C/1 h	**6g** (62)
8	**1c**	**2b**	0 °C/1 h	**6h** (40)
9	**1c**	**2c**	0 °C/1 h	**6i** (43)
10	**1d**	**2a**	0 °C/0.5 h	**6j** + **7j** (80; 2:1)
11	**1d**	**2b**	0 °C/0.5 h	**6k** + **7k** (70; 3:1)
12	**1d**	**2c**	0 °C/0.5 h	**6l** + **7l** (73; 2.5:1)

[a] See Experimental Section for standard procedure. [b] All yields given are based on isolated material after chromatographic purification.

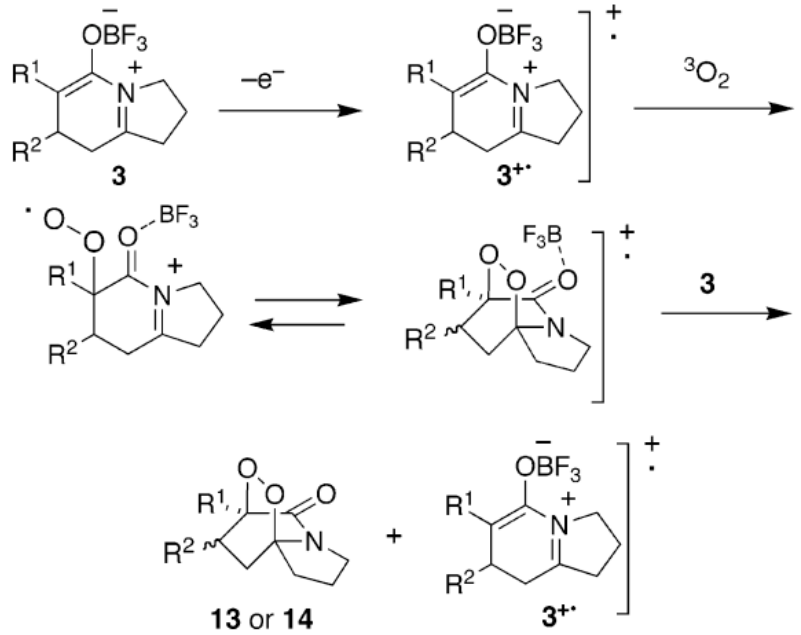
Song, D.; Rostami, A; West, F. G. *J. Am. Chem. Soc.* **2007,** *129,* 12019

Intramolecular Azide capture

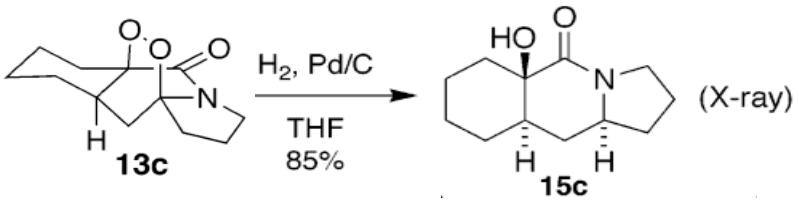


4 examples
36-69% yield

Scheme 4. Cation Radical Chain Mechanism for Peroxide Formation

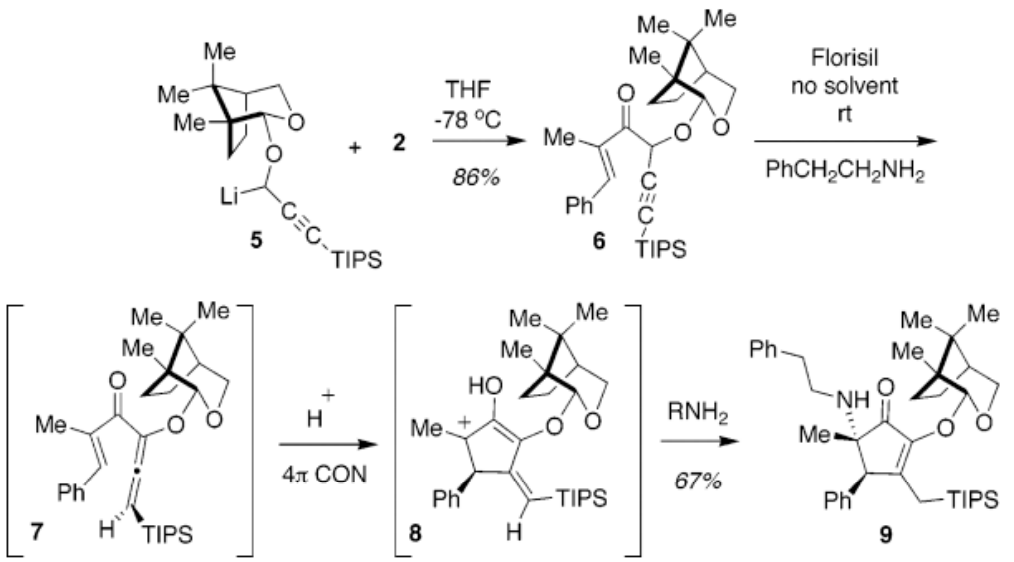


Scheme 5. Peroxide Hydrogenolysis

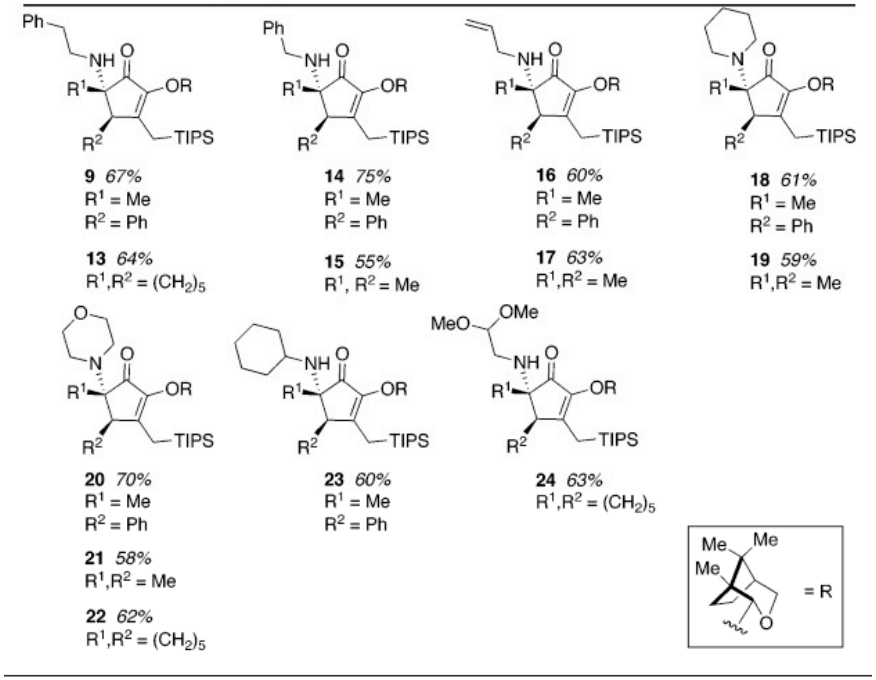


Rostami, A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703

Asymmetric Amine Intercepted Nazarov Cyclization



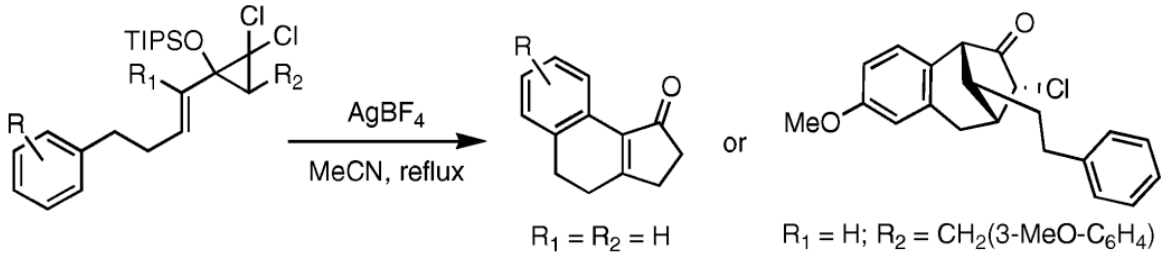
Single Diastereomer



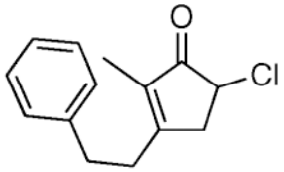
Auxiliary derived from camphor

Dhoro, F.; Kristenson, T. E.; Stockmann, V.; Yap, G. P. A.; Tius, M. A. , *J. Am. Chem. Soc.* **2007,** *129*, 7256

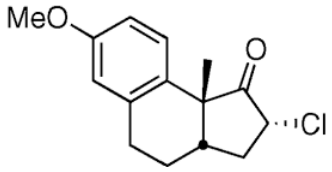
Electrocyclic Ring Opening/ Interrupted Nazarov



R^1=Me

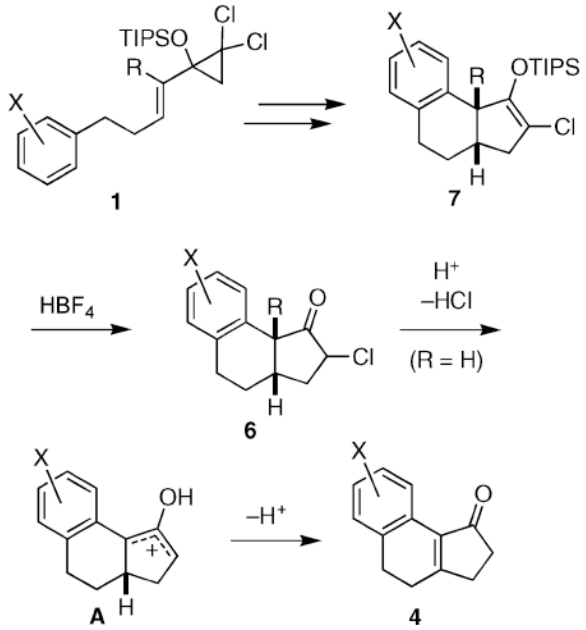


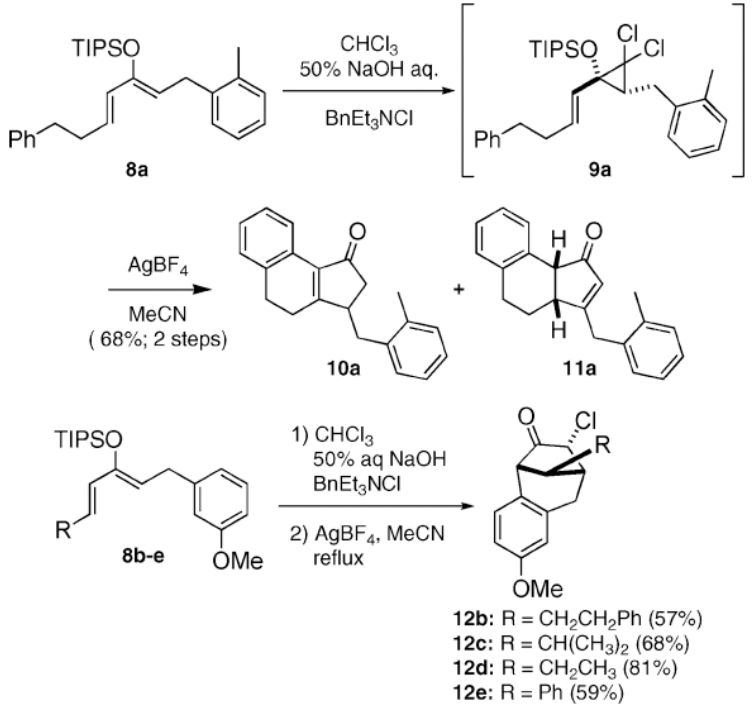
97%



89%

Scheme 2. Proposed Mechanism of Arene Trapping and Elimination





Conclusions

Many carbocyclic structures are accessible by interrupted Nazarov cyclization methods

Accessibility of starting materials is an issue for intramolecular cyclization methods.

Reviews:

Santelli-Rouvier, C.; Santelli, M. *Synthesis,* **1983**, 429
Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994,** *45,* 1-158
Pellissier, H. *Tetrahedron* **2005**, *61,* 6479
Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61,* 7577
Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193