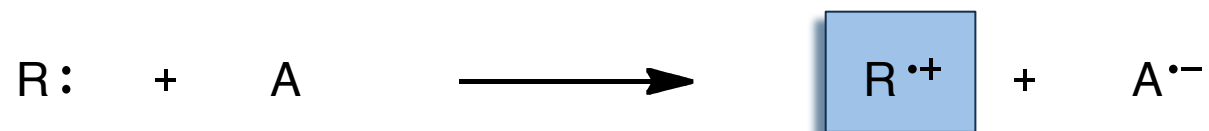


Radical Cations^{•+}: Generation, Reactivity, Stability



MacMillan Group Meeting
4-27-11
by
Anthony Casarez

Three Main Modes to Generate Radical Cations

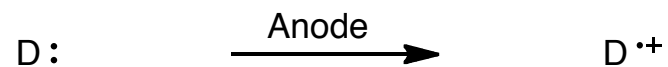
■ Chemical oxidation



■ Photoinduced electron transfer (PET)

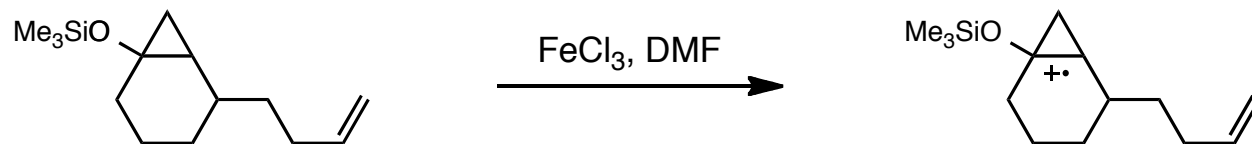
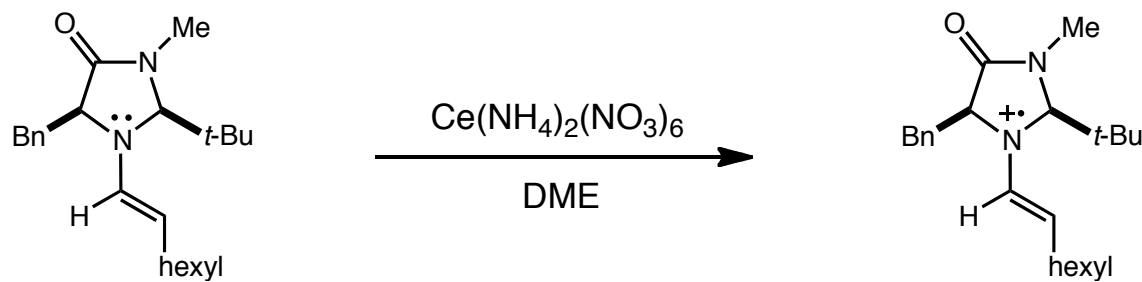


■ Electrochemical oxidation (anodic oxidation)



Chemical Oxidation

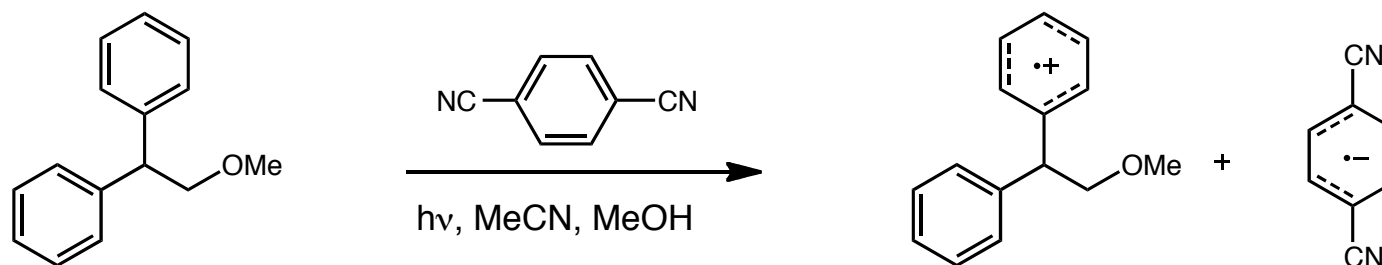
- Stoichiometric oxidant: SET



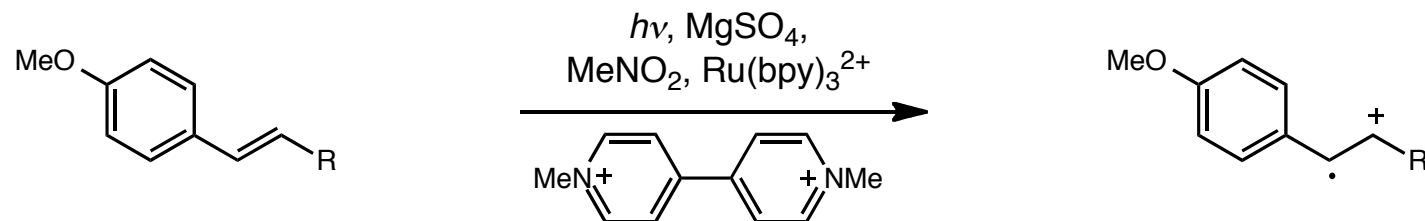
MacMillan et al. *Science* **2007**, 316, 582.
Booker-Milburn, K. I. *Synlett* **1992**, 809.

Photoinduced Electron Transfer

■ PET: Organic arene



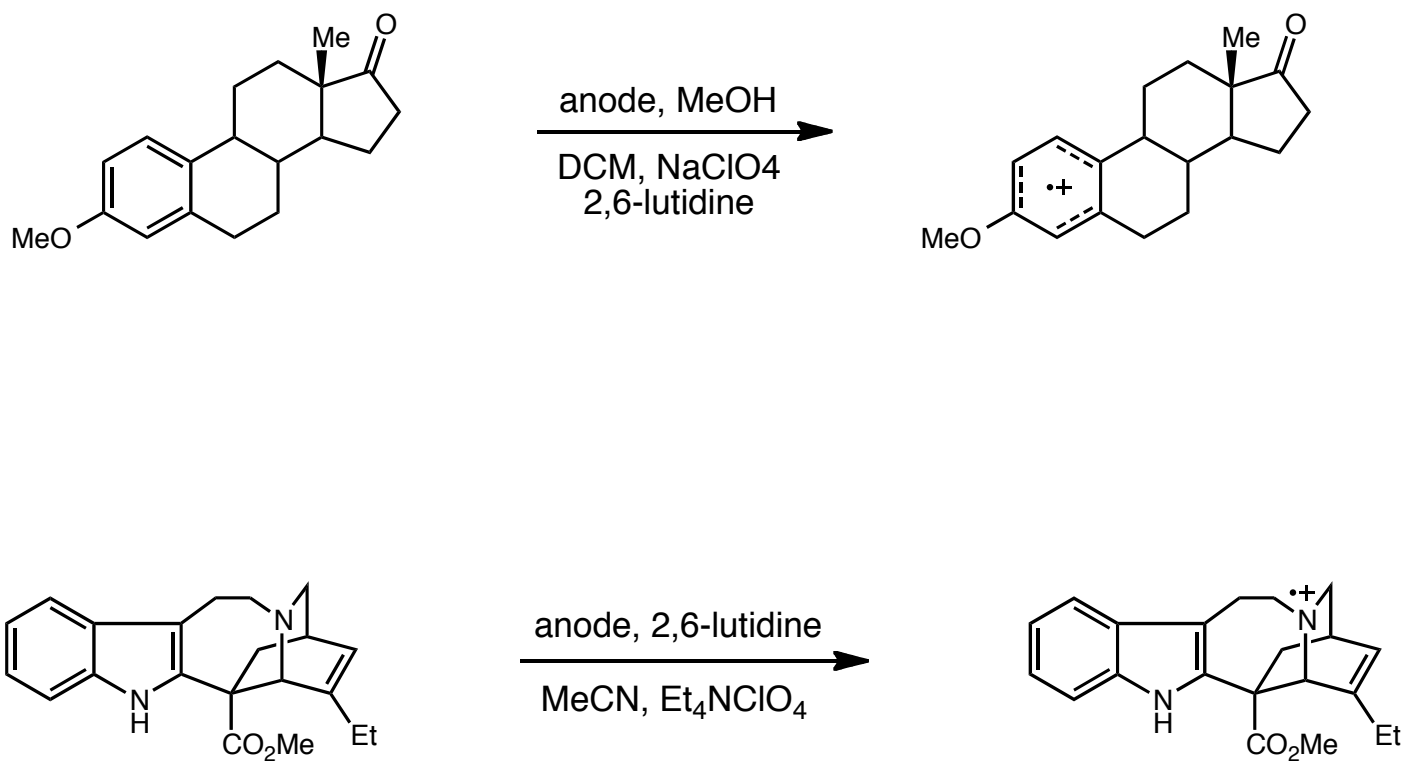
■ PET: Metal mediated



Arnold, D. R.; Maroulis, A. J. *J. Am. Chem. Soc.* **1976**, *98*, 5931.
Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572.

Electrochemical Oxidation

■ Anodic oxidation



Ponsold, K.; Kasch, H. *Tetrahedron Lett.* **1979**, 4463.
M. J. Gašić et al. *J. Chem. Soc. Chem. Comm.* **1993**, 1496.

Primary Fate of Radical Cations

Key Points

- A radical cation will be generated from the electrophore on the molecule with the lowest oxidation potential (usually π or n, where n = nonbonding electrons).
- The chemistry of the resultant radical cation is determined from the functionality around its periphery.
- Deprotonation of the radical cation is a major pathway, resulting in a radical which adheres to typical radical reactivity patterns.
- **Secondary reactions play a major role in our generation and use of radical cations.**

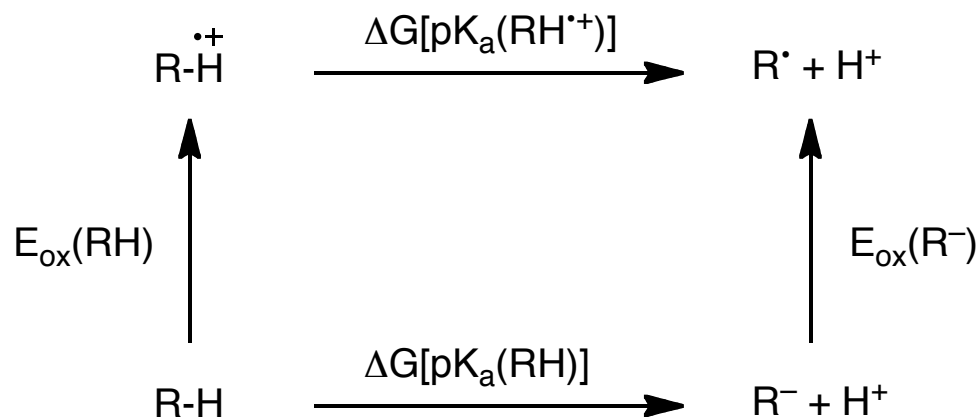
Primary Fate of Radical Cations

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CH	C–H deprotonation	$\pi\text{-C}^\cdot + \text{H}^+$ or $n\text{-C}^\cdot + \text{H}^+$	C	H
AH	A–H deprotonation	$\pi\text{-A}^\cdot + \text{H}^+$	O, N, S, X	H
AB	A–B bond cleavage	$\pi\text{-A}^\cdot + \text{B}^+$ or $\pi\text{-A}^+ + \text{B}^\cdot$	A	B
CC	C–C bond cleavage	$\pi\text{-C}^\cdot + \text{C}^+$	C	C
CX	C–X bond cleavage	$\pi\text{-C}^\cdot + \text{X}^+$	C	Si, Sn
Nu	Nu attack	$\text{Nu-}\pi\text{-A-B}^{\cdot+}$	A	B
CA	cycloaddition	cycloaddition	A	B
R	rearrangement	rearrangement	A	B
ET	electron transfer	$\pi\text{-A-B}$ or $\pi\text{-A-B}^{2+}$	A	B
Rad	radical attack	$\text{R-}\pi\text{-A-B}^+$	A	B
RA	radical anion attack	$\text{RA-}\pi\text{-A-B}$	A	B
H	hydrogen transfer	$\text{H-}\pi\text{-A-B}^+$	A	B
Dim	dimerization	$(\pi\text{-A-B})_2^{2+}$	A	B

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Dim	dimerization	$(\pi\text{-A-B})_2^{2+}$	A	B

Thermochemical Cycle: Calculating pKa's

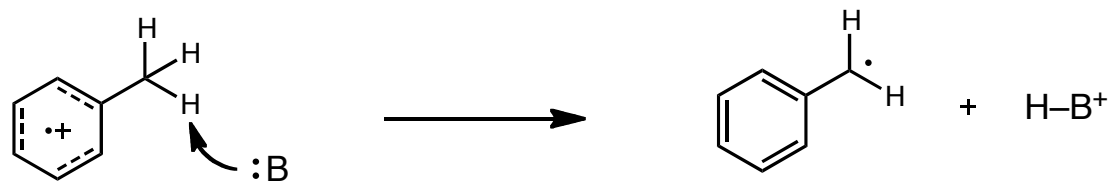


■ $\Delta G = -nF[E_{\text{ox}}(\text{RH}) - E_{\text{ox}}(\text{R}^-)]$

■ $\text{pK}_a(\text{RH}^{\cdot+}) = \Delta G/2.303RT$

Deprotonation

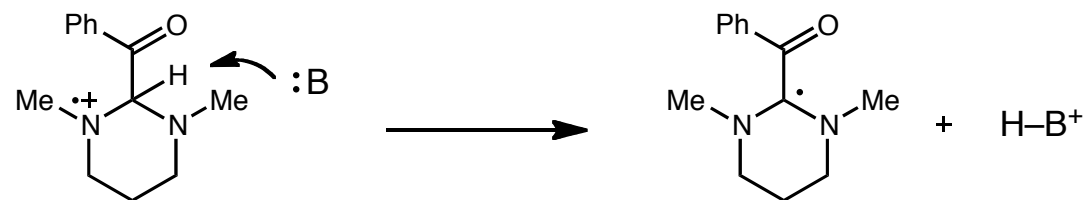
- Acidity of a radical cation is severely increased compared to the neutral counterpart.



R-H	pKa (π -RH ^{•+})	pKa (π -RH)	reference
PhCH ₂ CN	-32	21.9	a
PhCH ₂ SO ₂ Ph	-25	23.4	b
Ph ₂ CH ₂	-25	32.2	c
PhCH ₃	-20	43	c
indene (3-H)	-18	20.1	d
CpH	-17	18.0	c,e
fluorene (9-H)	-17	22.6	f
C ₅ Me ₅ H	-6.5	26.1	e

a) Bordwell et al. *J. Phys. Org. Chem.* **1988**, *1*, 209. b) Bordwell et al. *J. Phys. Org. Chem.* **1988**, *1*, 225. c) Bordwell, F. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1989**, *111*, 1792. d) Bordwell, F. G.; Satish, A. V. *J. Am. Chem. Soc.* **1992**, *114*, 10173. e) Bordwell, F. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1988**, *110*, 2872. f) Bordwell, F. G.; Cheng, J.-P.; Bausch, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 2867.

Deprotonation



R-H	pKa (RH ^{•+})	pKa (RH)
	-13	27.9
	-11	27.0
	-11	24.4

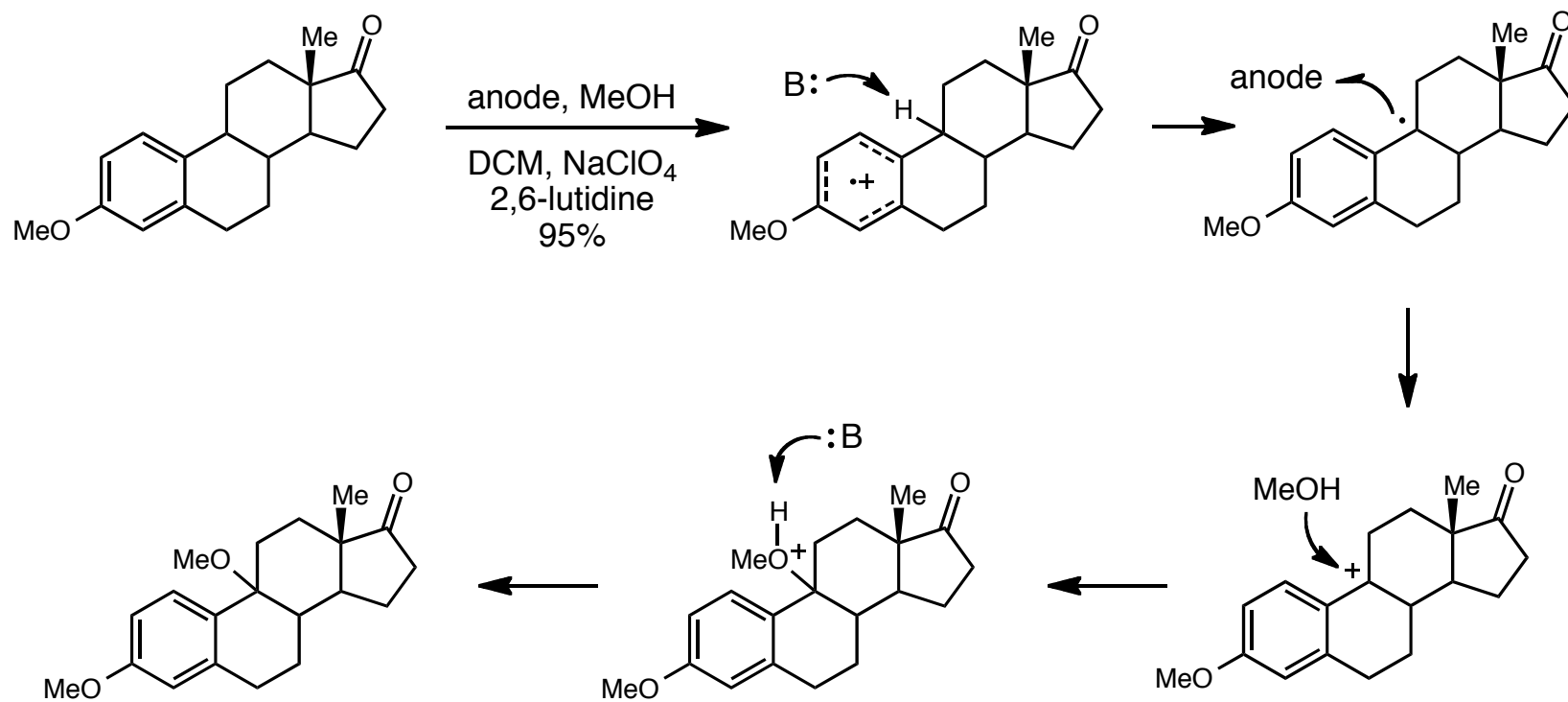
Secondary Reactions

- Secondary Reactions play a major role in “radical cation” chemistry.

Code	Secondary Rxn	Product	Oxidation System
R^{\cdot}_{ox}	$R^{\cdot} \rightarrow R^+$	cation	anode, chemical
R^{\cdot}_{red}	$R^{\cdot} \rightarrow R^-$	anion	PET
R^{\cdot}_{rad}	typical radical behavior	various	all
$R^{\cdot}_{add.ox}$	$R^{\cdot} + C=C \rightarrow R-C-C^{\cdot} \rightarrow R-C-C^+$	cation	anode, chemical
$R^{\cdot}_{add.red}$	$R^{\cdot} + C=C \rightarrow R-C-C^{\cdot} \rightarrow R-C-C^-$	anion	PET
R^{\cdot}_{RA}	$R^{\cdot} + R^{\cdot-} \rightarrow R-R^{\cdot-}$	anion	PET

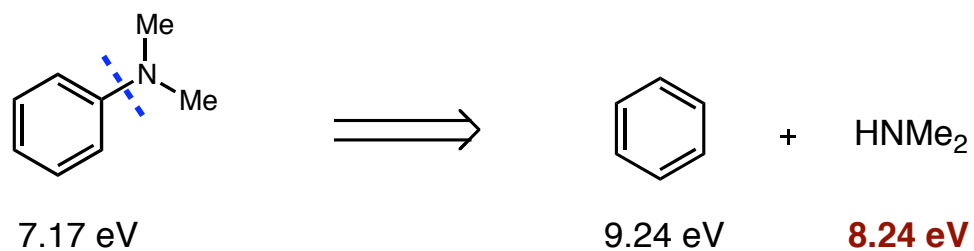
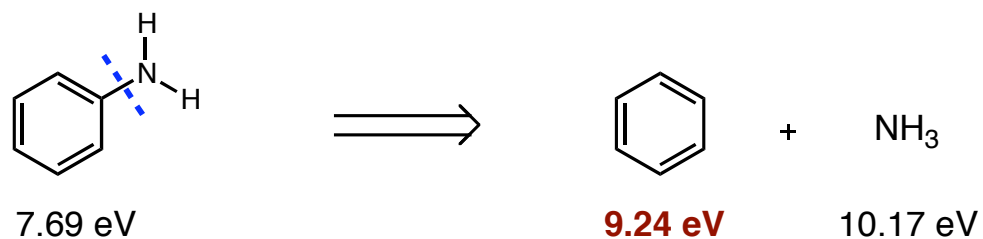
π -RH⁺ Deprotonation

- π -RH⁺ deprotonation followed by a secondary reactivity pathway (benzylic radical)



Determining n vs π Electrophores

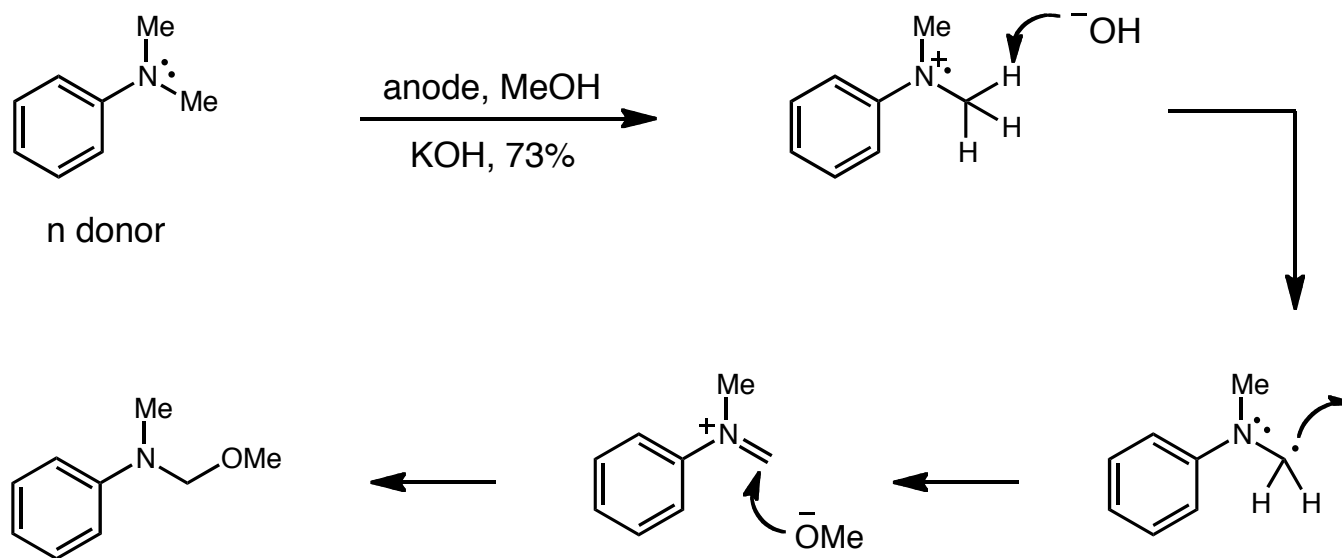
- Consider the ionization potential of the separate n - and π - moieties



- Oxidation with typically take place at the center with the lower ionization potential

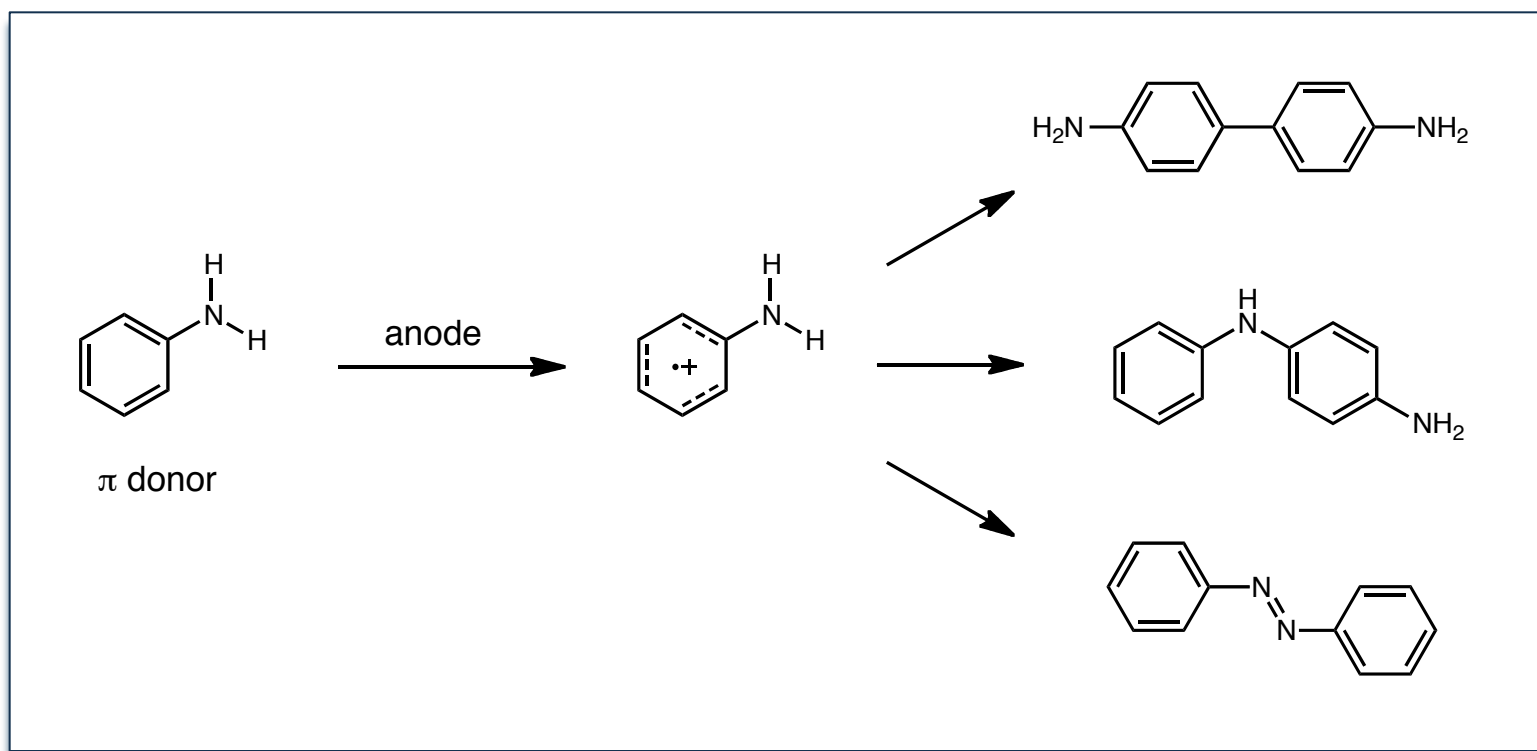
$n\text{-RH}^+$ Deprotonation

- $n\text{-RH}^+$ deprotonation followed by a secondary reactivity pathway (α -amino radical)



$n-RH^+$ Deprotonation

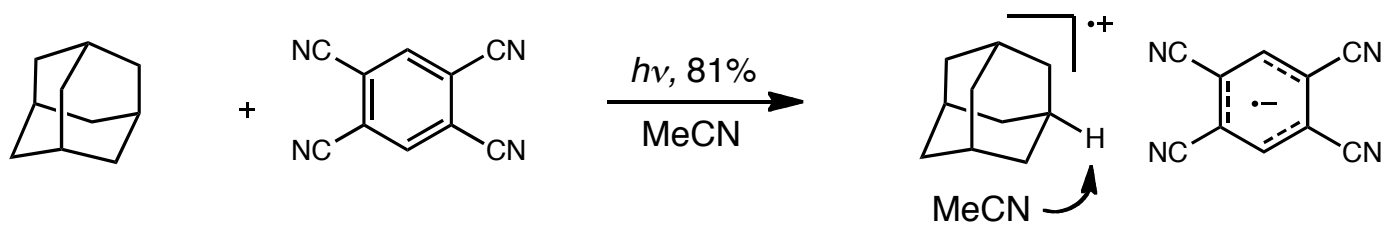
- Typical arene oxidation products are observed



- Observation of these products indicates that the arene is the site of oxidation, not N -lone pairs

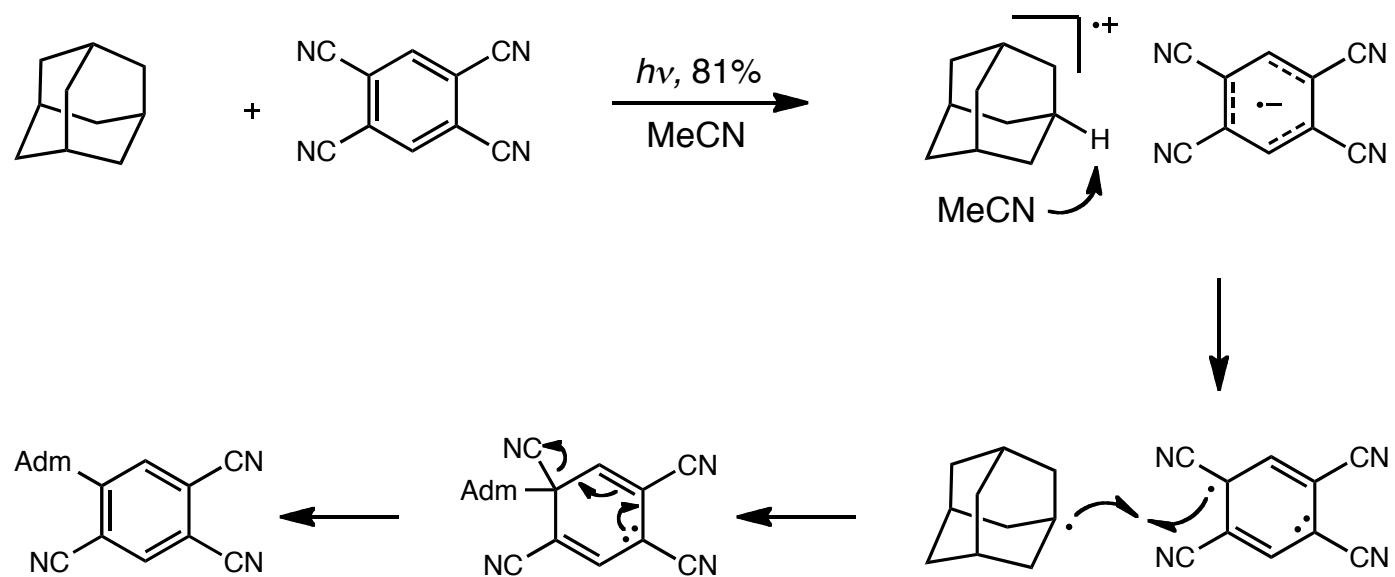
$\sigma\text{-CH}^+$ Deprotonation

- Deprotonation of the radical ion pair happens by the solvent



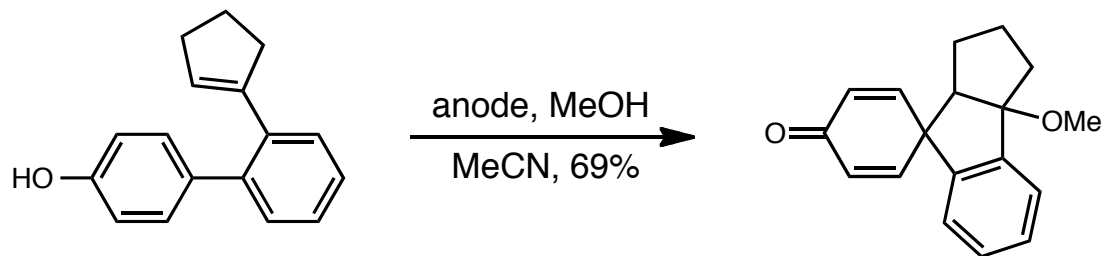
$\sigma\text{-CH}^+$ Deprotonation

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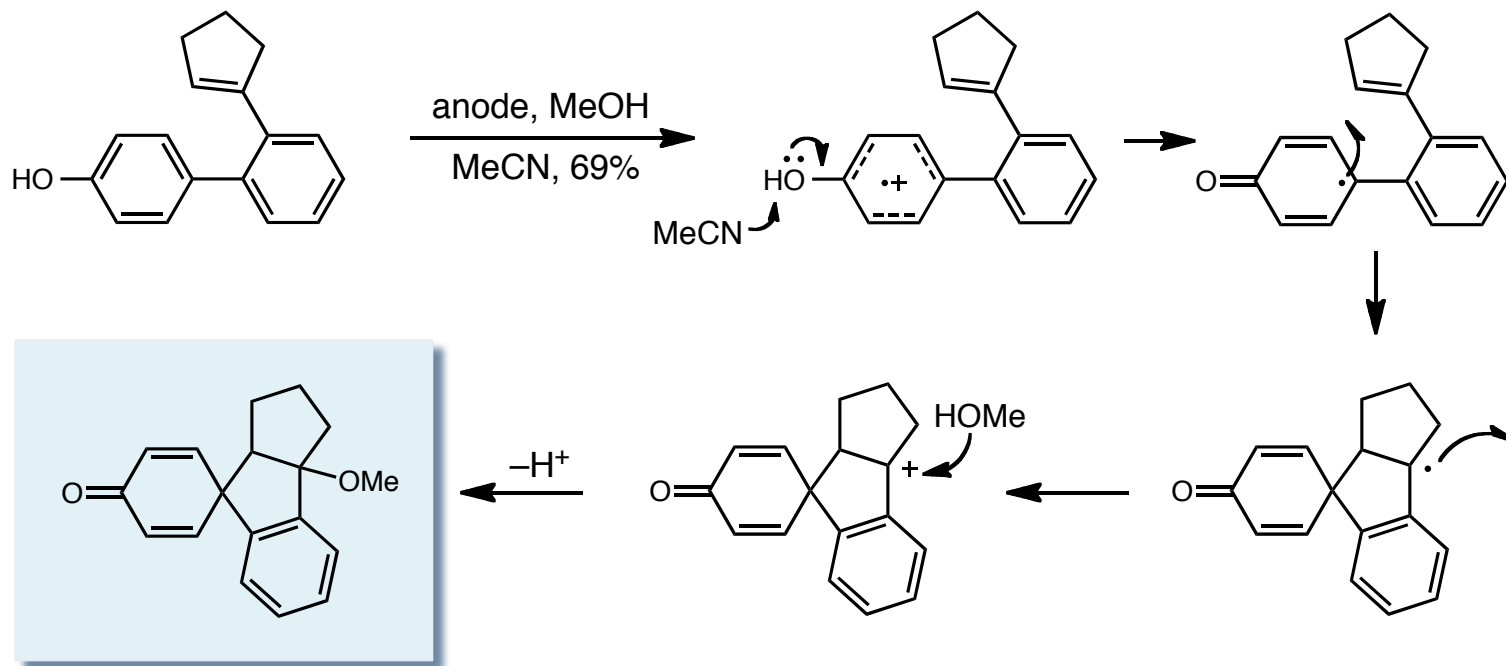
π -AH⁺ Deprotonation

- π -OH⁺ deprotonation is very prevalent while π -NH⁺ deprotonations are rare.



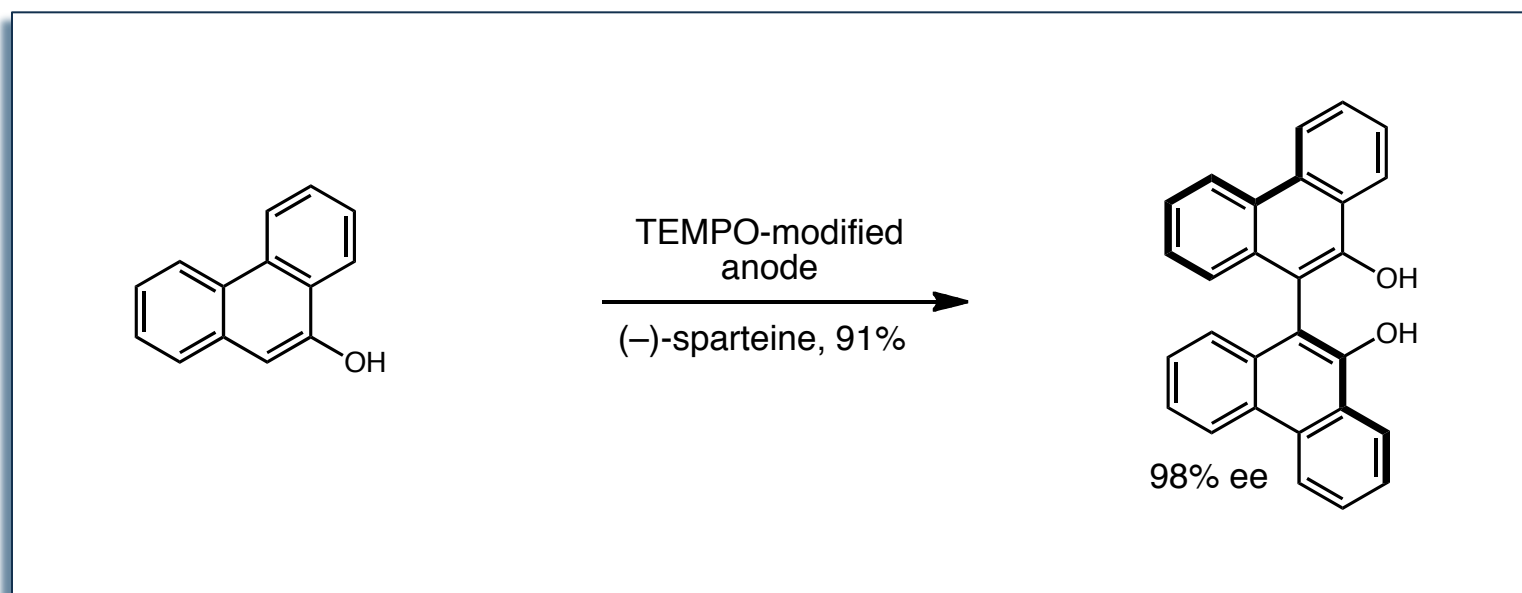
π -AH⁺ Deprotonation

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π -AH⁺ Deprotonation

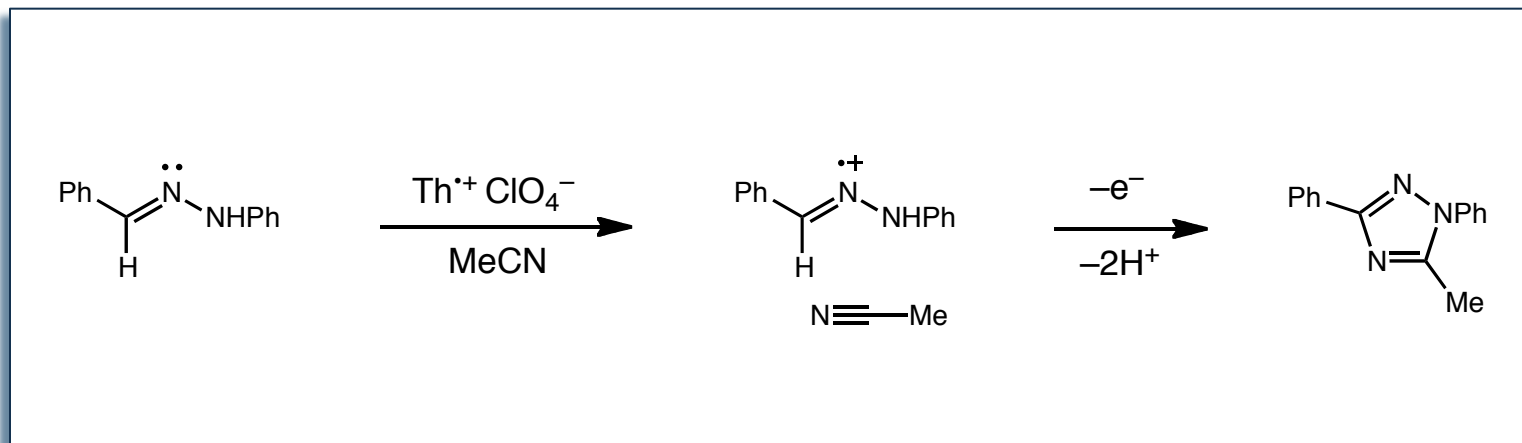
- Reaction at the ortho-position can also occur



- Implementing a biased substrate forces reaction at the ortho-position

n-AH⁺ Deprotonation: Very Limited

- The details surrounding the cycloaddition below are speculative at best.



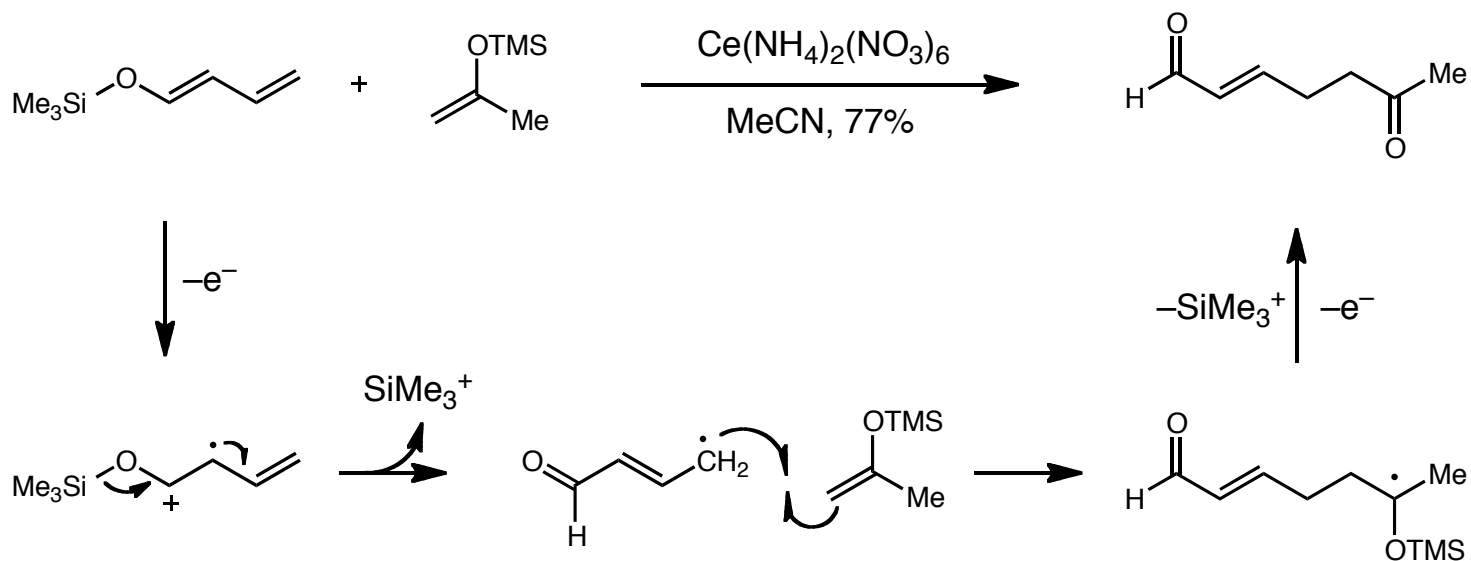
- The limited examples show how rare these deprotonations are

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RA	radical anion attack	$\text{RA-}\pi\text{-A-B}$	A	B
H	hydrogen transfer	$\text{H-}\pi\text{-A-B}^{\bullet+}$	A	B
Dim	dimerization	$(\pi\text{-A-B})_2^{2+}$	A	B

π -A-B⁺ Bond Dissociation

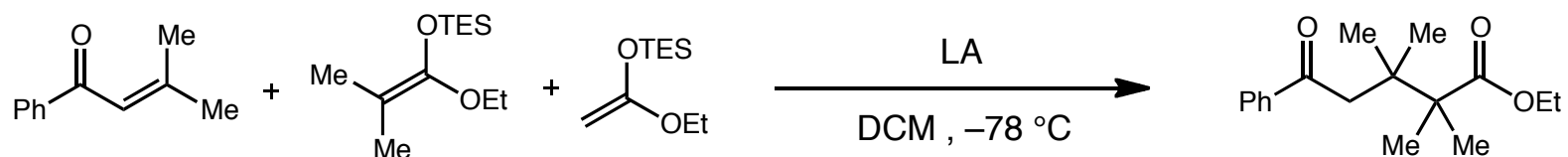
- Dienoether has a lower oxidation potential than the enoether



- Eventhough [O] may happen at n (lone pairs), the resonance structure affords the π -oxidized product.

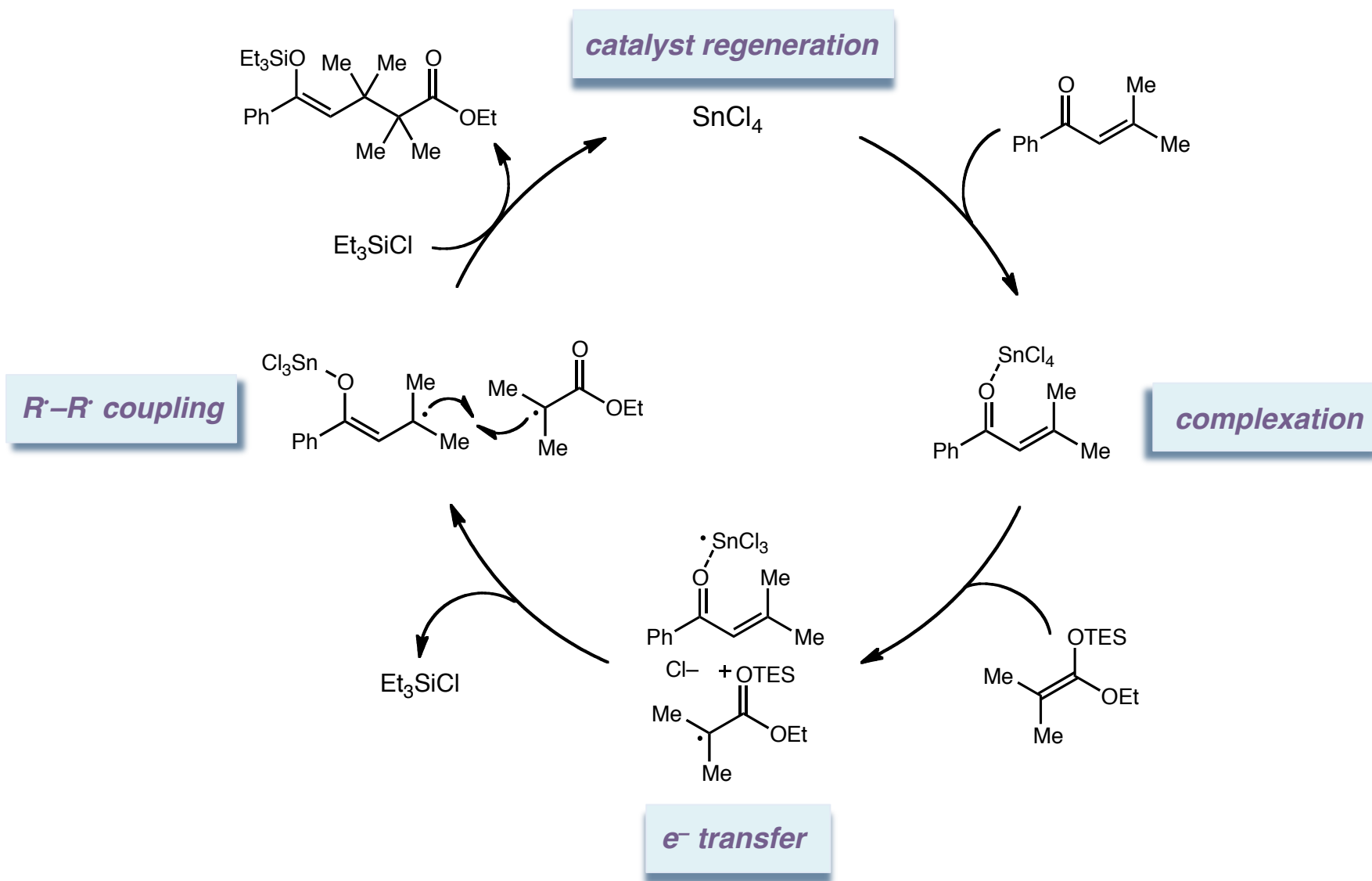
π -A-B⁺ Bond Dissociation

- Certain Mukaiyama–Michael reactions are postulated to operate via a radical cation initiated fragmentation



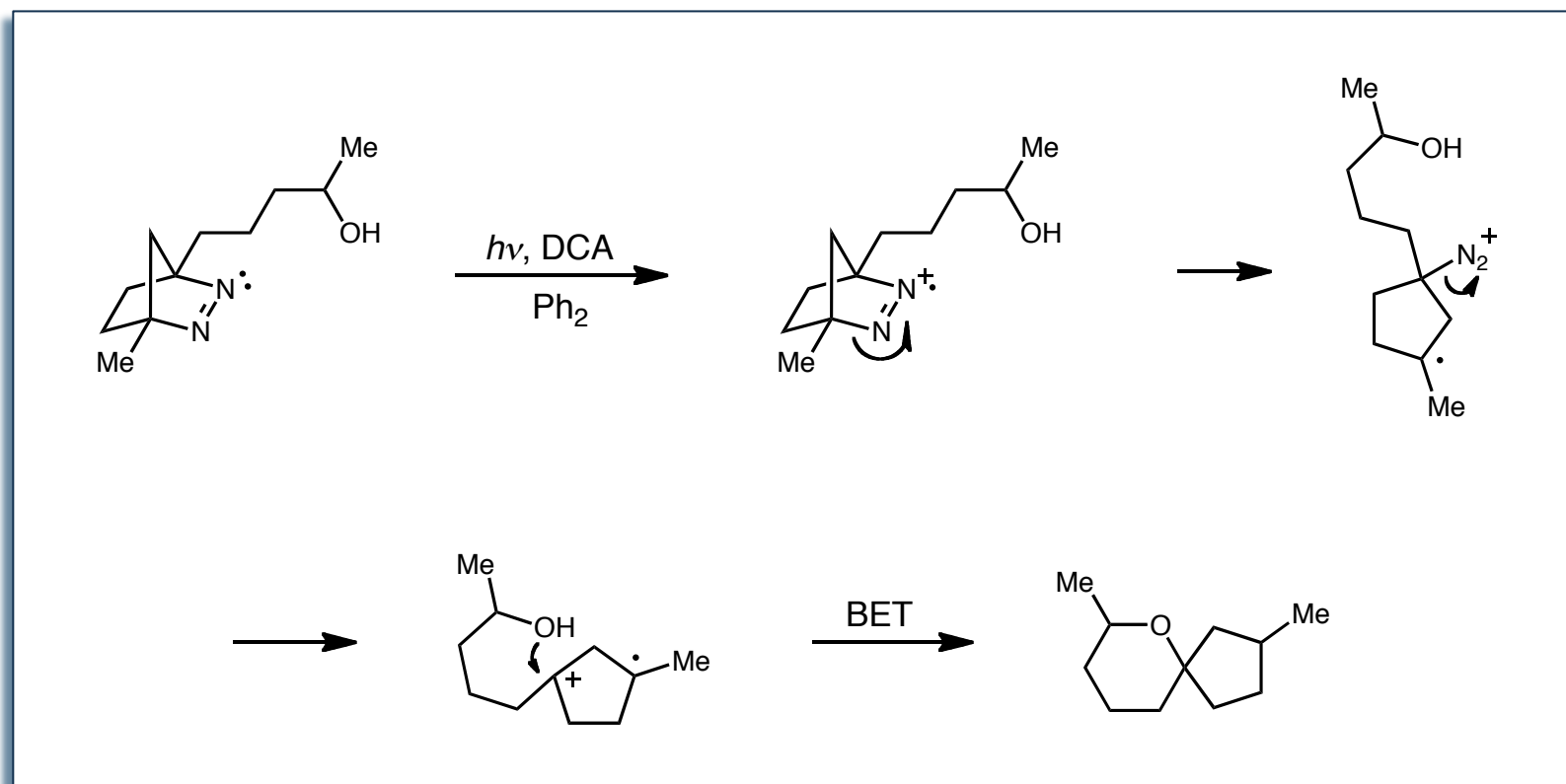
Lewis Acid	4°–4° product	4°–2° product	Product ratio
Bu ₂ Sn(OTf) ₂	85	0	100:0
SnCl ₄	95	0	100:0
Et ₃ SiClO ₄	93	0	100:0
TiCl ₄	97	2.4	97:3

Mukaiyama–Michael Proposed Catalytic Cycle



n-A-B⁺ Bond Dissociation

- Limited mostly to azoalkanes and triazines

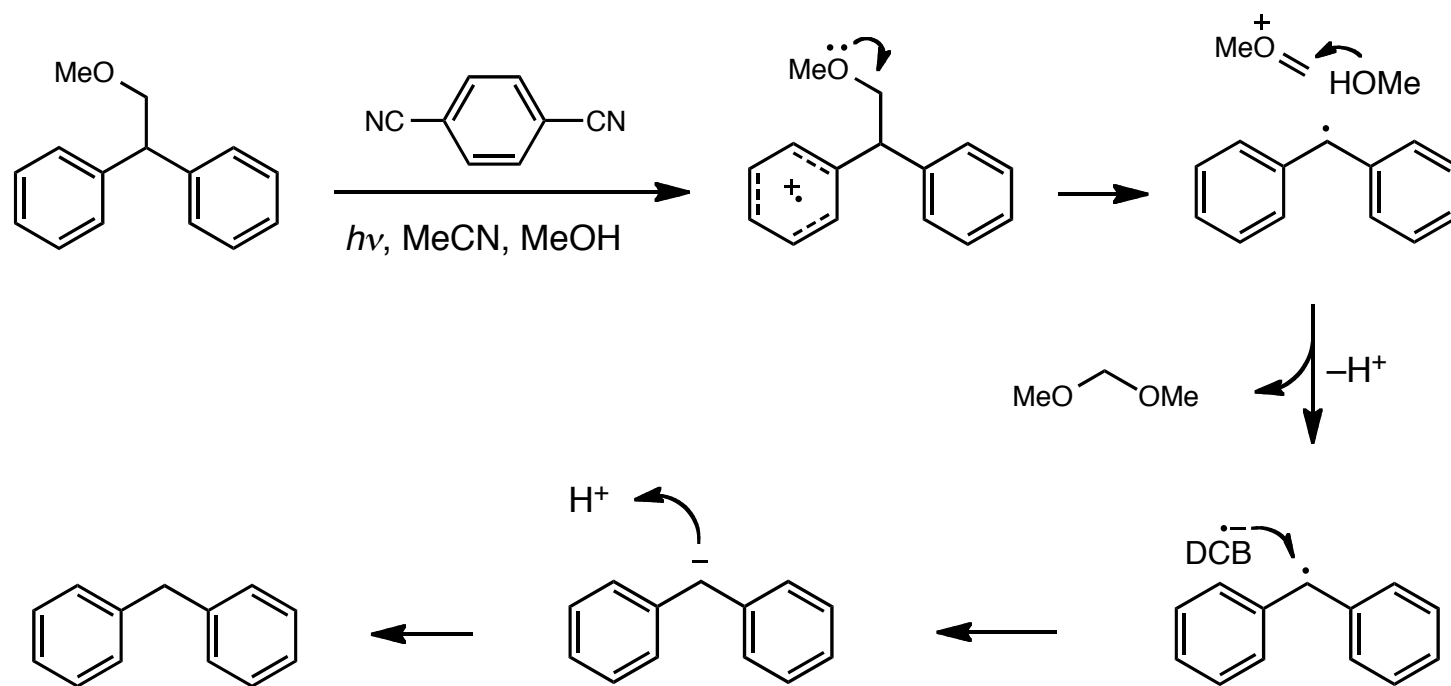


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Dim	dimerization	$(\pi\text{-A-B})_2^{2+}$	A	B

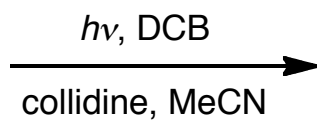
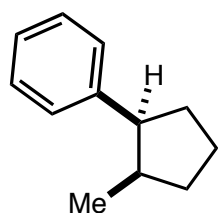
π -C-C⁺ Bond Dissociation

- Fragmentation of a β -ether generates an oxocarbenium ion

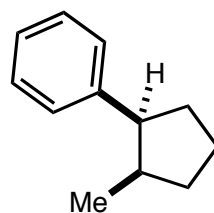
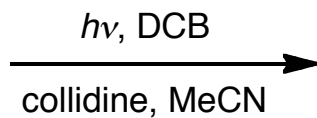
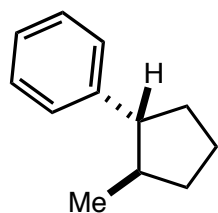


Stereoelectronic Effects in Deprotonation and Fragmentation

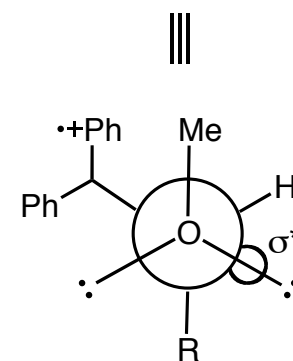
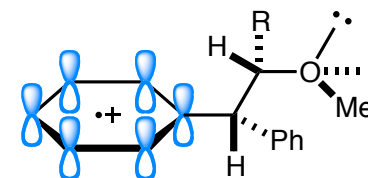
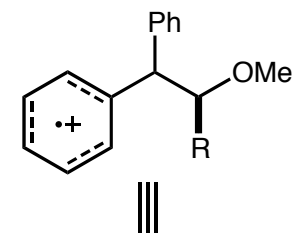
■ Deprotonation



N.R.



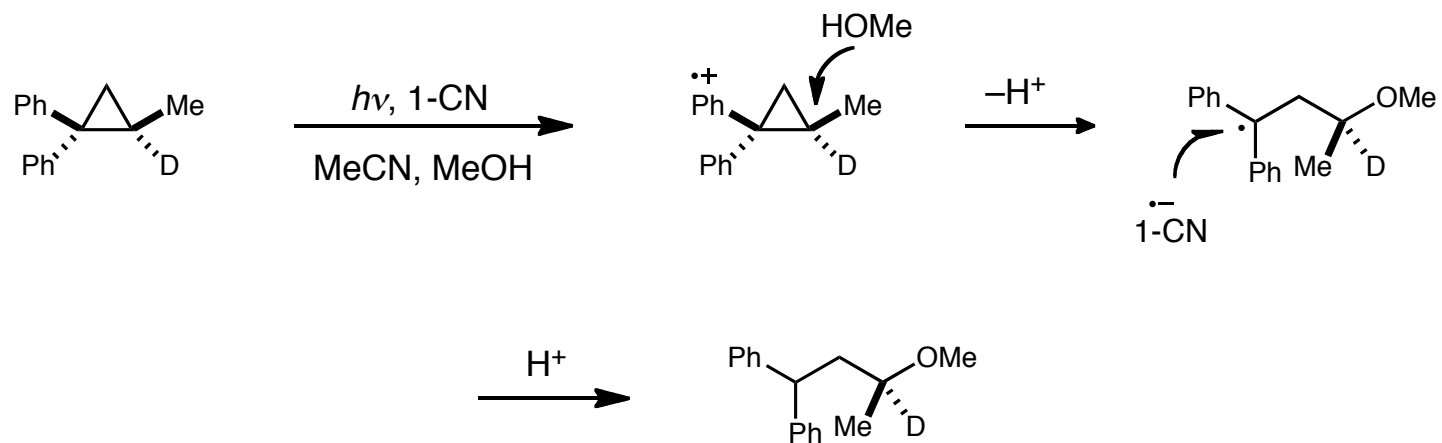
■ Fragmentation



Poniatowski, A.; Floreancig, P. A. In *Carbon-Centered Free Radicals and Radical Cations*; Forbes, M. E., Ed.; Wiley & Sons: New Jersey, **2010**; Vol 3., pp 43-60.
 D. R. Arnold et al. *Can. J. Chem.* **1997**, *75*, 384.

π -C-C⁺ Bond Dissociation

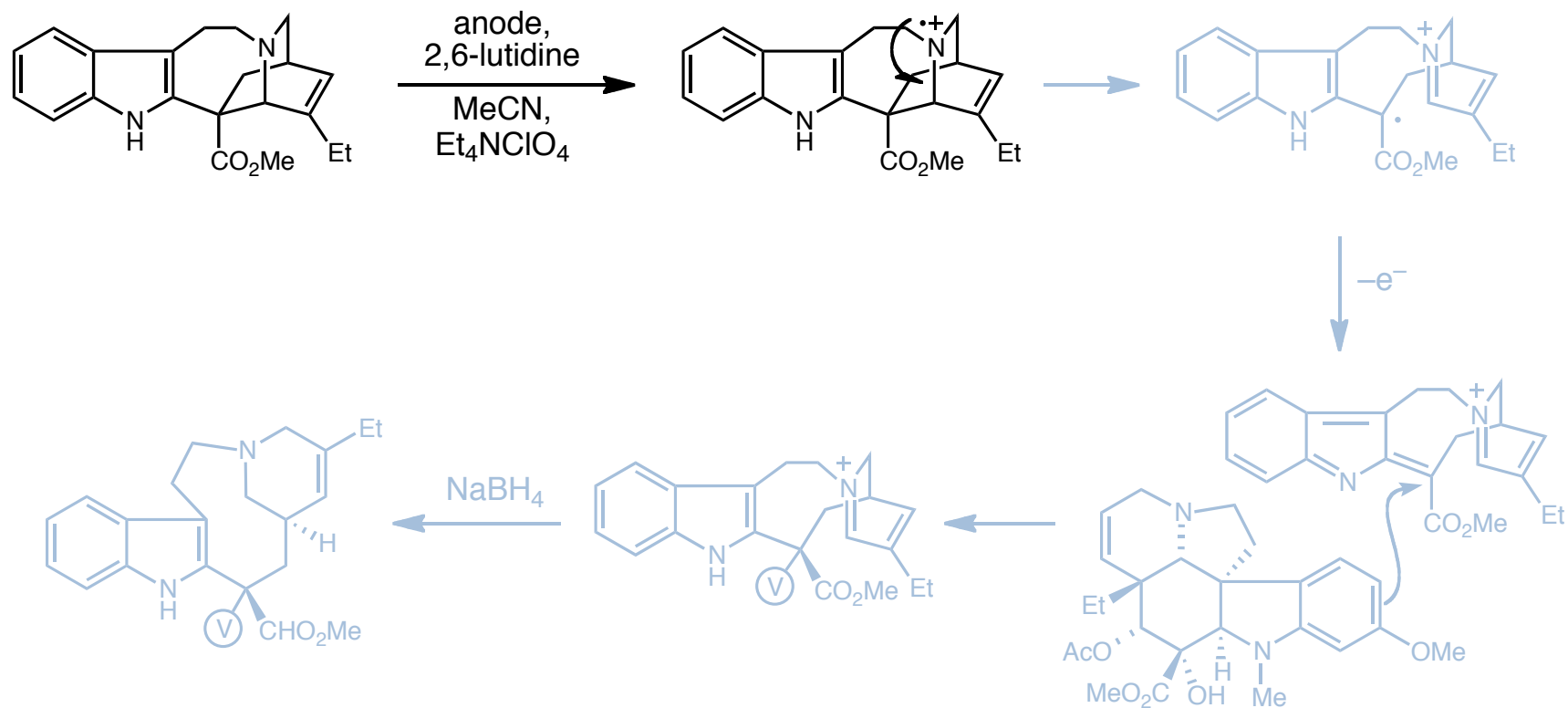
- Nucleophile assisted C–C bond fragmentation with complete inversion of stereochemistry



- Nucleophile assisted π -C-C⁺ fragmentation is limited to strained systems

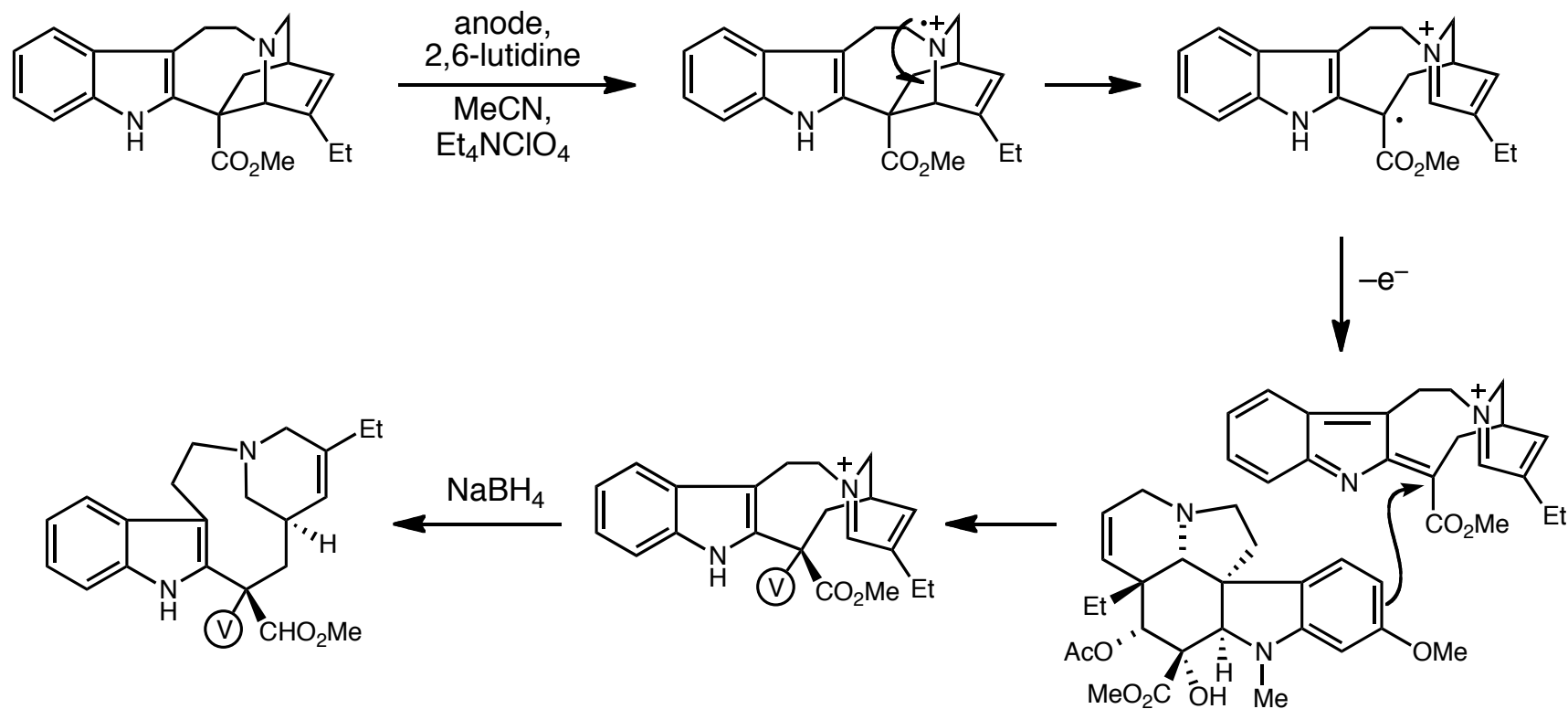
n-C-C⁺ Bond Dissociation

- To drive the reaction, the electrophore must be highly prone to oxidation or the resulting radical must be stabilized by a moiety on the molecule

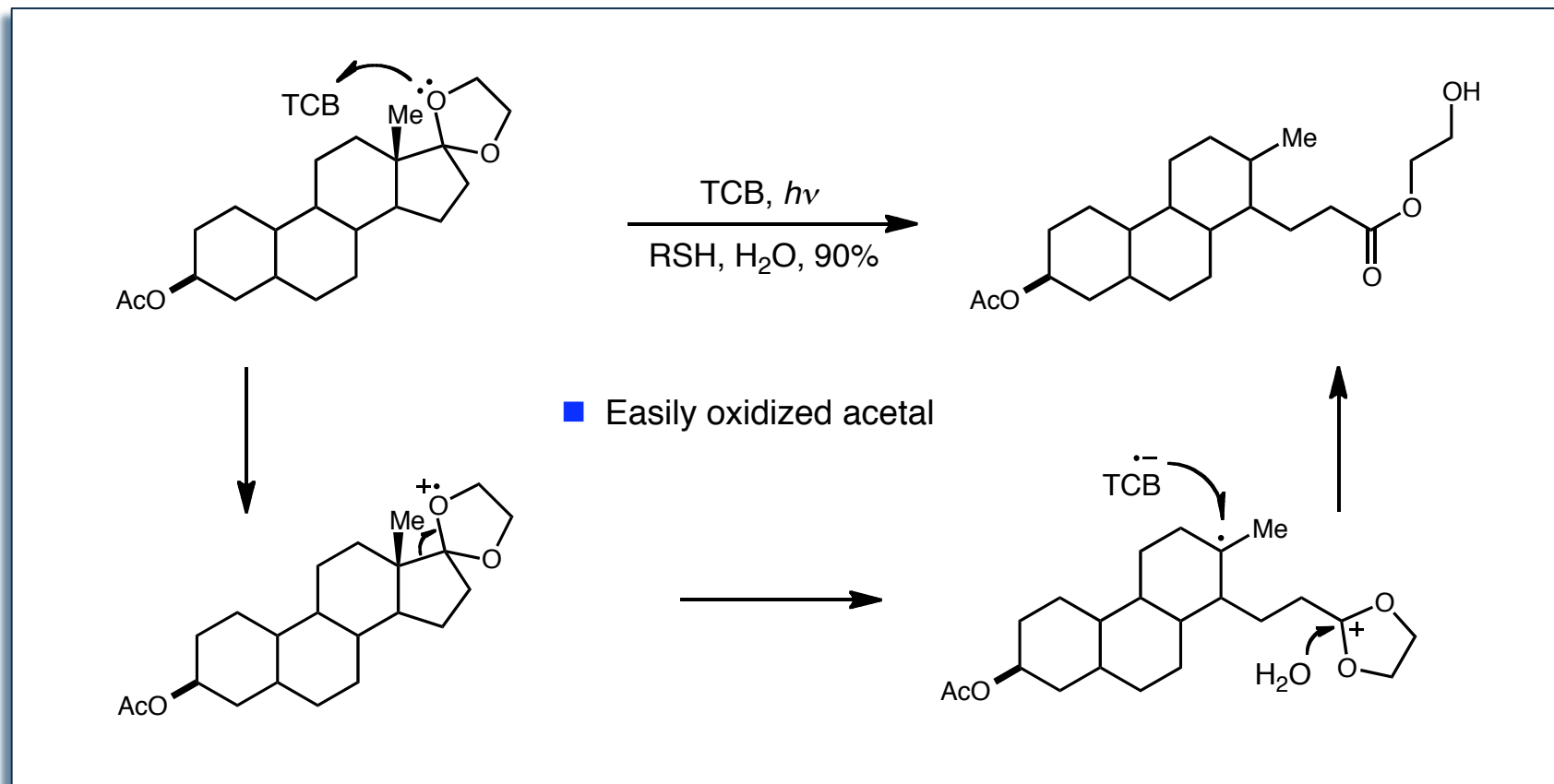


n-C-C^{•+} Bond Dissociation

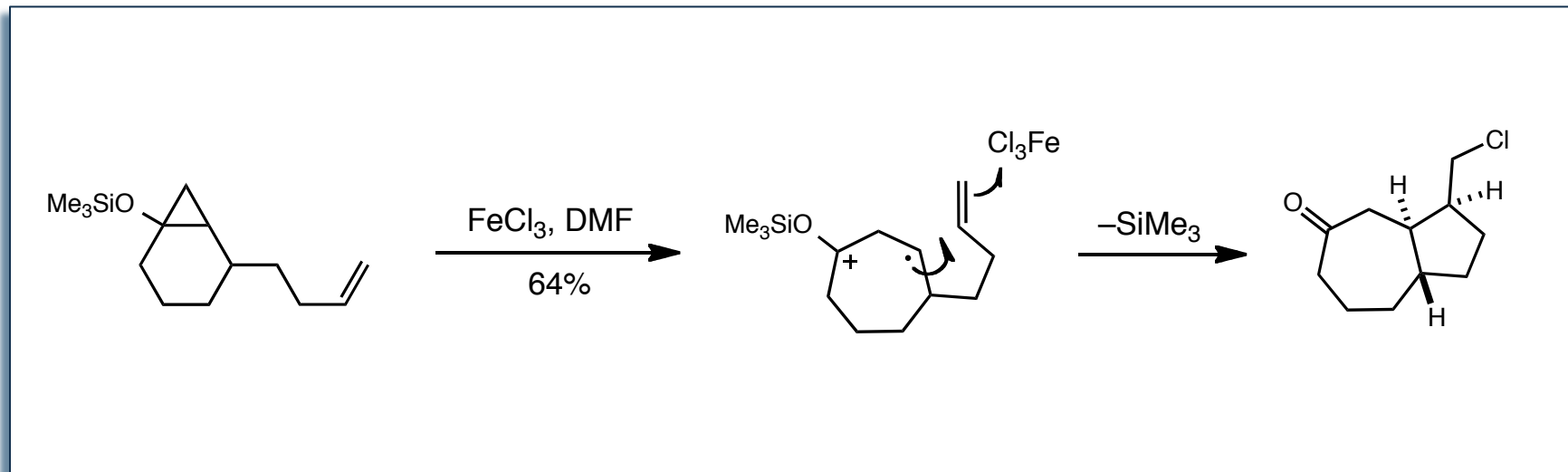
- To drive the reaction, the electrophile must be highly prone to oxidation or the resulting radical must be stabilized by a moiety on the molecule



n-C-C⁺ Bond Dissociation



σ -C-C⁺ Bond Dissociation



- ESR studies on strained systems show that the inner C-C bond is selectively weakened

- Trapping of the pendant olefin and Cl^\bullet abstraction from the bicycle

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H	hydrogen transfer	$\text{H-}\pi\text{-A-B}^{\bullet+}$	A	B
Dim	dimerization	$(\pi\text{-A-B})_2^{2+}$	A	B

π -C-X^{•+} Bond Dissociation: Calculated BDE's

- Aromatic ionization severely weakens the adjacent bond by ~30 kcal/mol on average
- Si and Sn are the most common X-groups used as fragmentation substrates

Reaction	$\Delta H_R(\text{p-C-X}^{\bullet+})$ BDE kcal/mol	$\Delta H_R(\text{p-C-X})$ BDE kcal/mol	Ref
PhCH ₂ -SiMe ₃ ^{•+} → PhCH ₂ [•] + Me ₃ Si ⁺	+30	+77	a
PhCH ₂ -Cl ^{•+} → PhCH ₂ ²⁺ + Cl [•]	+40	+72	b
PhCH ₂ -Br ^{•+} → PhCH ₂ ²⁺ + Br [•]	+26	+58	b
PhCH ₂ -OMe ^{•+} → PhCH ₂ ²⁺ + [•] OMe	+43	+71	b
PhCH ₂ -SMe ^{•+} → PhCH ₂ ²⁺ + [•] SMe	+38	+61	b
PhS-Xan ^{•+} → PhS [•] + Xan ⁺	-11	+26.4	c
PhS-TPCP ^{•+} → PhS [•] + TPCP ⁺	-18.6	+40.3	c

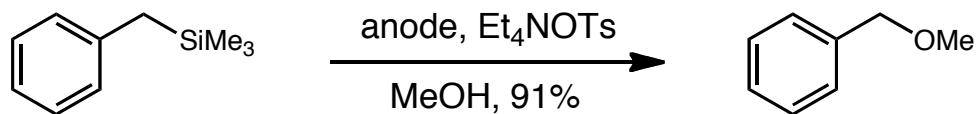
Xan = 9-xanthyl; TPCP = 1,2,3-triphenylcyclopropenyl

- a) J. P. Dinnocenzo et al. *J. Am. Chem. Soc.* **1989**, *111*, 8973.
 b) Schmittle, M.; Burghart, A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2550.
 c) E. M. Arnett et al. *J. Am. Chem. Soc.* **1992**, *114*, 221.

π -C-X⁺ Bond Dissociation

- R₃Si- and R₃Sn- moieties can be used as “super protons”

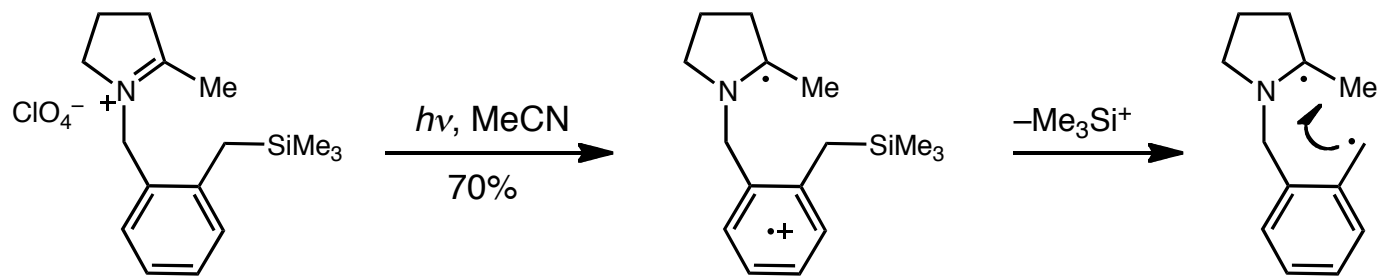
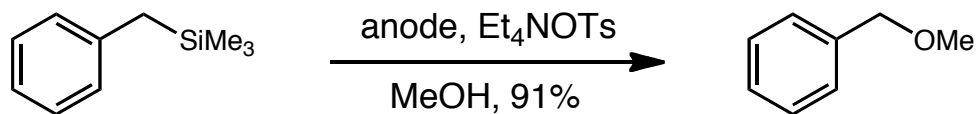
- The dependence of k on MeOH, H₂O, Bu₄NF indicates Nu-assisted Si-bond cleavage



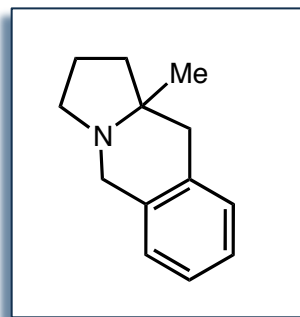
π -C-X⁺ Bond Dissociation

- R₃Si- and R₃Sn- moieties can be used as “super protons”

- The dependence of *k* on MeOH, H₂O, Bu₄NF indicates Nu-assisted Si-bond cleavage



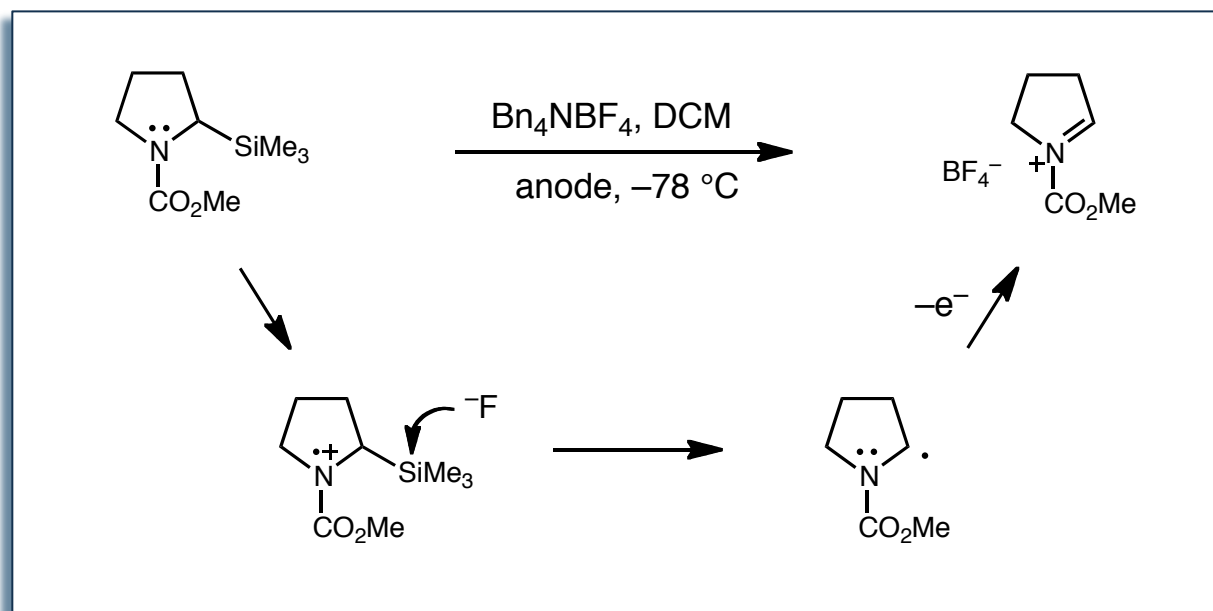
- Iminium salts can act as photo-oxidants under PET conditions



J. Yoshida et al. *Tetrahedron Lett.* **1986**, 27, 3373.
P. S. Mariano et al. *J. Am. Chem. Soc.* **1984**, 106, 6439.

n-C-X^{•+} Bond Dissociation

- Iminium ion used in the “cation pool” method is generated via *n*-C-X^{•+} cleavage



- F⁻ assisted C-Si bond cleavage

π -C-X⁺ Bond Dissociation

- “Cation pool” oxidizes benzylsilane directly



- Oxidation potential of benzylsilane must be ≤ 1.5 V, otherwise a catalytic benzylstannane can be added to initiate the reaction

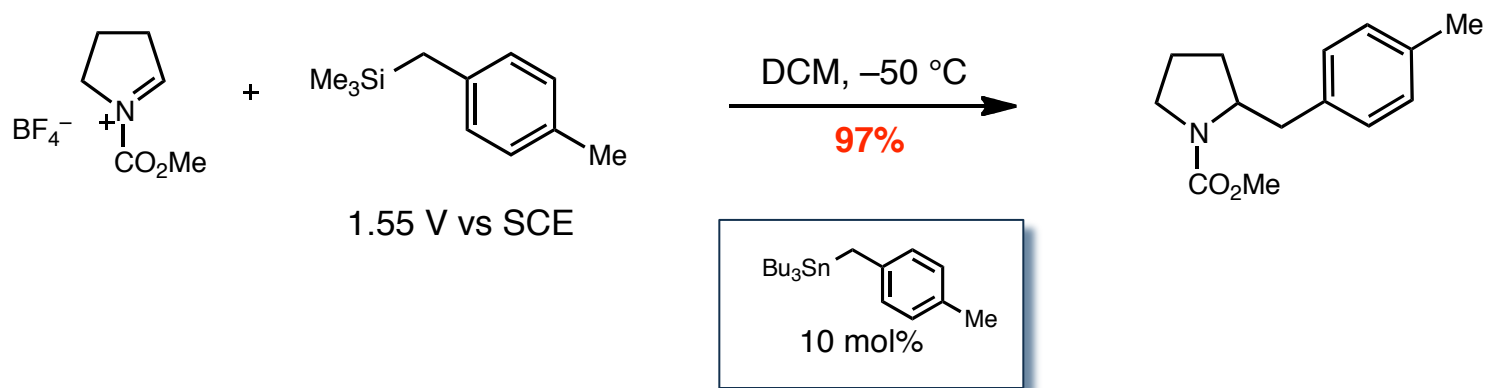


π -C-X⁺ Bond Dissociation

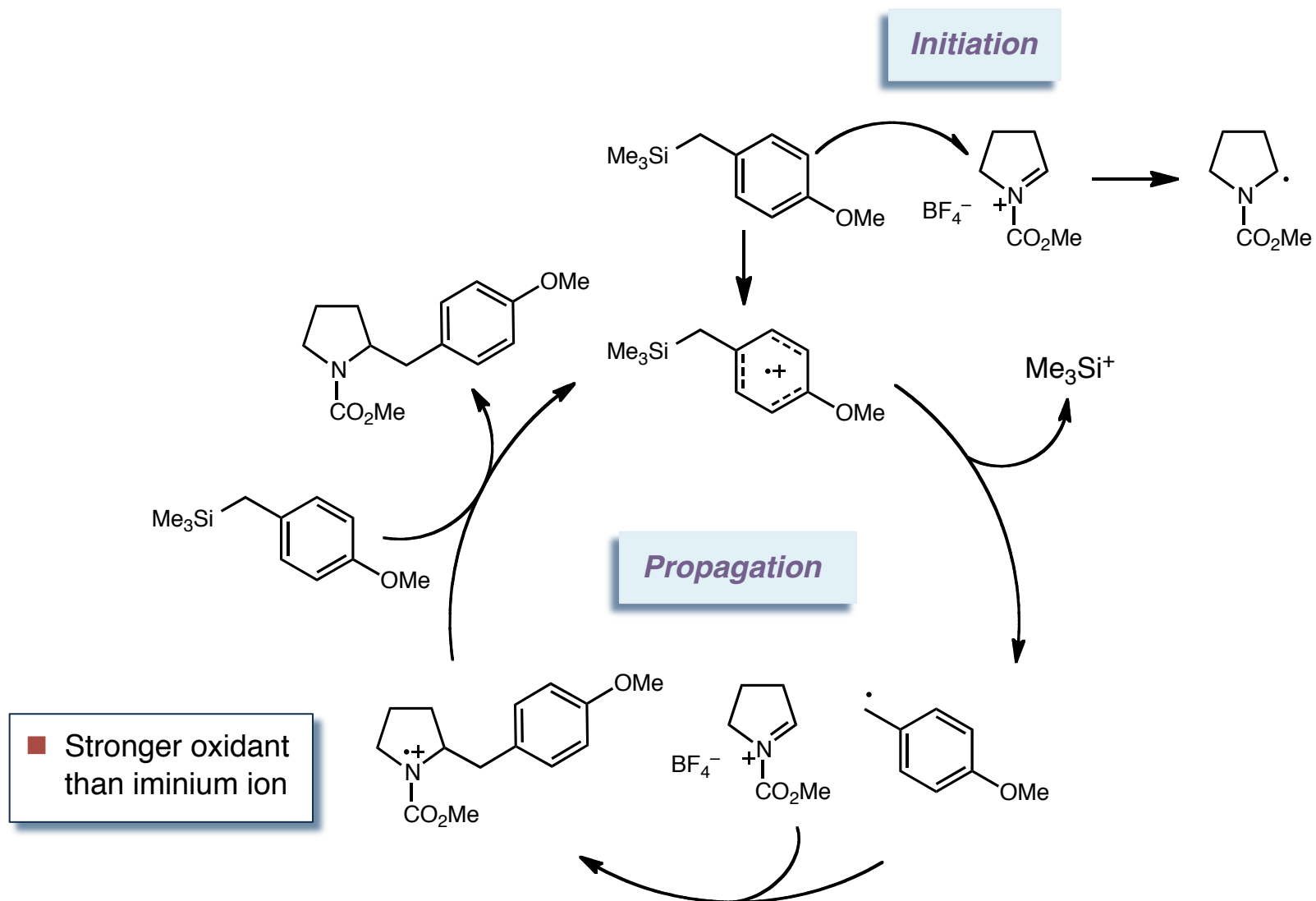
- “Cation pool” oxidizes benzylsilane directly



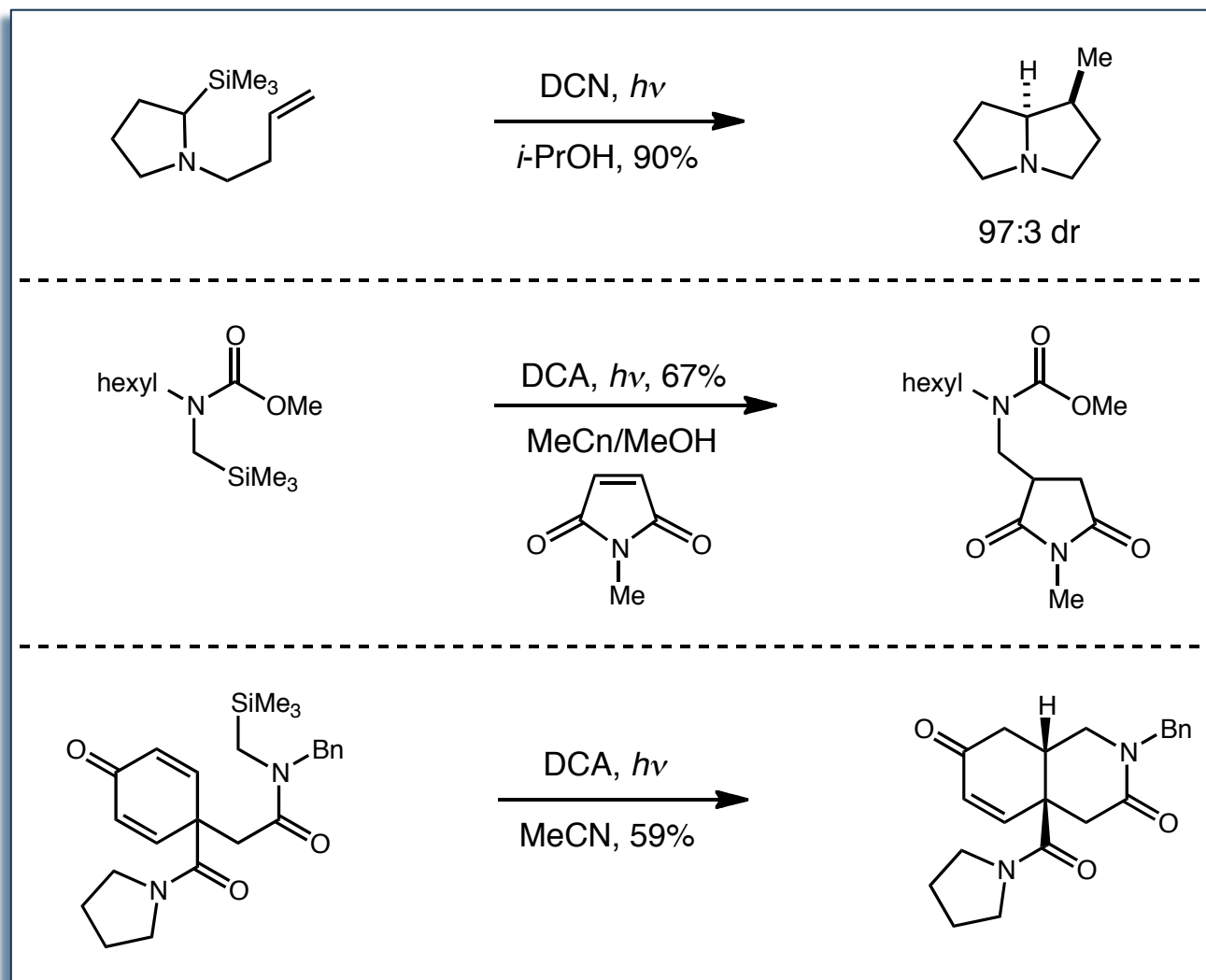
- Oxidation potential of benzylsilane must be ≤1.5 V, otherwise a catalytic benzylstannane can be added to initiate the reaction



Proposed Mechanism

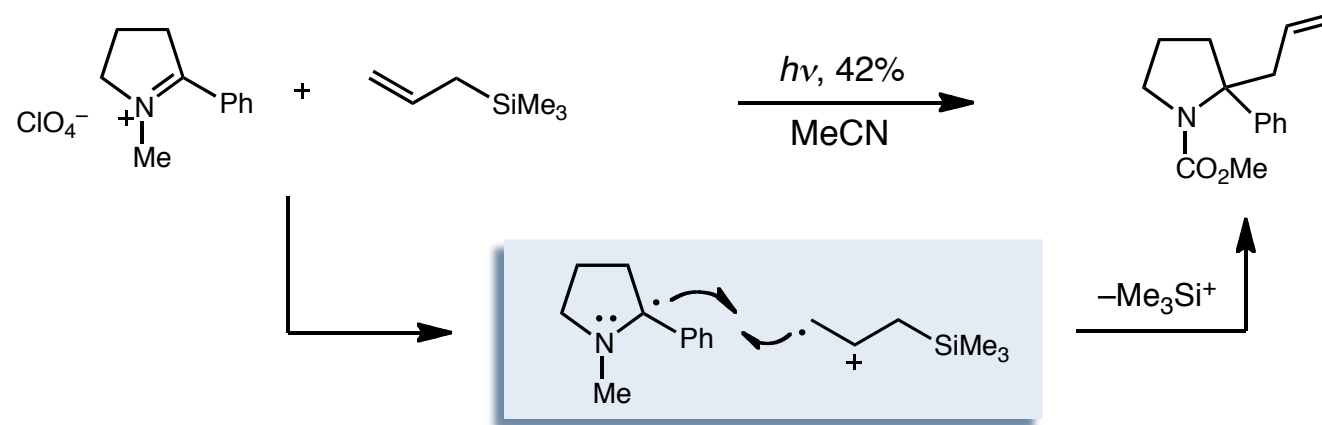


$n\text{-C-X}^+$ Bond Dissociation

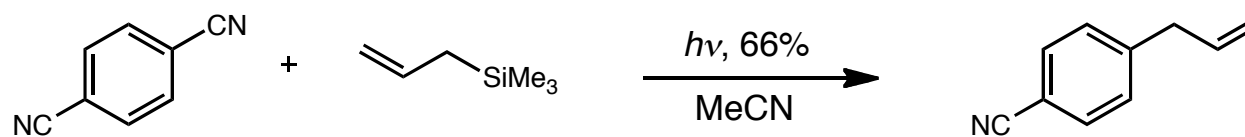


Pandy, G.; Reddy, G. D. *Tetrahedron Lett.* **1992**, *33*, 6533. Steckhan et al. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2137. Mariano et al. *J. Org. Chem.* **1992**, *57*, 6037.

σ -C-X⁺ Bond Dissociation



- Coupling of the radical cation to the oxidant is the prominent primary fate after σ -C-X⁺ cleavage



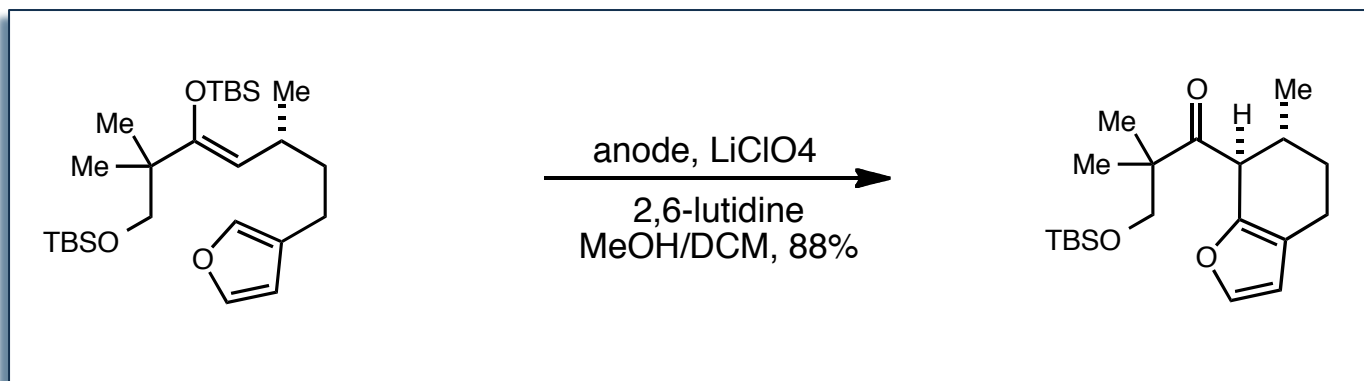
Mariano P. S.; Ohga, K. *J. Am. Chem. Soc.* **1982**, *104*, 617.
Otsuji et al. *Tetrahedron Lett.* **1985**, *26*, 461.

Primary Fate of Radical Cations

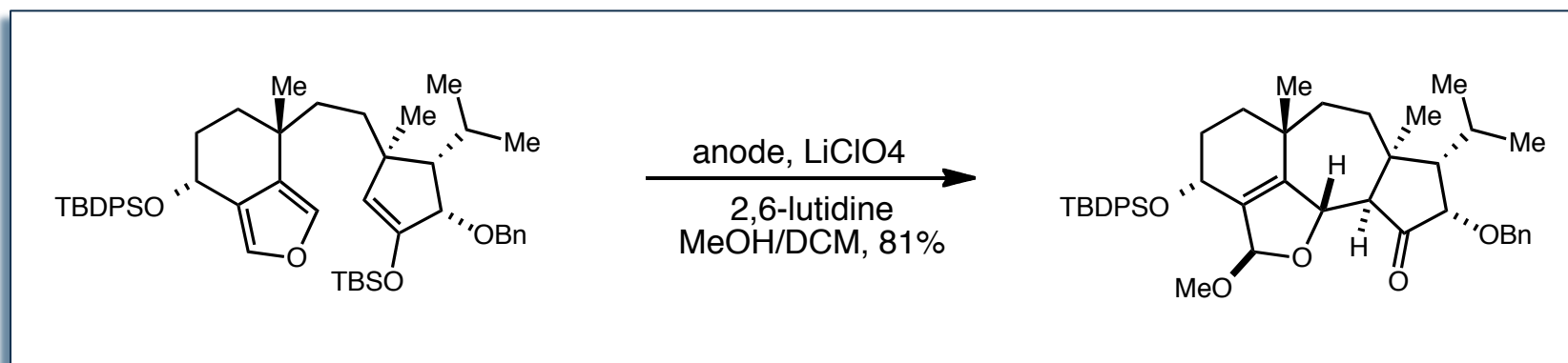
Symbol	Classification	Primary Product	A	B
CH	C–H deprotonation	$\pi\text{-C}^\bullet + \text{H}^+$ or $\text{n-C}^\bullet + \text{H}^+$	C	H
AH	A–H deprotonation	$\pi\text{-A}^\bullet + \text{H}^+$	O, N, S, X	H
AB	A–B bond cleavage	$\pi\text{-A}^\bullet + \text{B}^+$ or $\text{n-A}^\bullet + \text{B}^+$	A	B
CC	C–C bond cleavage	$\pi\text{-C}^\bullet + \text{C}^+$	C	C
CX	C–X bond cleavage	$\pi\text{-C}^\bullet + \text{X}^+$	C	Si, Sn
Nu	Nu attack	$\text{Nu-}\pi\text{-A-B}^{\bullet+}$	A	B
CA	cycloaddition	cycloaddition	A	B
R	rearrangement	rearrangement	A	B
ET	electron transfer	$\pi\text{-A-B}$ or $\pi\text{-A-B}^{2+}$	A	B
Rad	radical attack	$\text{R-}\pi\text{-A-B}^{\bullet+}$	A	B
RA	radical anion attack	$\text{RA-}\pi\text{-A-B}$	A	B
H	hydrogen transfer	$\text{H-}\pi\text{-A-B}^{\bullet+}$	A	B
Dim	dimerization	$(\pi\text{-A-B})_2^{2+}$	A	B

$Nu-\pi-A-B^+$

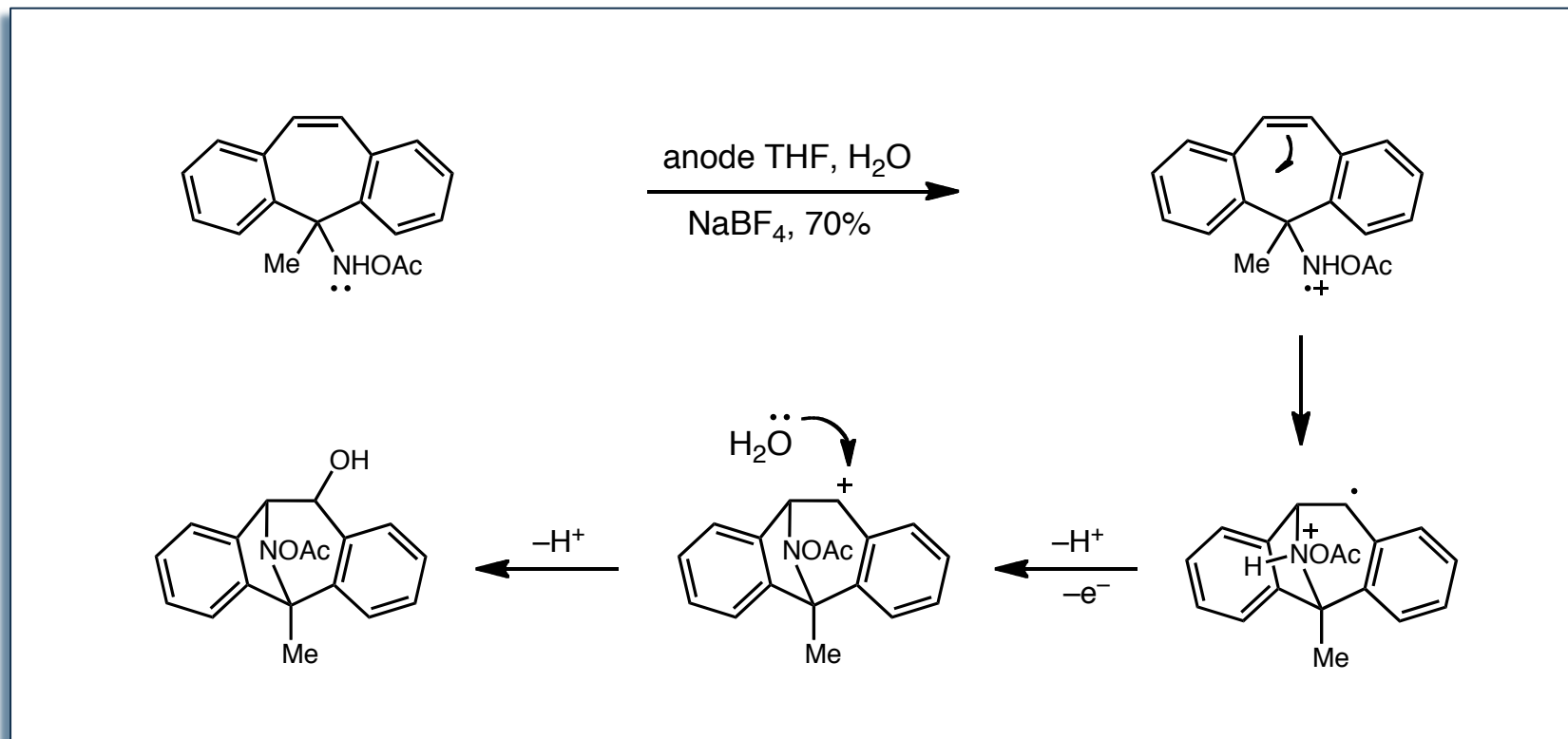
■ Moeller en route to (-)-alliacol A



■ Trauner en route to (-)-guanacastepene E

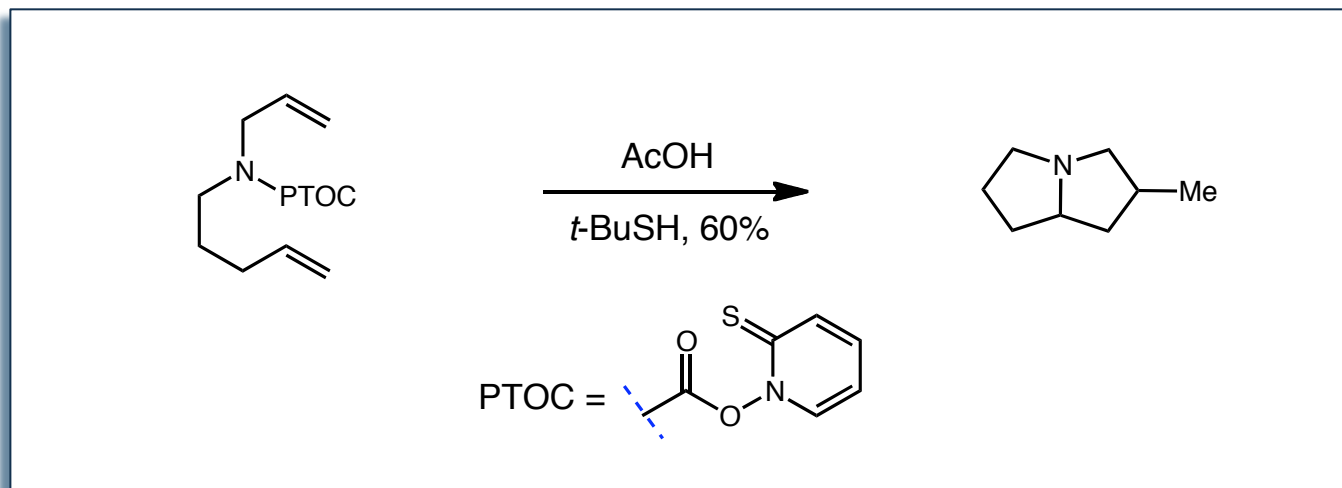


Nu-n-A-B^{•+}

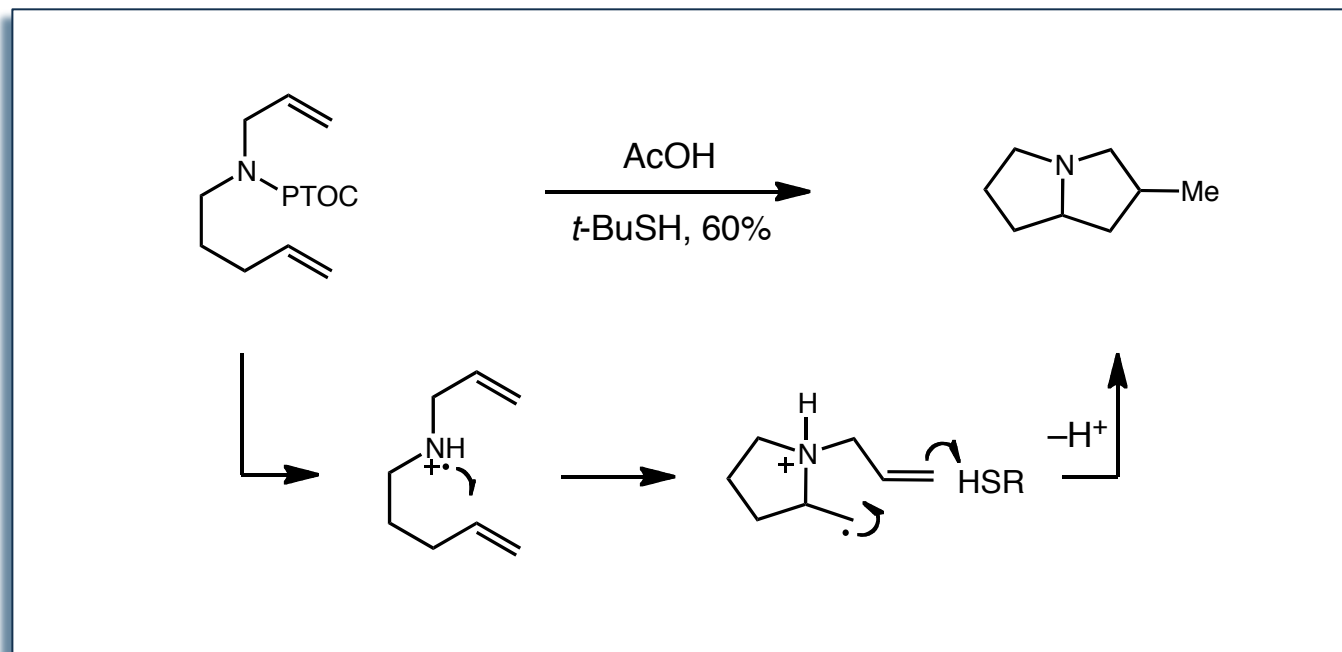


- The authors do not rule out the possibility of olefin oxidation as an alternative mechanism

$Nu-n-A-B^+$



$Nu-n-A-B^+$



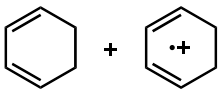
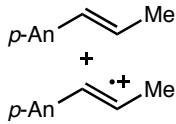
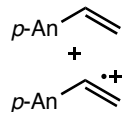
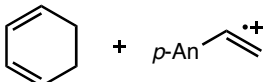
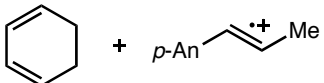
- Initially formed nitrene is immediately protonated

Primary Fate of Radical Cations

Symbol	Classification	Primary Product	A	B
CH	C–H deprotonation	$\pi\text{-C}^\cdot + \text{H}^+$ or $\text{n-C}^\cdot + \text{H}^+$	C	H
AH	A–H deprotonation	$\pi\text{-A}^\cdot + \text{H}^+$	O, N, S, X	H
AB	A–B bond cleavage	$\pi\text{-A}^\cdot + \text{B}^+$ or $\text{n-A}^\cdot + \text{B}^+$	A	B
CC	C–C bond cleavage	$\pi\text{-C}^\cdot + \text{C}^+$	C	C
CX	C–X bond cleavage	$\pi\text{-C}^\cdot + \text{X}^+$	C	Si, Sn
Nu	Nu attack	$\text{Nu-}\pi\text{-A-B}^{\cdot+}$	A	B
CA	cycloaddition	cycloaddition	A	B
R	rearrangement	rearrangement	A	B
ET	electron transfer	$\pi\text{-A-B}$ or $\pi\text{-A-B}^{2+}$	A	B
Rad	radical attack	$\text{R-}\pi\text{-A-B}^{\cdot+}$	A	B
RA	radical anion attack	$\text{RA-}\pi\text{-A-B}$	A	B
H	hydrogen transfer	$\text{H-}\pi\text{-A-B}^{\cdot+}$	A	B
Dim	dimerization	$(\pi\text{-A-B})_2^{2+}$	A	B

Cycloaddition

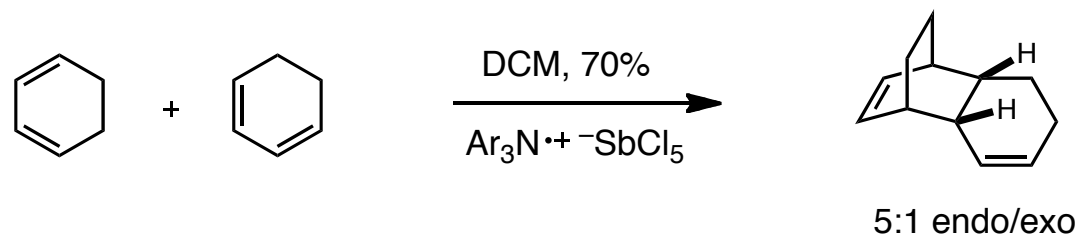
■ Experimental kinetic data for radical cation cycloadditions (rt)

Reaction	k [$M^{-1}s^{-1}$]	comments	reference
	3×10^8	Mostly [4 + 2] endo adduct; ratio of/to [2 + 2] varied by concentration	a, b
	$<6.7 \times 10^7$	1) [2 + 2] terminated by C-H [•] deprotonation 2) concerted reaction	b
	1) 1.4×10^9 2) 1.4×10^9 3) 1×10^{10}	1) concerted cycloaddition assumed 2) distonic 1,4-radical cation intermediate	c,d
	7×10^8	21% Diels–Alder adduct	e
	1.5×10^6	80% Diels–Alder adduct	e

a) Calhoun, G. C.; Schuster, G. B. *J. Am. Chem. Soc.* **1984**, *106*, 6870. b) Lorenz, K. T.; Bauld, N. L. *J. Am. Chem. Soc.* **1987**, *109*, 1157. c) Takamuku et al. *J. Org. Chem.* **1991**, *56*, 6240. d) Schepp, N. P; Johnston, L. J *J. Am. Chem. Soc.* **1994**, *116*, 6895. e) Schepp, N. P; Johnston, L. J *J. Am. Chem. Soc.* **1994**, *116*, 10330.

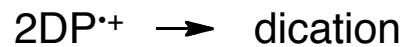
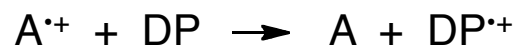
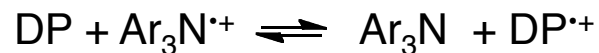
Diels–Alder [4 + 2] Cycloaddition

- Shown to operate via a cation radical chain mechanism



Suprafacial selectivity observed

$$k = 3 \times 10^8 \text{ [M}^{-1}\text{s}^{-1}\text{]}$$



> Propagation

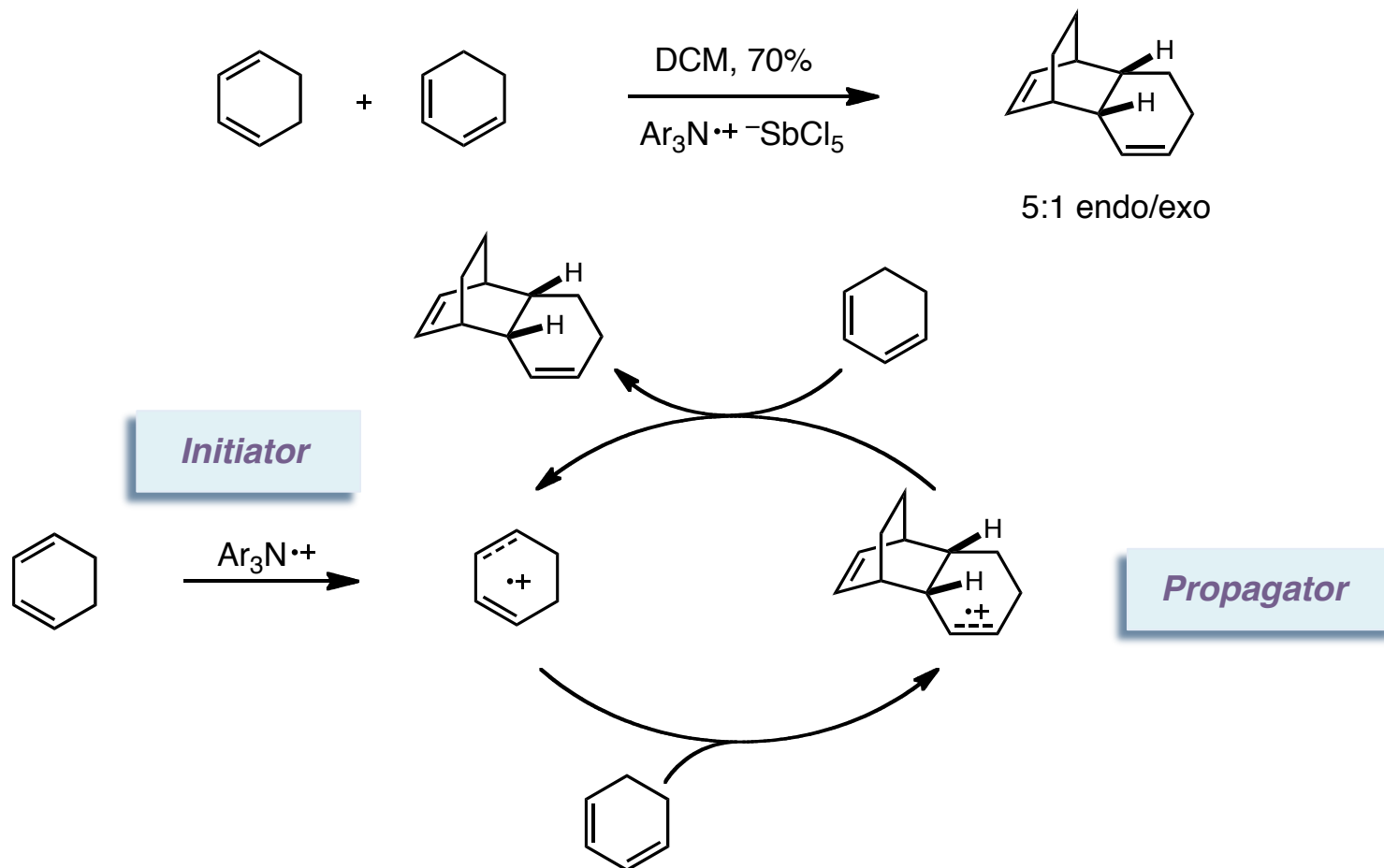
> Termination

Bauld et al. *J. Am. Chem. Soc.* **1981**, *109*, 3163.

Lorenz, K. T.; Bauld, N. L. *J. Am. Chem. Soc.* **1987**, *109*, 1157

Diels–Alder [4 + 2] Cycloaddition

- Shown to operate via a cation radical chain mechanism

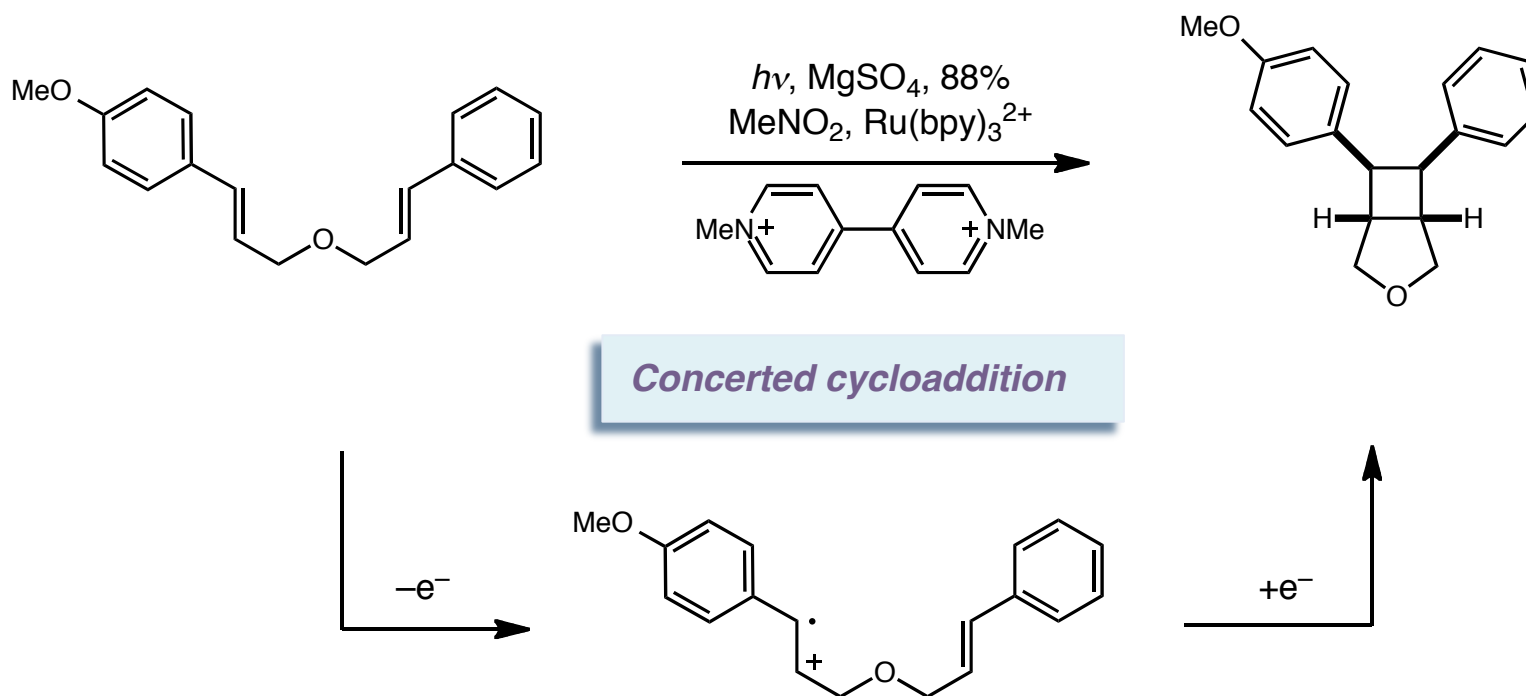


Bald et al. *J. Am. Chem. Soc.* **1981**, *109*, 3163.

Lorenz, K. T.; Bald, N. L. *J. Am. Chem. Soc.* **1987**, *109*, 1157

[2 + 2] Cycloaddition

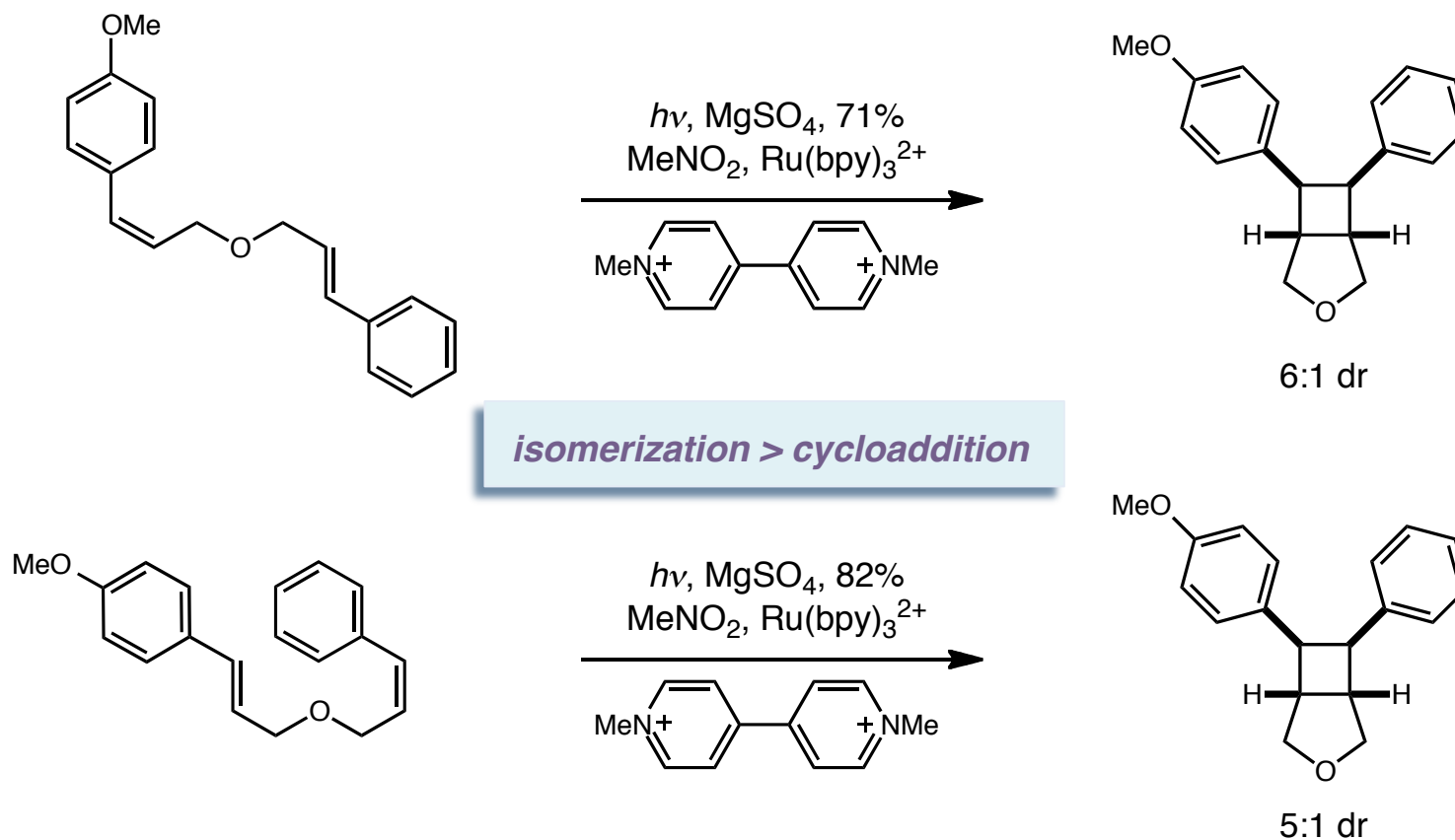
- Photoredox catalyzed radical cation formation



- Electron donating substituent on the arene is necessary to promote the initial oxidation

[2 + 2] Cycloaddition

■ Stereoconvergent transformation

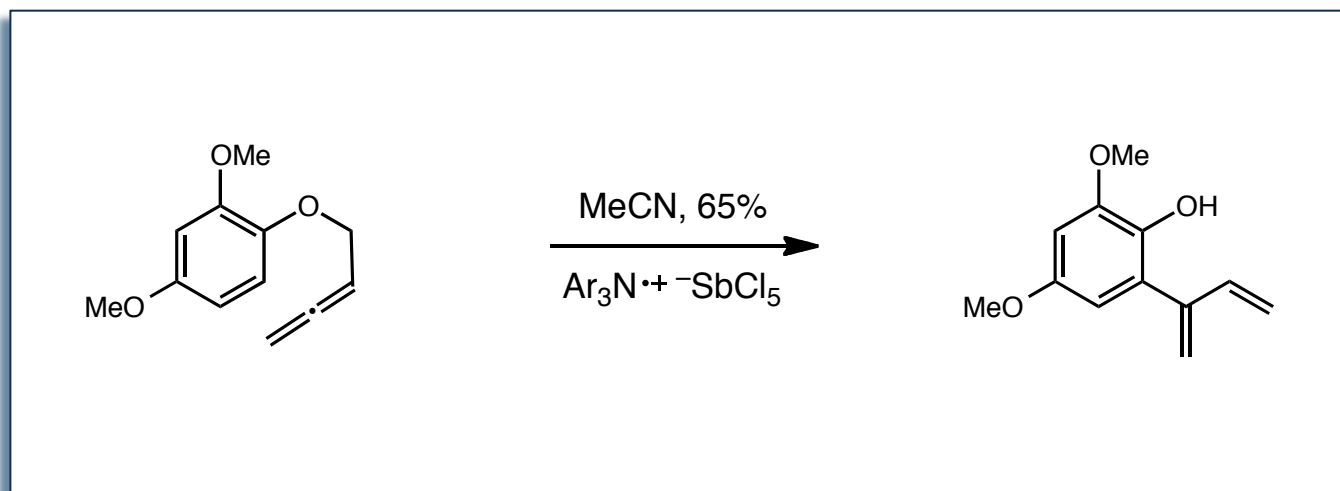


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AB	A–B bond cleavage	$\pi\text{-A}^\bullet + \text{B}^+$ or $n\text{-A}^\bullet + \text{B}^+$	A	B
CC	C–C bond cleavage	$\pi\text{-C}^\bullet + \text{C}^+$	C	C
CX	C–X bond cleavage	$\pi\text{-C}^\bullet + \text{X}^+$	C	Si, Sn
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CA	cycloaddition	cycloaddition	A	B
R	rearrangement	rearrangement	A	B
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Rad	radical attack	$\text{R}-\pi\text{-A-B}^{\bullet+}$	A	B
RA	radical anion attack	$\text{RA}-\pi\text{-A-B}$	A	B
H	hydrogen transfer	$\text{H}-\pi\text{-A-B}^{\bullet+}$	A	B
Dim	dimerization	$(\pi\text{-A-B})_2^{2+}$	A	B

Claisen Rearrangement: A Representative Example

- Though potentially powerful, the radical cation Claisen rearrangement has found very limited use in synthesis



- The radical cation Cope rearrangement seems to be limited to aryl substituted systems.

Primary Fate of Radical Cations

- Both radical (Rad) and radical anion (RA) have been previously discussed

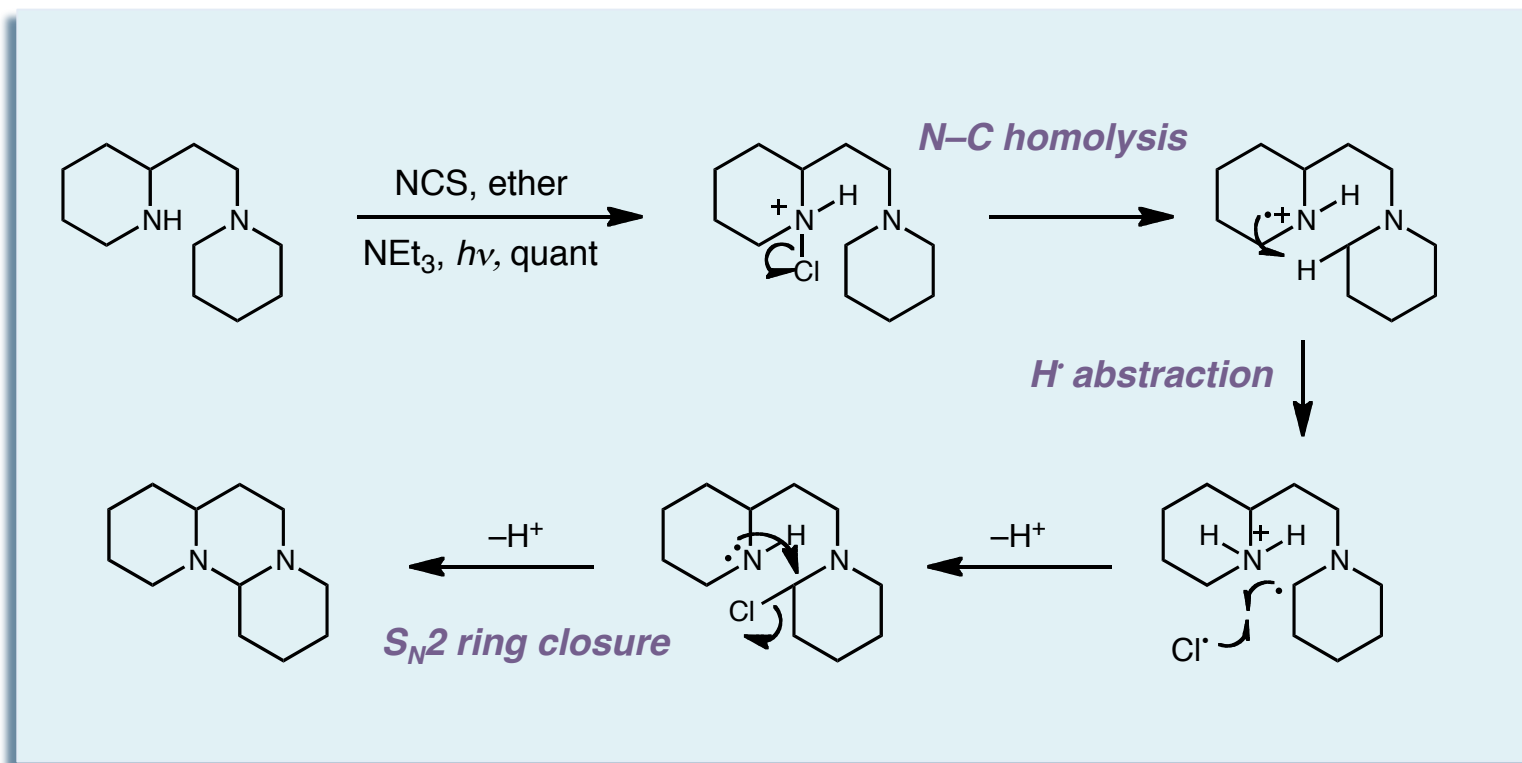
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CX	C–X bond cleavage	$\pi\text{-C}^\bullet + \text{X}^+$	C	Si, Sn
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Rad	radical attack	$\text{R-}\pi\text{-A-B}^+$	A	B
RA	radical anion attack	$\text{RA-}\pi\text{-A-B}$	A	B
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CX	C–X bond cleavage	$\pi\text{-C}^\cdot + \text{X}^+$	C	Si, Sn
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CA	cycloaddition	cycloaddition	A	B
R	rearrangement	rearrangement	A	B
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RA	radical anion attack	$\text{RA-}\pi\text{-A-B}$	A	B
H	hydrogen transfer	$\text{H-}\pi\text{-A-B}^{\cdot+}$	A	B
Dim	dimerization	$(\pi\text{-A-B})_2^{2+}$	A	B

Hydrogen Transfer

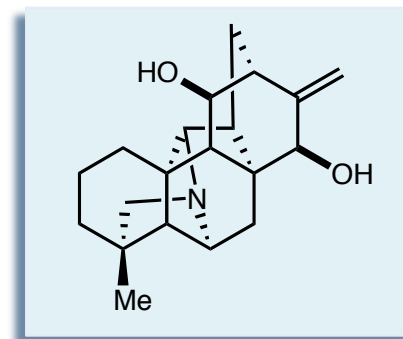
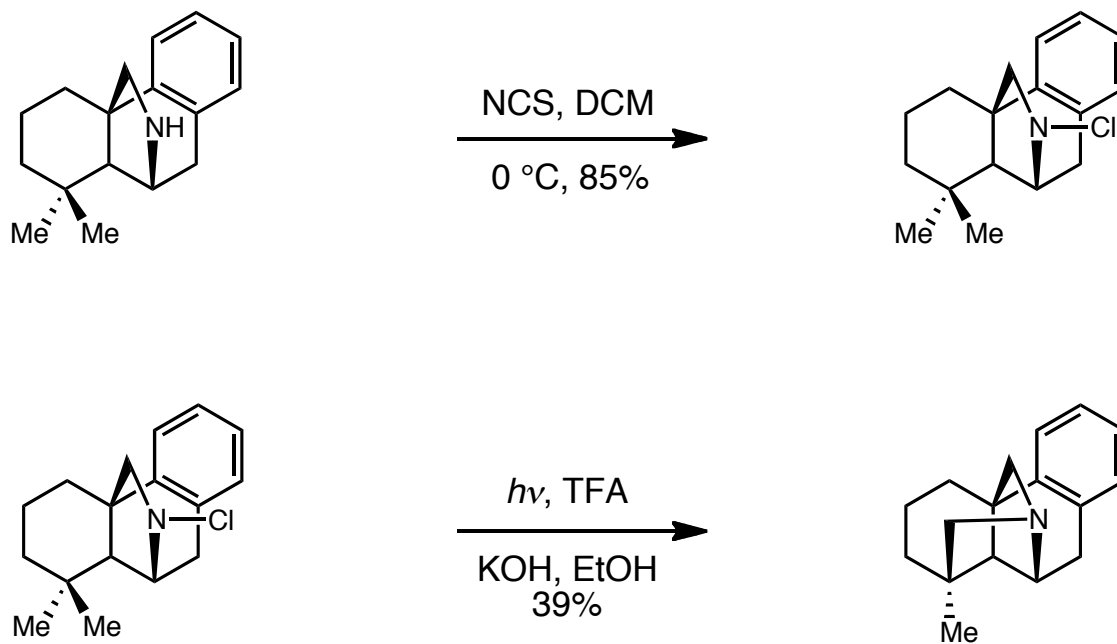
- The Hofmann–Löffler–Freitag reaction



- Typically a 1,5-H-atom abstraction

Hydrogen Transfer

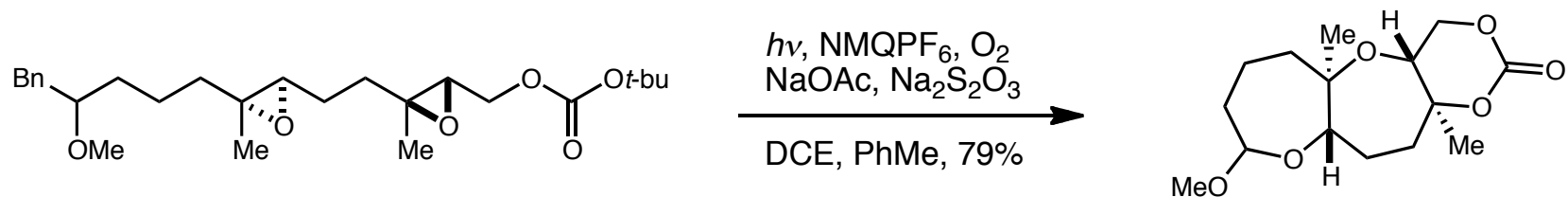
- The Hofmann–Löffler–Freitag reaction



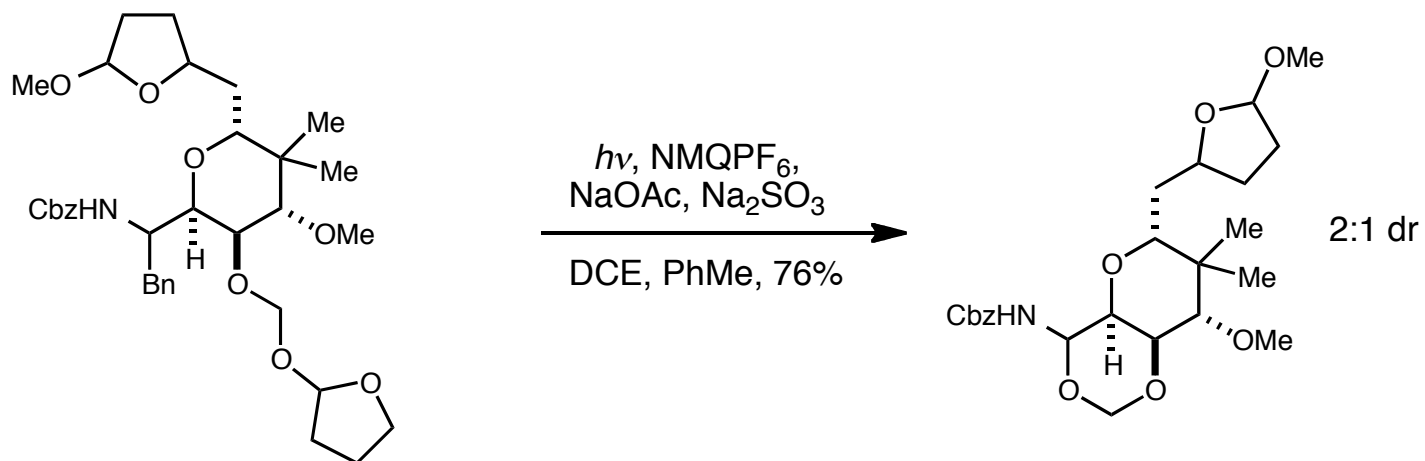
- Intermediate en route to the synthesis of kobusine

Radical Cations in Synthesis: Floreancig Lab

■ Epoxonium cyclization

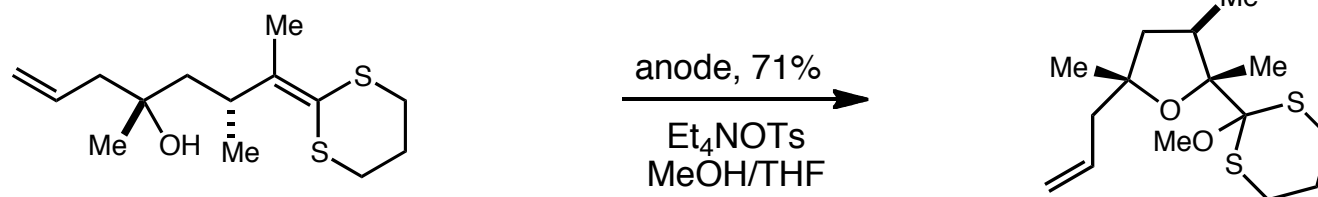


■ Cyclic acetal formation en route to theopederin D

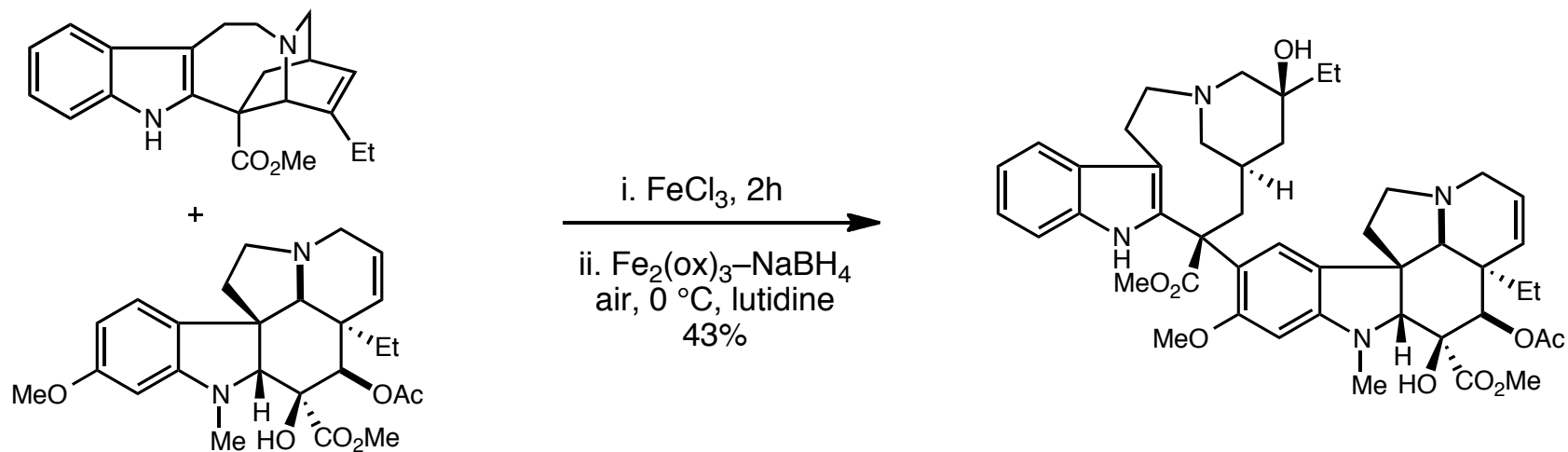


Radical Cations in Synthesis

- Used in Moeller's synthesis of nemorensic acid



- Boger's synthesis of vinblastine



Moeller et al *J. Am. Chem. Soc.* **2002**, *124*, 10101.
Boger et al *J. Am. Chem. Soc.* **2008**, *130*, 420.

Radical Cations in Synthesis: MacMillan Lab

