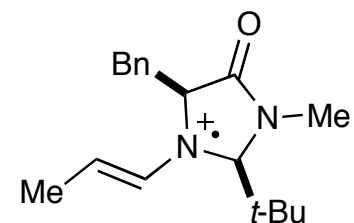
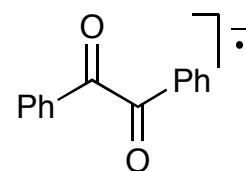
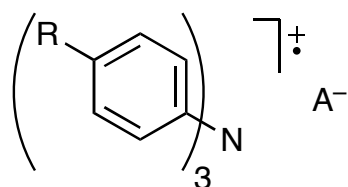


Radicals III: Radical Ions and SOMO Catalysis



Jason J. Beiger

November 13, 2009

Selected References

Radical Ions

- Bauld, N.L. *Radicals, Ion Radicals, and Triplets: The Spin-Bearing Intermediates of Organic Chemistry*. Wiley-VCH: NY, 1997.
- Kaiser, E.T.; Kevan, L.; eds. *Radical Ions*. John Wiley & Sons: New York, 1968.
- Todres, Z.V. *Organic Radical Ions: Chemistry and Applications*. Marcel Dekker: New York, 2003.

- Zimmerman, J.; Sibi, M.P. *Top. Curr. Chem.* **2006**, 263, 107–162.
- Albert, M.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Top. Curr. Chem.* **2006**, 264, 1–62.
- Walton, J.C. *Top. Curr. Chem.* **2006**, 264, 163–200.
- Donoghue, P.J.; Wiest, O. *Chem. Eur. J.* **2006**, 12, 7018–7027.
- Roth, H.D. *Tetrahedron* **1986**, 42, 6097–6100.
- Todres, Z.V. *Tetrahedron* **1985**, 41, 2771–2823.

Radical Cations

- Wiest, O.; Oxgaard, J.; Saettel, N.J. *Adv. Phys. Org. Chem.* **2003**, 38, 87–109.
- Saettel, N.; Oxgaard, J.; Wiest, O. *Eur. J. Org. Chem.* **2001**, 8, 1429–1439.
- Schmittel, M.; Burghart, A. *Angew. Chem. Intl. Ed.* **1997**, 36, 2550–2589.
- Roth, H.D. *Top. Curr. Chem.* **1992**, 163, 131–245.
- Bauld, N.L. *Tetrahedron* **1989**, 45, 5307–5363.
- Bauld, N.L., *et al.* *Acc. Chem. Res.* **1987**, 20, 371–378.
- Ledwith, A. *Acc. Chem. Res.* **1972**, 5, 133–139.

Radical Anions

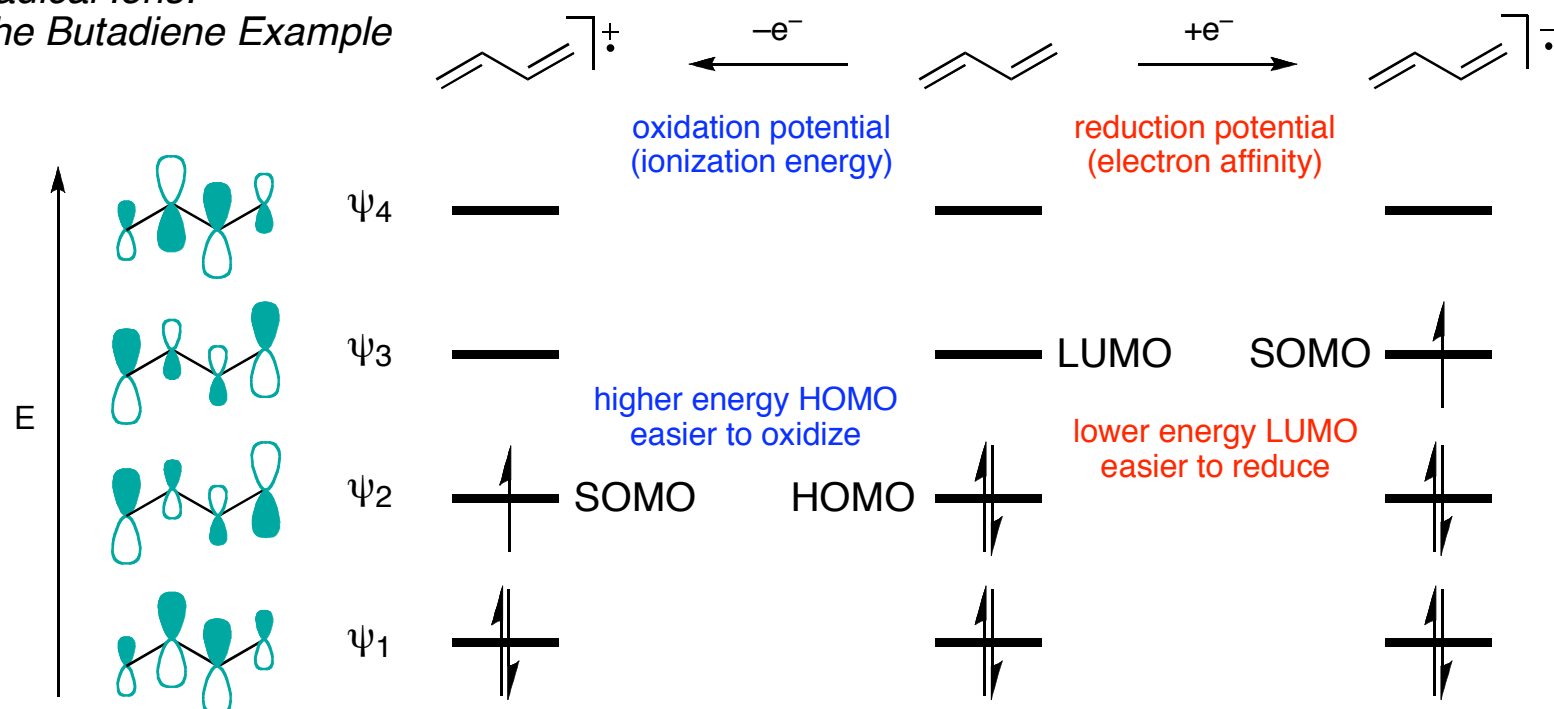
- Gansäuer, A., *et al.* *Top. Curr. Chem.* **2006**, 263, 39–69.
- Cuerva, J.M.; Justicia, J.; Oller-López, J.L.; Oltra, J.E. *Top. Curr. Chem.* **2006**, 264, 63–91.
- Rossi, R.A.; Pierini, A.B.; Penenory, A.B. *Chem. Rev.* **2003**, 103, 71–168.
- Gansäuer, A.; Narayan, S. *Adv. Synth. Cat.* **2002**, 344, 465–475.
- Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, 100, 2771–2788.
- Rossi, R.A. *Acc. Chem. Res.* **1982**, 15, 164–170.
- Kornblum, N. *Angew. Chem. Intl. Ed.* **1975**, 14, 734–745.

Presentation Outline

- Introduction
 - Classification
 - Generation
 - Historical Context
- Analysis
 - Electron Spin Resonance (ESR) Spectroscopy
 - NMR (CIDNP)
- Structure and Properties
 - Spin and Charge Densities
 - pKa
- Radical Anions
 - Reductive Epoxide Openings
 - S_{RN}1
- Radical Cations
 - Diels-Alder [4+2] Cycloaddition
 - SOMO Catalysis

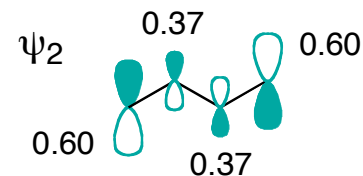
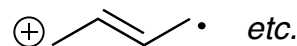
Introduction to Radical Ions

Radical Ions: The Butadiene Example



- For simple hydrocarbon radical ions, the spin and charge densities are tightly coupled and are determined by the SOMO coefficients (c_i)

despite resonance formalism:



- Pairing Theorem** (for Alternant Hydrocarbons):

spin and charge densities in cation and anion radicals predicted to be the same

$$(c_{i,\text{HOMO}}^2 = c_{i,\text{LUMO}}^2 = \rho_i)$$

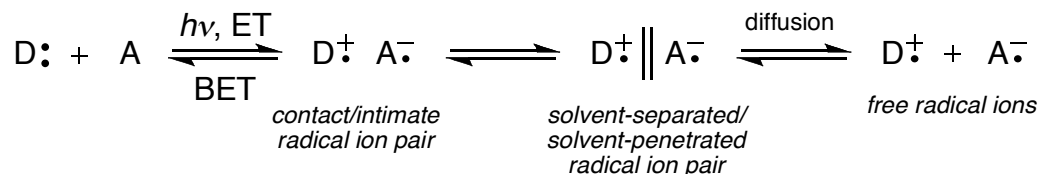
Generation

<i>Method</i>	<i>Conditions</i>	<i>Comments</i>
Electrochemical	<ul style="list-style-type: none">– anodic oxidation, cathodic reduction (working electrodes: Au, Ag, Pt, C)– bulk electrolysis, cyclic voltammetry	<ul style="list-style-type: none">– Useful for structural studies (ESR cavity) but rarely applicable as a preparative method– Need good temperature and potential control
Radiolytic	<ul style="list-style-type: none">– X- or γ-radiation (e^- bombardment)– pulse radiolysis: create solvent holes, "hole transfer" to substrate	<ul style="list-style-type: none">– Useful for mass spectrometry (EI, CI)– Slow dissipation of excess energy (some ionized intermediates do not survive)
Chemical	<ul style="list-style-type: none">– oxidants: Ar_3N^+, SbCl_6^-, NO^+, Br_2, O_2, $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ (CAN), conc. H_2SO_4, DDQ, chloranil, Sb^{3+}, Sb^{5+}, Pb^{4+}, Mn^{3+}, Fe^{2+}, Ti^{3+}, Cu^+, Cr^{2+}– reductants: alkali M in $\text{NH}_3(\text{l})$ or ethereal solvent, colloidal M (Zn), SmI_2	<ul style="list-style-type: none">– Reagent choice based upon ox./red. potential for one ET (and not two)– Limited by strong acid generation (rad. cations)
Photochemical	<ul style="list-style-type: none">– photoinduced electron transfer (PET)	<ul style="list-style-type: none">– Limited by back electron transfer (BET)– May lead to triplet chemistry (via ISC) and unexpected atom abstractions– Ion pairs may participate in acid-base rxn.

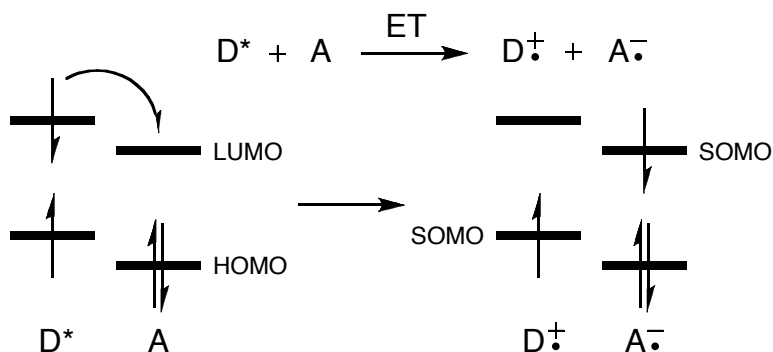
Other methods include: zeolites (crystalline aluminosilicates), thermal electron transfer, montmorillonite clays, semiconductor surfaces (TiO_2), cation radical polymers, laser excitation

Generation: Photoinduced Electron Transfer (PET)

Overall Process

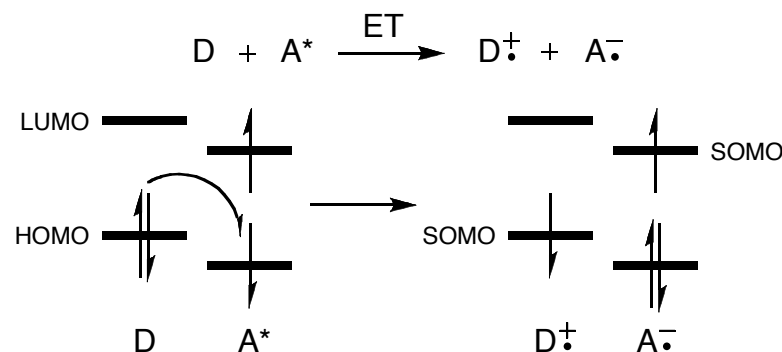


Two Electron Transfer (ET) Modes



excited state (D^*) offers lower oxidation potential:
electron in higher energy orbital, good donor

example donors: R_3N , R_3P



excited state (A^*) offers lower reduction potential:
vacancy in lower energy orbital, good acceptor

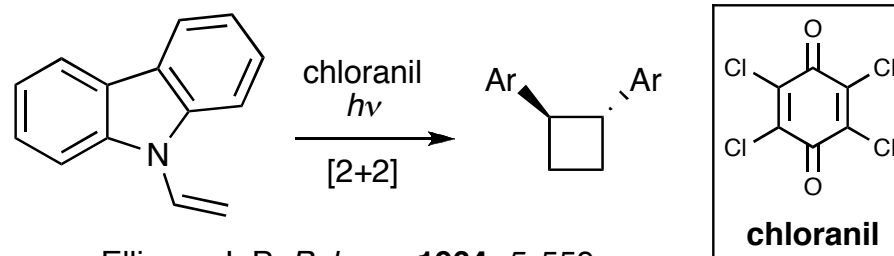
example acceptors: chloranil, 1,4-dicyanobenzene

Rehm-Weller Equation:

$$\Delta G_{\text{ET}} = E_{\text{ox}}(D) - E_{\text{red}}(A) - E_{\text{excit}}$$

- assumes electrostatic interaction between radical ions negligible in polar solvents (CH_3CN)
- if $\Delta G < 0$, ET approaches diffusion control (often exergonic by 5–23 kcal/mol)
- limit back ET (BET) by solvent separation (often exergonic by 46–69 kcal/mol)

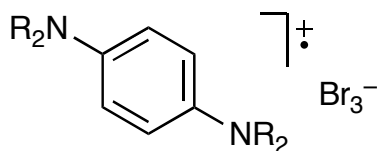
Early Example:



Ellinger, L.P. *Polymer* **1964**, 5, 559.
Ledwith, A. *Acc. Chem. Res.* **1972**, 5, 133.

Historical Context

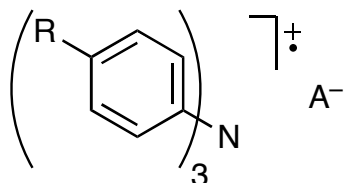
Cation Radicals



R = H, Me

Wurster (1879)

- indefinitely stable

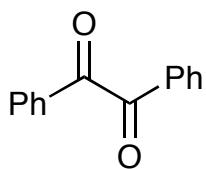


	R	A ⁻	
Wieland (1907)	Me	Br ₃ ⁻	
Weitz (1926)	Me	ClO ₄ ⁻	→
Walter (1955)	Br	SbCl ₆ ⁻	→

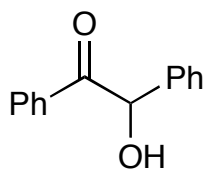
monomeric "cation radicals"
"aminium ion" nomenclature

readily available, shelf stable salt

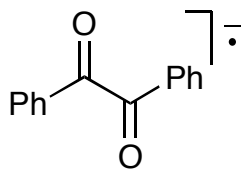
Anion Radicals



benzil

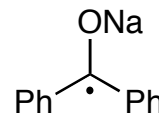


benzoin



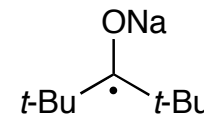
benzil semidione

monomeric radical anions ← Michaelis & Fletcher (1936)



benzophenone ketyl

Schlenk (1911)



aliphatic ketyl

Favorsky & Nazarov (1934)

equilibrium with dimer (pinacolate) suspected (1930s)

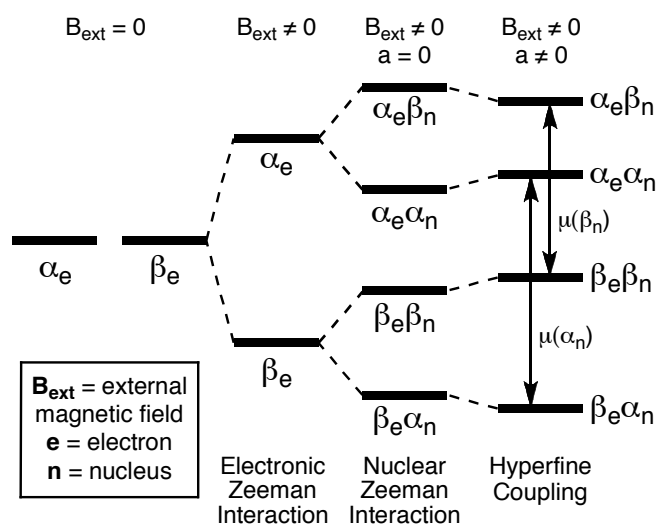
Analytical Methods: Electron Spin Resonance (ESR) Spectroscopy

Objectives:

- establish the presence of chemical species bearing unpaired electrons (lifetime ≥ 1 ms)
- quantify the distribution of electron spin density

Origin of Hyperfine Splitting (hfs):

- absorptions in ESR spectra are often split

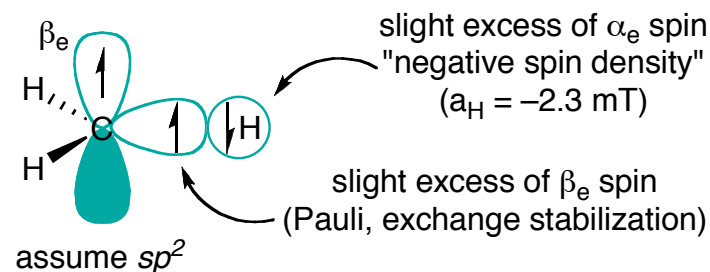


- hfs interaction stabilizing if magnetic moments aligned
- ESR (microwave) transitions invert electron spin
- hyperfine splitting constant = $a = \mu(\alpha_n) - \mu(\beta_n)$

- a reflects the extent of localization of the unpaired e^-

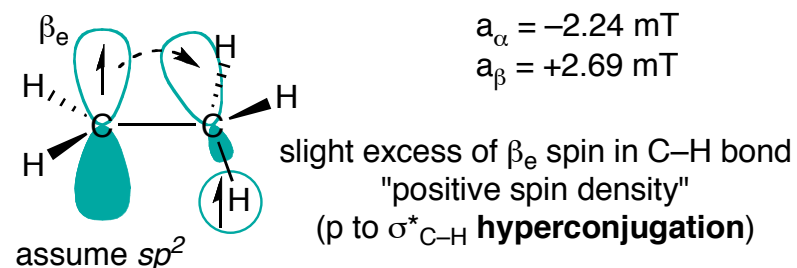
Radical	a (mT)	
$\cdot\text{H}$	+50.7	transmitted from C($2p_z$)! (expect $a \sim 0$ since H in nodal plane)
$\cdot\text{CH}_3$	-2.3	

α Hyperfine Splitting: The Methyl Radical

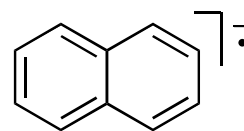


- **spin polarization**: induction of unsymmetrical spin distribution in C-H bonds by unpaired e^- due to exchange stabilization

β Hyperfine Splitting: The Ethyl Radical



First ESR of Radical Ion: Weissman (1953)



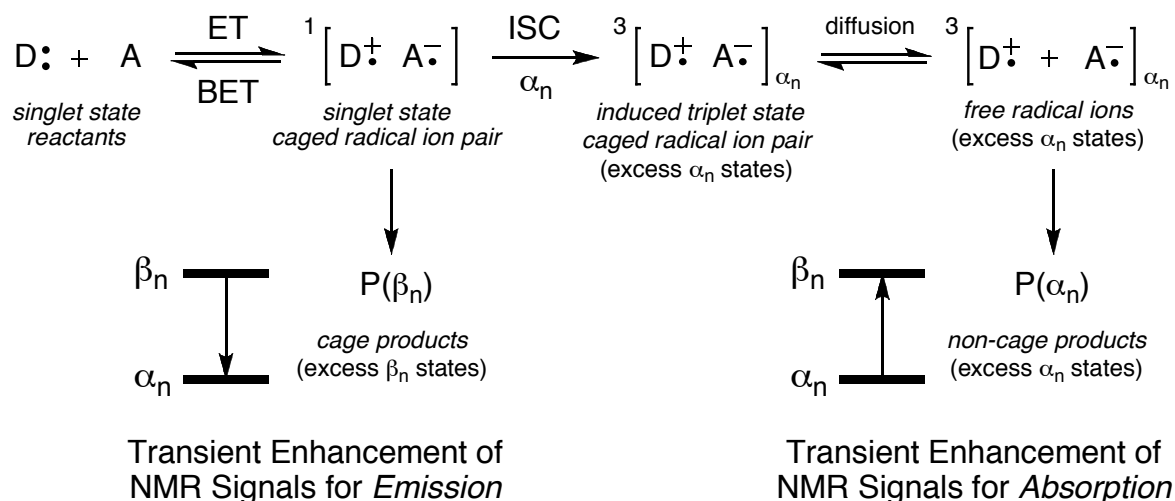
Weissman, S.I., et al.
J. Chem. Phys. **1953**, 21, 2227

Analytical Methods: Chemically Induced Dynamic Nuclear Polarization (CIDNP)

Objectives:

- use NMR to detect radical pairs as intermediates (optimal lifetime ~1 ns)
- quantify the distribution of electron spin density

Overall Process



Spin Sorting

- intersystem crossing (ISC) induced by magnetic interaction with nearby nucleus
- generally, one nuclear spin state induces ISC more often than the other (above example: $\alpha_n > \beta_n$)
- singlet state cage recombination spin-allowed, but triplet state spin-forbidden (persistence permits escape)
- **spin sorting**: observation that cage and non-cage products exhibit non-equilibrium populations of nuclear spin states

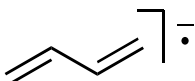
Method Development

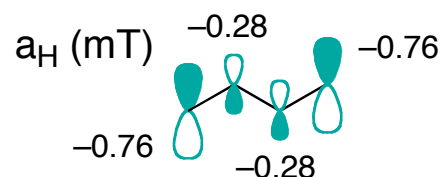
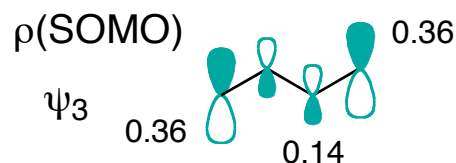
- discovery (1967)
Bargon, J.; Fischer, H.; Johnson, U. *Naturforsch.* **1967**, *22*, 1551.
Ward, H.R.; Lawler, R.G. *J. Am. Chem. Soc.* **1967**, *89*, 5518.
- extension to radical cations (1972)
Roth, H.D.; Lamola, A.A. *J. Am. Chem. Soc.* **1972**, *94*, 1013.
- quantitative theory (1970s):
patterns of signal directions and intensities may be related to signs and magnitudes of hyperfine coupling (**a**)

Relating Charge and Spin Densities

1,3-Butadiene

– spin density determined by the SOMO coefficients

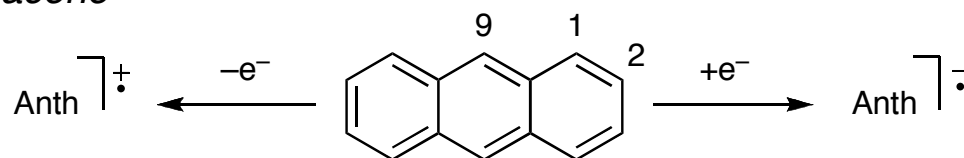
$$\boxed{c_i^2 = \rho}$$




Carbonyls

– spin (ρ) and charge (Q) densities are uncoupled if the molecule is polar (contains heteroatoms): MOs other than the SOMO contribute to charge density

Anthracene

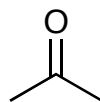


a_i (mT)	$\rho_i(\text{SOMO})$	a_i (mT)
-0.306	$\rho_1 = 0.096$	-0.266
-0.138	$\rho_2 = 0.047$	-0.153
-0.653	$\rho_9 = 0.192$	-0.528

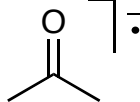
– cation radicals tend to have larger a , but still linearly related to ρ_i

McConnell Equation: $\boxed{a_i = Q \cdot \rho_i}$

ketone

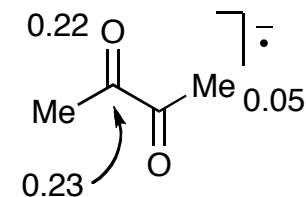


ketyl



– spin densities (ρ) from ESR:

Q_O	-0.448	-0.724
Q_C	+0.448	-0.276
ρ_O	–	0.276
ρ_C	–	0.724



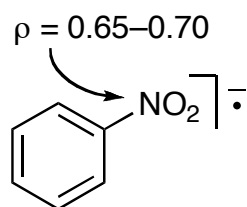
semidione

Hyperfine Coupling Observed in Radical Ions

– the magnitude of the hfs constant (**a**) reflects the extent of localization of the unpaired e⁻

Nitro Radical Anions

RNO ₂	a _N (mT)
alkyl	2.4–2.5
Ph	1.0

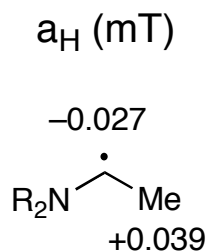


Hammett Analysis

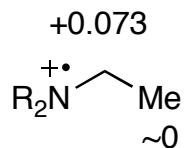
R	σ_m
NO ₂	+0.71
NO ₂ ^{-•}	-0.17
NH ₂	-0.16

Amino Radical Cations

– hyperfine splitting constants used to distinguish between radical intermediates



aminoalkyl radical

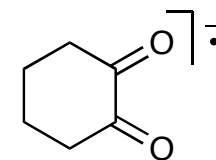
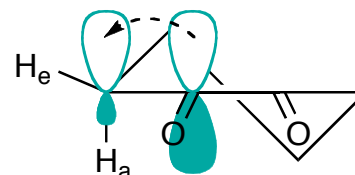


aminium radical ion

Semidiones: Hyperconjugation Effects

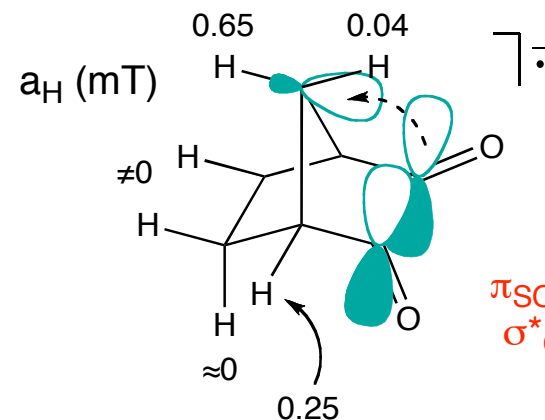
Cyclohexane semidione

π_{SOMO} to $\sigma^*_{\text{C-H(ax)}}$



H	a _H (mT)
axial	1.42
equat.	0.69

Norbornane semidione

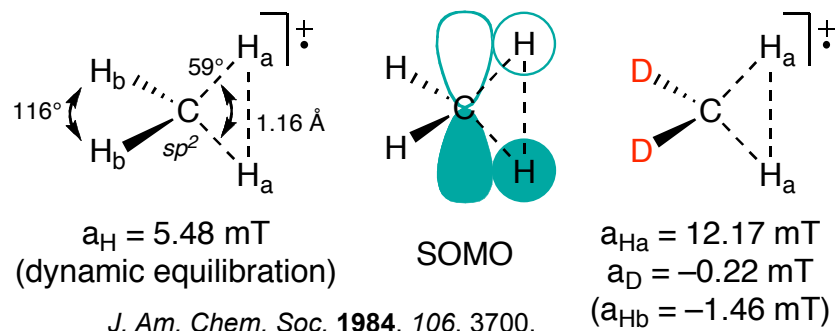


π_{SOMO} to $\sigma^*_{\text{C-H}}$?

Structural Investigations of Radical Ions

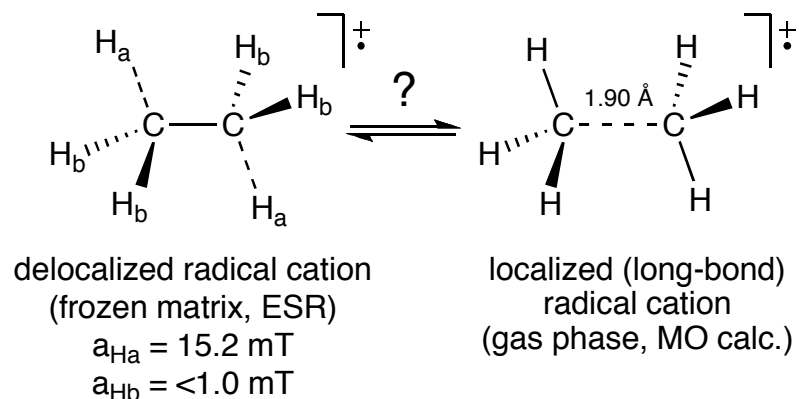
Methane Radical Cation

- resembles carbene complexed to H_2 (ESR)



Ethane Radical Cation

- resembles staggered E2 transition state
- SOMO concentrated in two *anti* C-H_a bonds



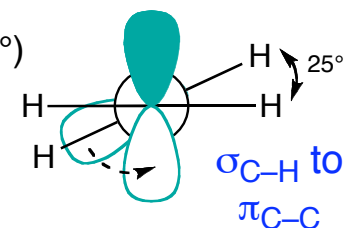
- does the HOMO of the neutral molecule necessarily correspond to the SOMO of the cation radical?

J. Chem. Phys. **1982**, *77*, 5891.

Ethene Radical Cation

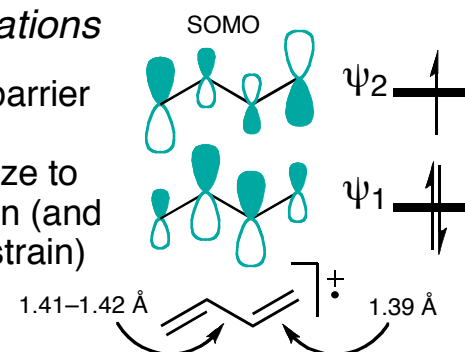
J. Am. Chem. Soc. **1982**, *104*, 294.

- unique twisted structure (25°)
- relieves torsional strain between vicinal C-H bonds
- increases hyperconjugation between SOMO and σ_{C-H}



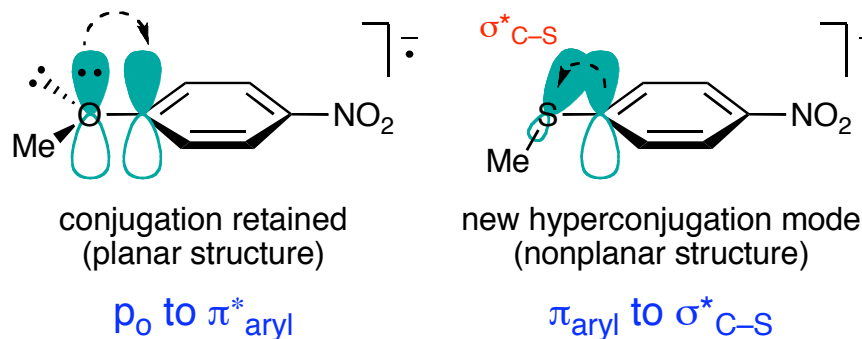
Butadiene Radical Cations

- increased rotation barrier ($\sim 28.1 \text{ kcal/mol}$)
- C₂ and C₃ rehybridize to maintain conjugation (and preserve torsional strain) during rotation



Arene Radical Anions

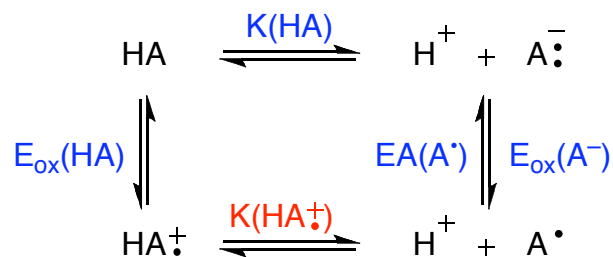
- thiomethyl substituent becomes electron acceptor in radical anion (a_N decreases relative to $PhNO_2$)



pKa Considerations

Enhanced Acidities of Radical Cations

– estimated pK_a(DMSO) values



ArH	pK _a (ArH)	pK _a (ArH ^{•+})	ΔpK _a
PhCH ₃	43	-20	63
Ph ₂ CH ₂	32.2	-25	57.2
PhCH ₂ CN	21.9	-32	53.9
CpH ₂	18.0	-17	35
PhOH	18.0	-8.1	26.1
PhNH ₂	30.6	+6.5	24.1
PhSH	10.3	-12	22.3

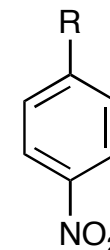
Bordwell, F.G.; Cheng, J.-P.
J. Am. Chem. Soc. **1989**, *111*, 1792–1795.

- despite superacidity, deprotonation slow for "carbon acids" (C–H dissociation)
- if rds, accelerate with py. base additive

Attenuated Acidities of Radical Anions

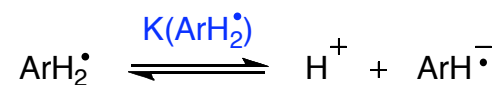
– estimated pK_a(DMSO) values

R	pK _a (ArH)	pK _a (ArH ^{•-})	ΔpK _a
CH ₂ CN	12.3	23.4	11.1
OH	10.8	21.0	10.2
SH	5.5	15.5	10.0
NHPh	16.9	26.1	9.2
CO ₂ H	9.0	13.6	4.6
CH(Me)NO ₂	10.3	14.7	4.4



Bordwell, F.G.;
Zhao, Y.
J. Org. Chem. **1996**,
61, 2530–2535.

Basicities of Radical Anions



ArH	pK _a (ArH ₂ ^{•-})	pK _a (ArH ^{•-})	ΔpK _a
PhH	-23	>13.5	>36
PhNO ₂	-11.3	3.2	14.5
PhCN	-10.4	7.3	17.7
PhCOR'	–	–	7.8–17.6

Bil'kis, I.I.;
Shteingarts, V.D.
Izv. SO AN SSSR,
Ser. Khim. Nauk.
1987, 105.

R' = H, Ph, Me,
NH₂, OH

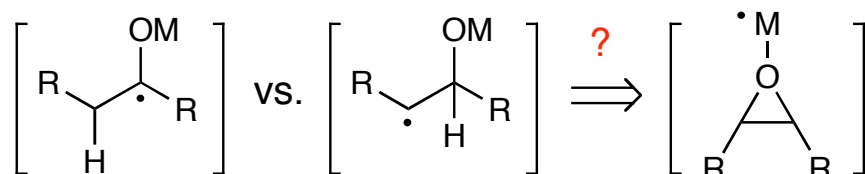
- for aliphatic hydrocarbon cation radicals, proton loss involves C–H bond with highest unpaired e⁻ density (bond elongation)

Radical Anions: Reaction Overview

- **Reductive Epoxide Openings**
- **S_{RN}1 Reactions**
- Reactions of Ketyl Radical Anions
- Dissolving Metal Reductions
 - Birch Reduction
 - Alkyne Reduction to *trans* Alkenes
- Pericyclic Reactions
 - DNA Photolyase Retro-[2+2] Reaction
 - [1,2]-Wittig Rearrangement
- Reduction of C–X Bonds
 - Benzyl Ether Removal (C–O)
 - α -Deoxygenation of Ketones (C–O)
 - Reformatsky Reaction (C–Br)
 - Metal Halogen Exchange (C–I, C–Br)
 - Grignard Formation (C–Hal)
- Single Electron Transfer Mechanisms
 - S_N2 Reactions
 - Grignard Additions

Radical Anions: Reductive Epoxide Ring-Openings

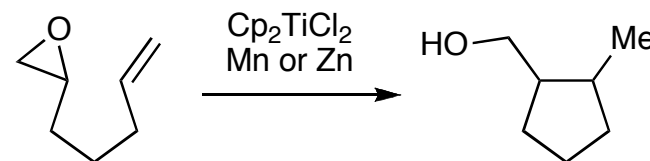
A Ketyl Radical Anion Homologue



ketyl
radical anion

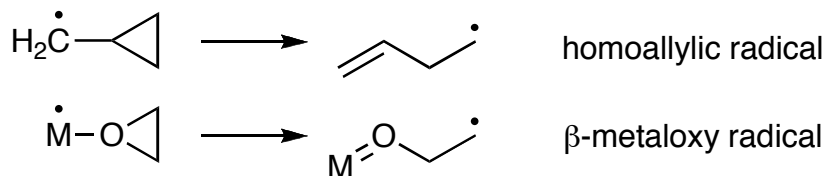
isomeric distonic
radical anion

Overall Reaction



– may be Ti-promoted or catalyzed

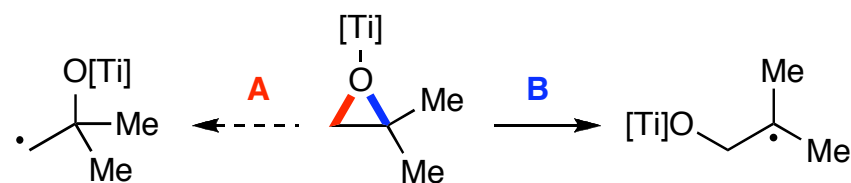
Ring-Opening Step Analogy



M	Results
V ⁺²	epoxide deoxygenation
Sml ₂	Lewis acidic, S _N 2 opening with I ⁻
CrCl ₂	unreactive
(Cp ₂ TiCl) ₂	reductive epoxide opening

– reduction of β-metaloxy radical needs to be slower than radical transforms desired (i.e. cyclization)

Regioselective Control

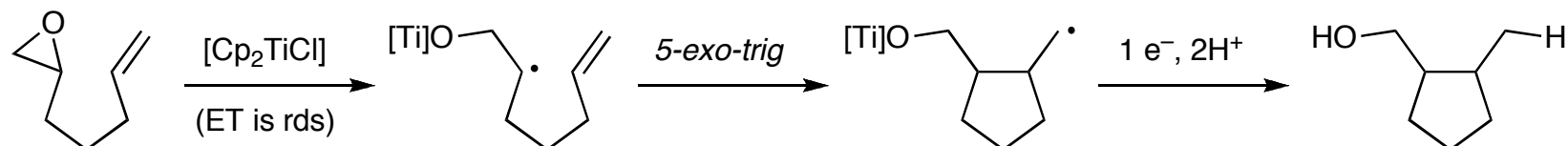


DFT	A	B
ΔG (kcal/mol)	-2.7	-6.3
ΔG [‡] (kcal/mol)	+9.1	+7.9

- opening driven by release of ring strain
- contributing factors:
 - steric interactions between epoxide substituents and Ti-metal complex (i.e. Cp ligands) [*major*]
 - radical stability [*minor*]
- complementary to S_N2-type epoxide openings

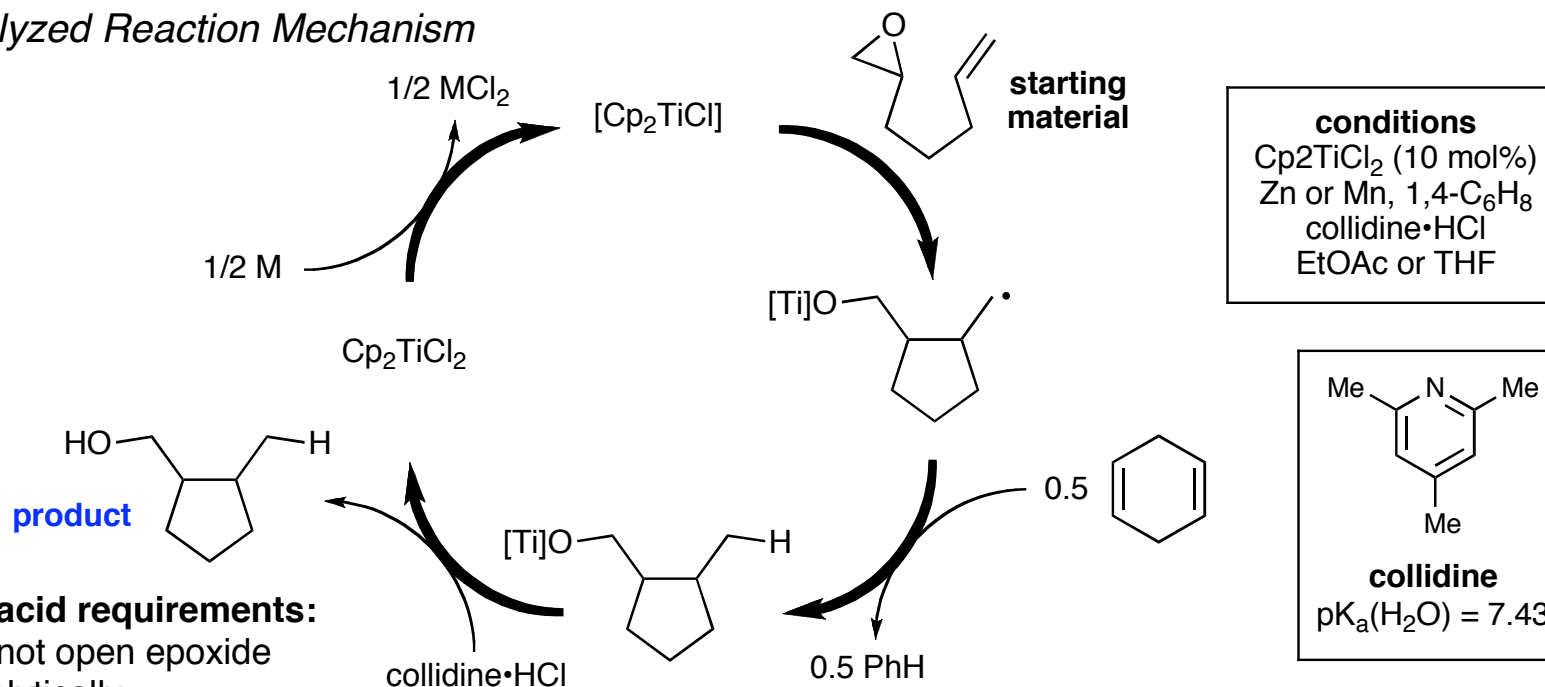
Radical Anions: Reductive Epoxide Ring-Opening Mechanisms

Ti-Promoted Reaction Mechanism



- hydrogen abstraction from solvent (i.e. THF) may terminate non-nucleophilic radical intermediates
- β -hydride elimination may compete with protonation of Ti-C bonds

Ti-Catalyzed Reaction Mechanism



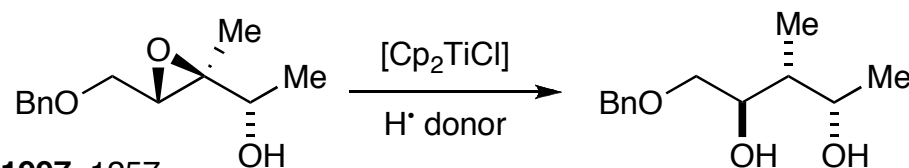
- protic acid requirements:

- does not open epoxide heterolytically
- protonates Ti-O bonds
- proposed pK_a range: 5.25–12.5

Active [Ti] species: *J. Am. Chem. Soc.* **2004**, 126, 7853.

Radical Anions: Reductive Epoxide Ring-Opening Applications

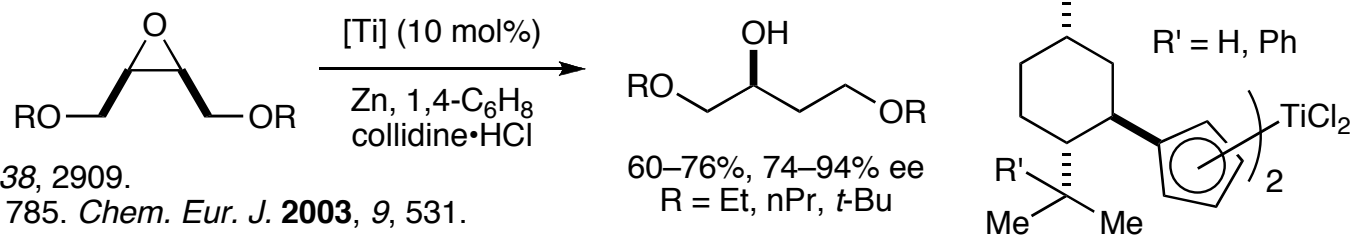
Diastereoselective Reductive Opening



donor	yield	dr
1,4-C ₆ H ₈	85%	78:22
THF	62%	>98:2

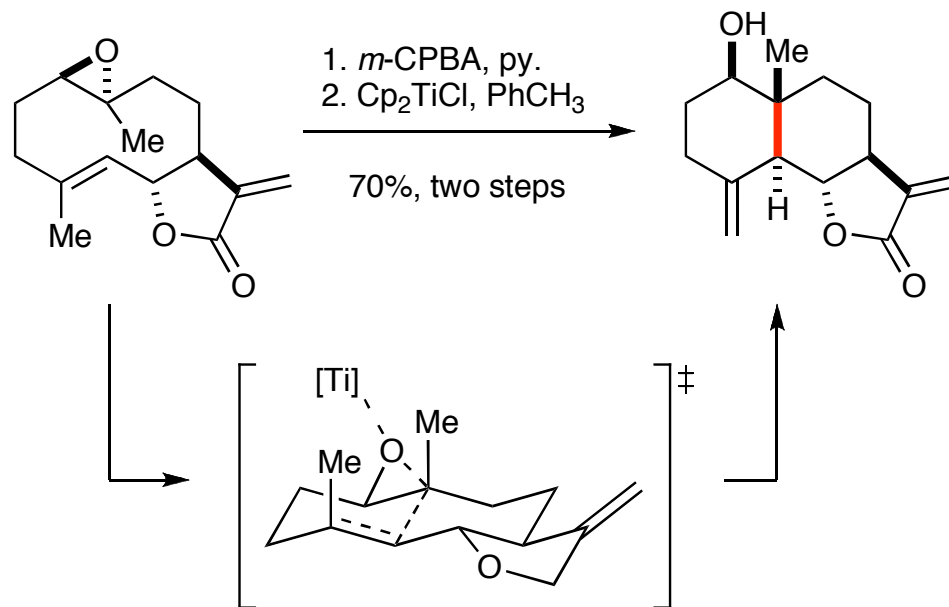
Chakraborty T.K.; Dutta, S.
J. Chem. Soc. Perkin Trans. 1 **1997**, 1257.
 Chakraborty T.K.; Das, S. *Tetrahedron Lett.* **2002**, 43, 2313.

Enantioselective meso-Epoxide Opening



Gansäuer, H., et al.
Angew. Chem. Int. Ed. **1999**, 38, 2909.
Adv. Synth. Catal. **2001**, 343, 785. *Chem. Eur. J.* **2003**, 9, 531.

Diastereoselective Transannular Cyclization

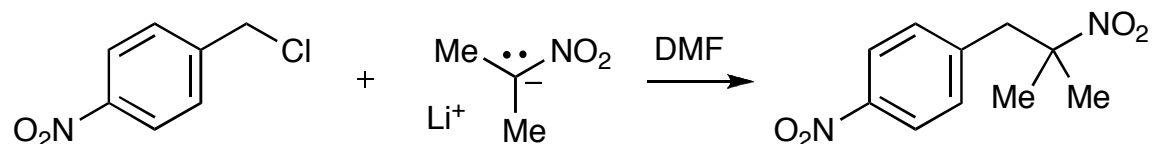


Eudesmanolides:
 Barrero, A.F.; Oltra, J.E.;
 Cuerva, J.M.; Rosales, A.
J. Org. Chem. **2002**, 67, 2566–2571.
Org. Lett. **2003**, 5, 1935–1938.

Radical Anions: $S_{RN}1$ Reactions

Discovery

- radical chain process discovered independently by Kornblum and Russell (1966)



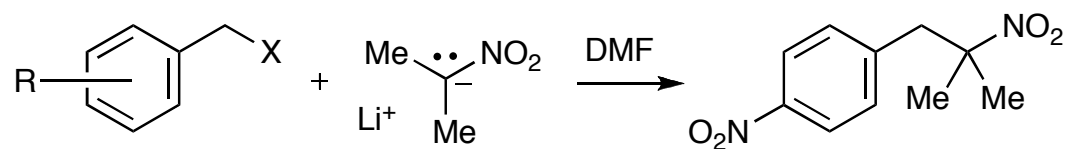
Russell, G.A.; Danen, W.C.
J. Am. Chem. Soc.
1966, *88*, 5663–5665.

- inhibited by radical scavengers (CuCl_2 , O_2)
- " $S_{RN}1$ " proposed: *substitution, radical-nucleophilic, unimolecular*
- LGs: Cl^- , NO_2^- , PhSO_2^- , NMe_3 , N_3 for benzylic substrates
- other nucleophiles: RS^- , ArO^- , malonate esters, quinuclidine

Bunnett, J.F.; Kim, J.K.
J. Am. Chem. Soc. **1970**, *92*, 7463–7464.

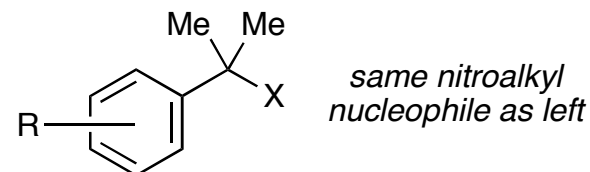
Substrate Sensitivity

- product selectivity and rate acceleration (radical process) dependent upon LG and aryl substitution



Entry	R	X	yield	product
1	<i>p</i> -NO ₂	Cl	83–95%	C-alkylation (radical)
2	<i>o</i> -NO ₂	Cl	37–46%	C-alkylation (radical)
3	<i>m</i> -NO ₂	Cl	0%	–
4	<i>p</i> -NO ₂	I	86%	O-alkylation (S_N2)
5	H	X, OTs	82–84%	O-alkylation (S_N2)

- reaction provides carbon skeletons inaccessible by normal S_N2 processes



Entry	R	X	yield
1	<i>p</i> -NO ₂	NO ₂	95%
2	<i>p</i> -NO ₂	Cl	95%
3	<i>p</i> -CN	NO ₂	94%
4	H	NO ₂	21%

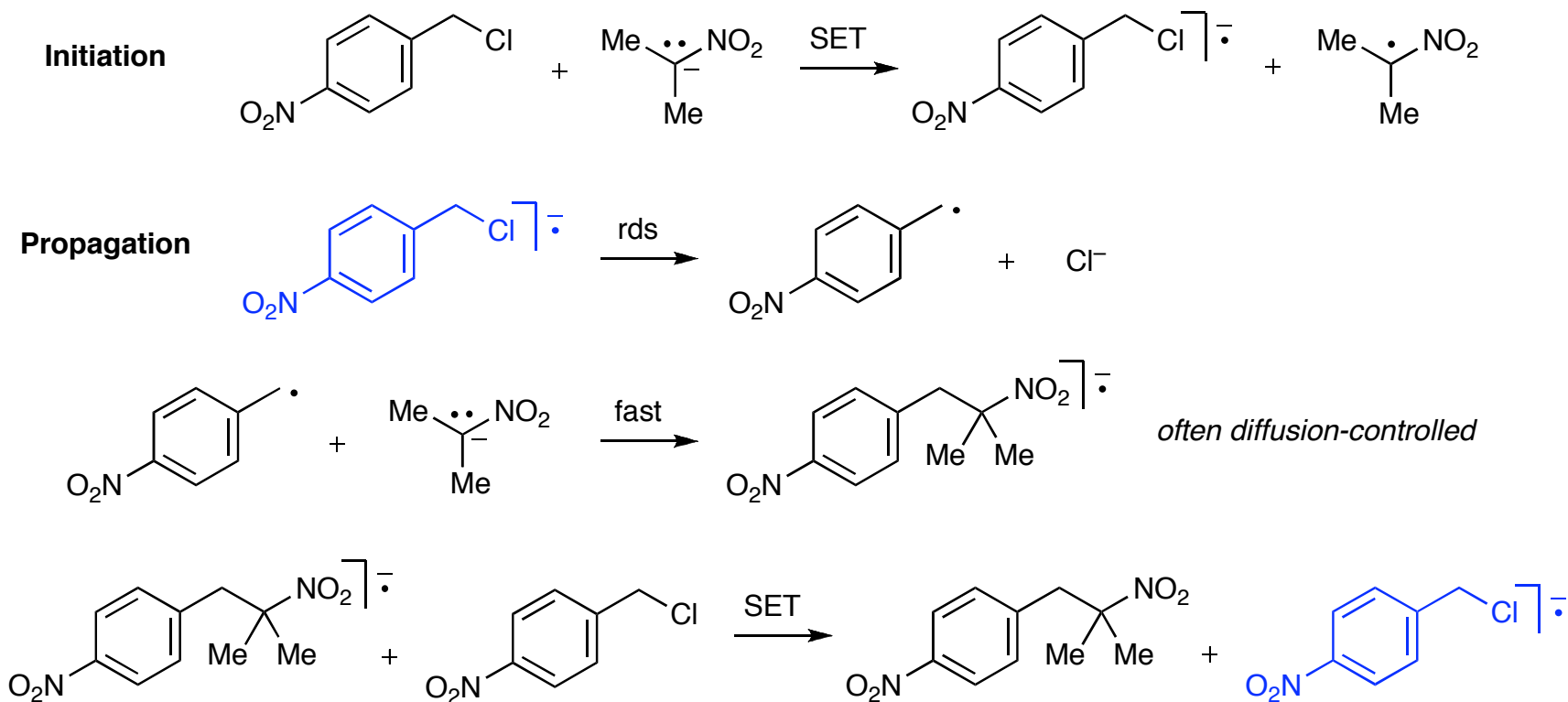
Radical Anions: $S_{RN}1$ Reaction Mechanism

Mechanism

– radical chain process proposed by Kornblum (1966)

Kornblum, N.; Michel, R.E.; Kerber, R.C.
J. Am. Chem. Soc. **1966**, *88*, 5660–5662; 5662–5663.

using Russell's reaction as an example:



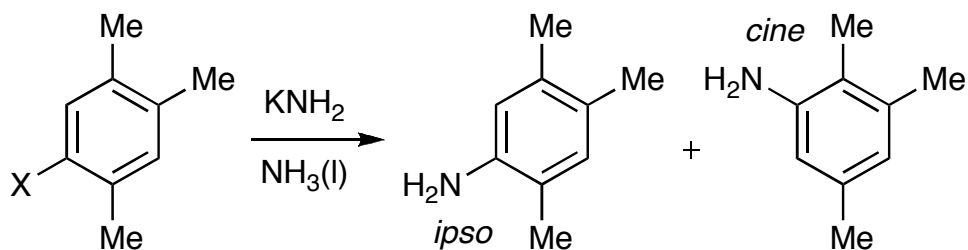
- EWGs (like NO_2) on Ar lowers LUMO energy and facilitates ET
- when LG = Cl, substrate more reactive than expected for $S_{\text{N}}2$ and more selective for C-alkylation
- intermediates favored by polar aprotic solvents (DMSO, DMF)

Radical Anions: $S_{RN}1$ Reactions with Aryl Substrates

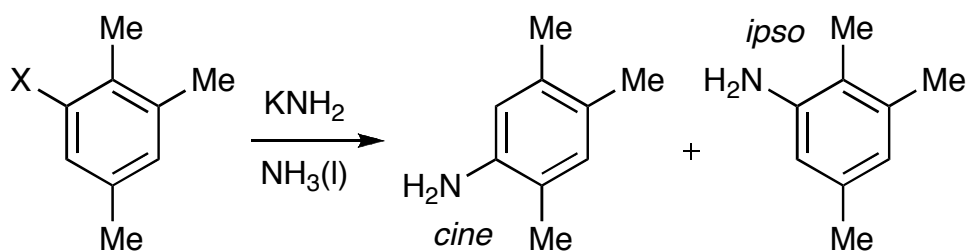
Discovery

– radical chain process for aryl substrates proposed by Bunnett (1970)

Bunnett, J.F.; Kim, J.K. *J. Am. Chem. Soc.* **1970**, *92*, 7463–7464, 7464–7466.

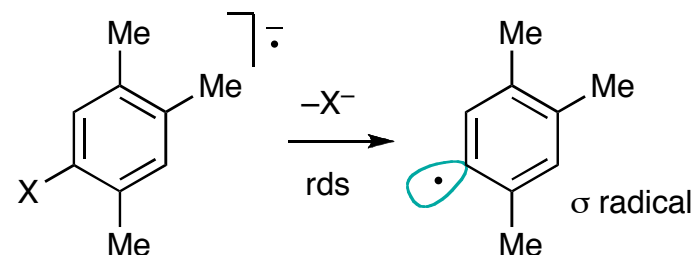


Entry	X	Additive	5-NH ₂	6-NH ₂	Mechanism
1	Br,Cl	–	1	1.5	benzyne
2	I	–	1.6	1	mix
3	I	K ⁰	1	0	$S_{RN}1$

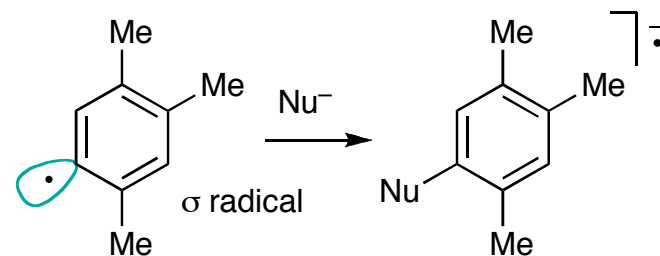


Entry	X	Additive	5-NH ₂	6-NH ₂	Mechanism
1	Br,Cl	–	1	1.5	benzyne
2	I	–	1	5.9	mix
3	I	Ph_4N_2	1	1.4	benzyne
4	I	K ⁰	~0	1	$S_{RN}1$

MO Considerations for Aryl Substrates



- dehalogenation proceeds as intramolecular ET from π system to $\sigma^*_{\text{C-X}}$
- faster at positions of greater spin density

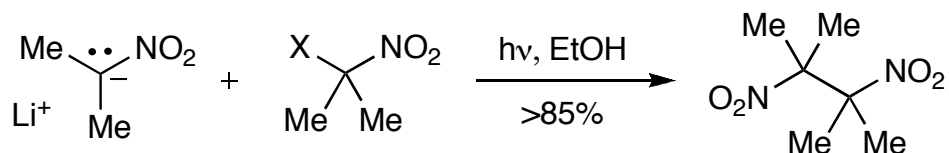


- as bond forms, energy of $\sigma^*_{\text{C-Nu}}$ increases such that π^* becomes LUMO
- internal transfer of odd e^- from $\sigma^*_{\text{C-Nu}}$ to π^*
- lower energy π^* results in faster transfers
- since not rds, reaction not sensitive to Ar substituents, although EWGs favor this step

Radical Anions: $S_{RN}1$ Reactions with Aliphatic Substrates

Discovery

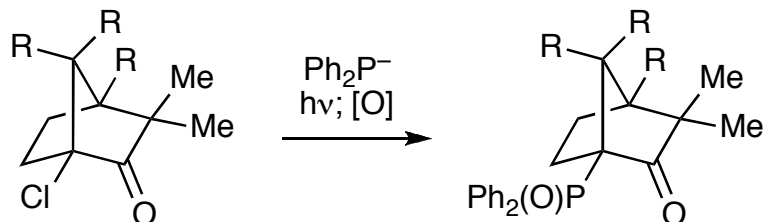
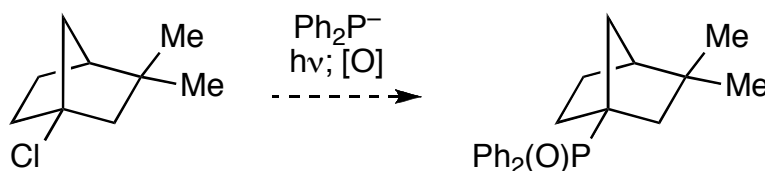
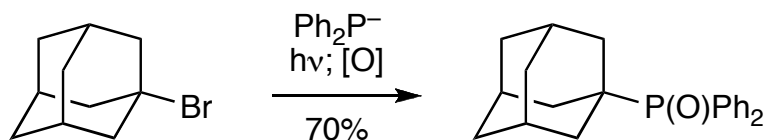
– radical chain proposed for aliphatic substrates (1966)



Russell, G.A.; Danen, W.C. *J. Am. Chem. Soc.* **1966**, *88*, 5663–5665.

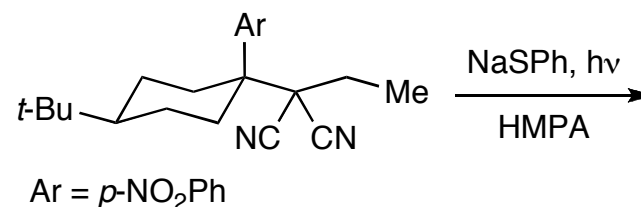
– bonds may be formed between highly branched centers

Substrate Peculiarities

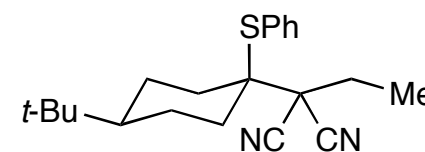


Rossi, R.A.; Palacios, S.M.; Santiago, A.N. *J. Org. Chem.* **1982**, *47*, 4654–4657.

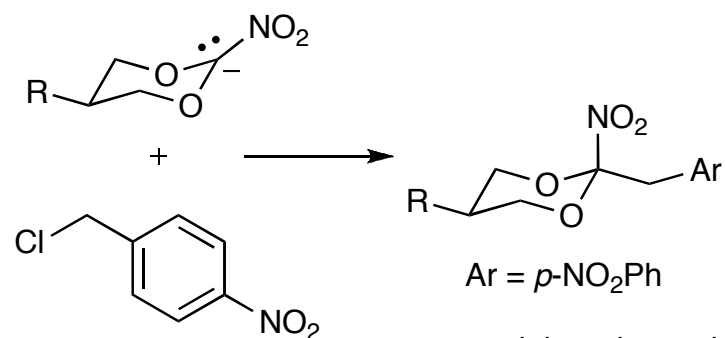
Steric and Torsional Effects



Norris, R.K.; Smyth-King, R.J. *Tetrahedron* **1982**, *38*, 1051.



axial product only
(torsional effect)



Zh. Org. Khim. **1983**, *19*, 426.

equatorial product only
(steric effect)

Radical Cations: Reaction Overview

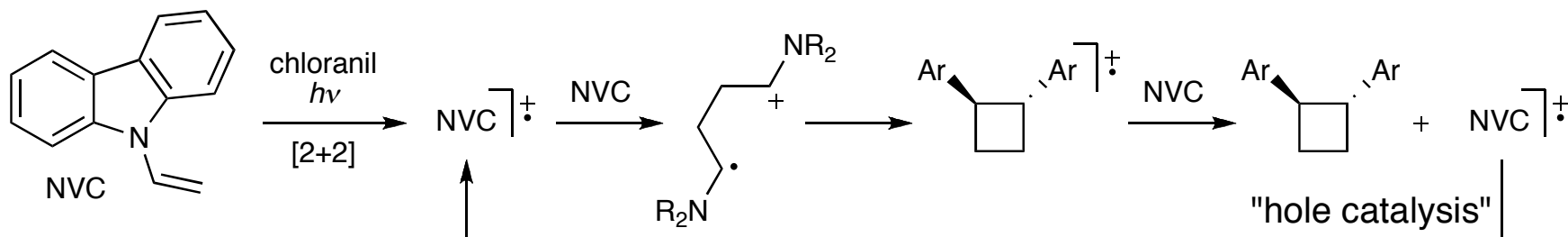
- **Diels-Alder [4+2] Cycloaddition**
- **SOMO Catalysis**
- Nucleophilic Additions to Aryl and Vinyl Radical Cations
- Hofmann-Löffler-Freitag Reaction
- Fragmentations
 - Mesolytic Cleavages
 - Mass Spectrometry
- Electrocyclizations
- Cycloadditions and Cycloreversions
- Sigmatropic Rearrangements
- Aminium Radical Ion Proton Transfer

Radical Cations: Cycloadditions

Discovery

- cation radical chain proposed for cyclodimerization of *N*-vinylcarbazole (1969)

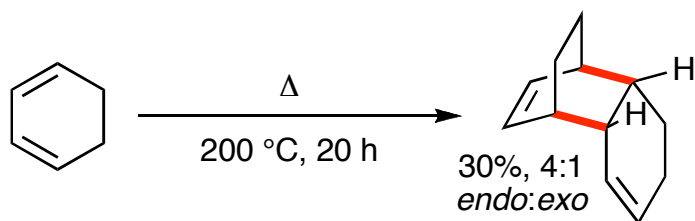
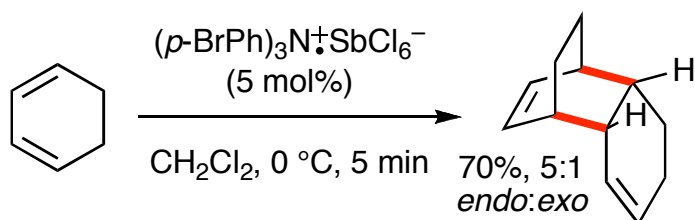
Ledwith, A.
Acc. Chem. Res. **1972**, 5, 133.



- "stereospecific" formation of *trans*-cyclobutane, but proceeds via open distonic intermediate
- cation radical chain proposed for [4+2] cyclodimerization of 1,3-cyclohexadiene (1969)
- further investigations by Bauld and coworkers

Schutte, R.; Freeman, G.R. *J. Am. Chem. Soc.* **1969**, 91, 3715.
Penner, T.L.; Whitten, D.G.; Hammond, G.S. **1970**, 92, 2861.
Bauld, N.L., *et al.* *Acc. Chem. Res.* **1987**, 20, 371–378.

Comparisons with Thermal Diels-Alder



- structure-weakening effects allow deformations with diminished activation barriers (E_a) = *faster rates*
- maintains *endo*- and regioselectivities of thermal DA
- advantages over thermal DA:
 - sterically hindered substrates
 - e^- -rich or conjugated dienophiles (readily ionized)
- dienophile shows suprafacial selectivity ("stereospecificity")
- **mechanism?**

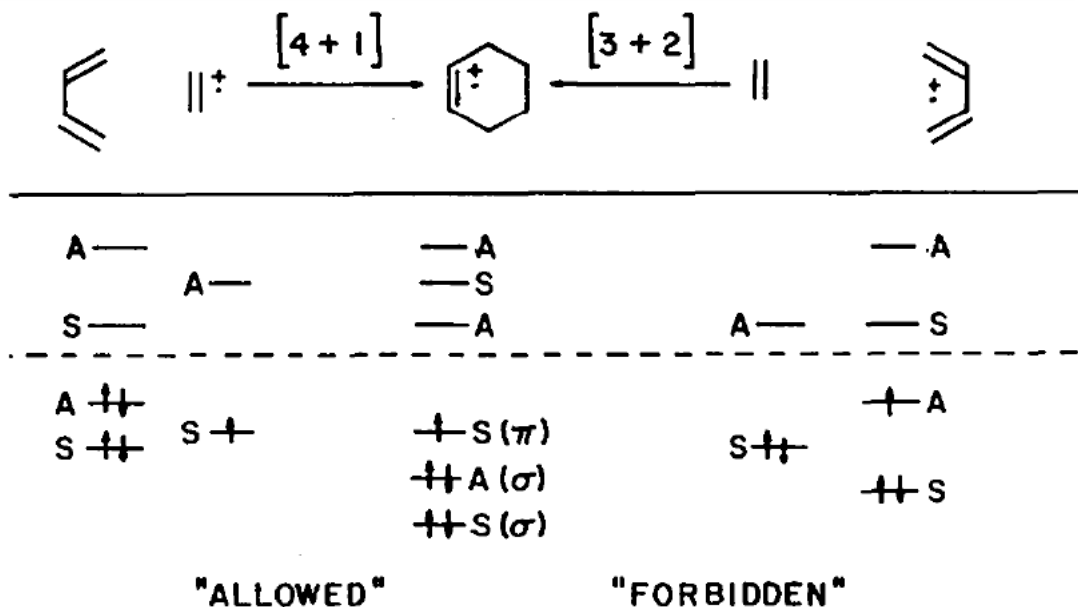
Radical Cations: The Diels-Alder [4+2] Cycloaddition

Mechanism

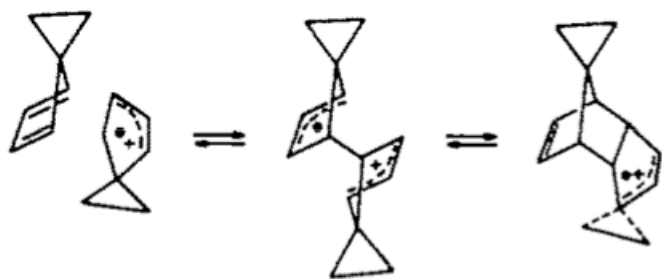
- orbital correlation diagram for the radical cation DA

Bellville, D.J.; Bauld, N.L.
Tetrahedron **1986**, 42, 6167–6173.

- predict **role selectivity**: neutral diene and radical cation dienophile
- pericyclic effects minimized through highly nonsynchronous TSs
- experiments show little or no inherent preference for [4+1] or [3+2] modes



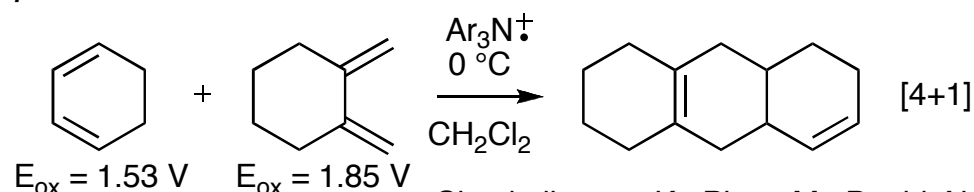
Support for Stepwise Cycloaddition



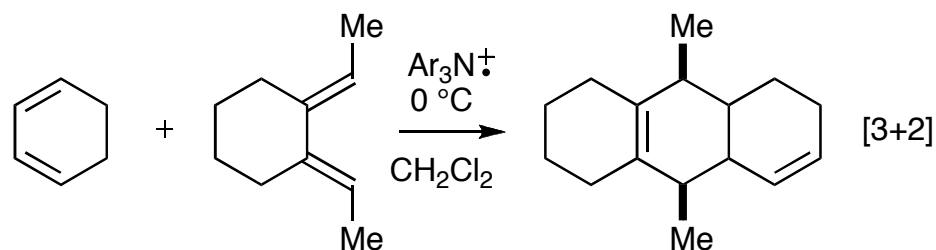
Roth, H.D.; Schilling, M.L.M.; Abelt, C.J.
Tetrahedron **1986**, 42, 6157–6166.

- CIDNP effects suggest existence of two different delocalized dimer radical cations

Experimental Observations

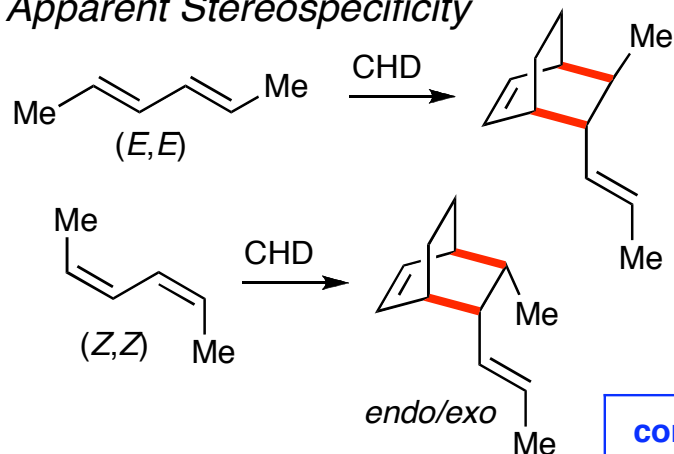


Chockalingam, K.; Pinto, M.; Bauld, N.L.
J. Am. Chem. Soc. **1990**, 112, 447–448.



Radical Cations: The Diels-Alder [4+2] Cycloaddition

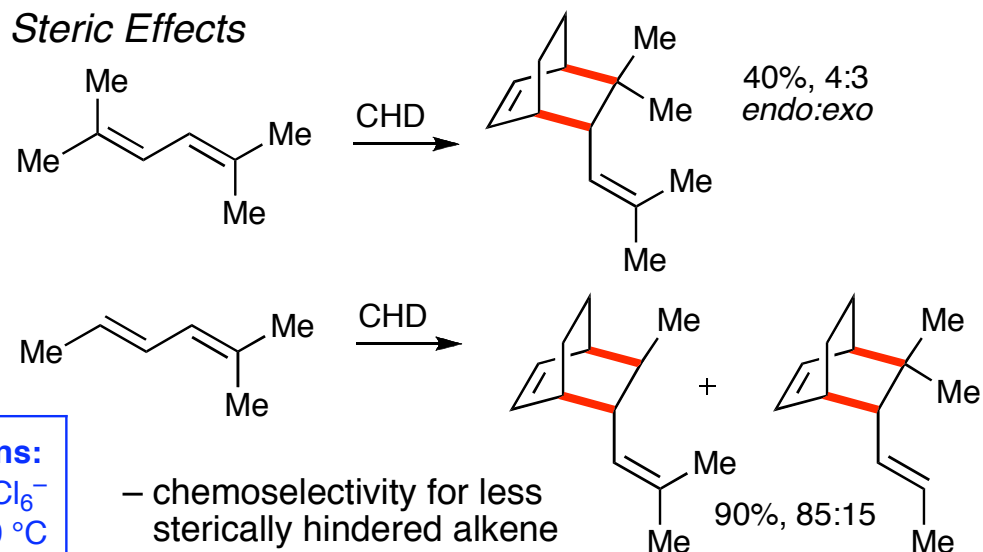
Apparent Stereospecificity



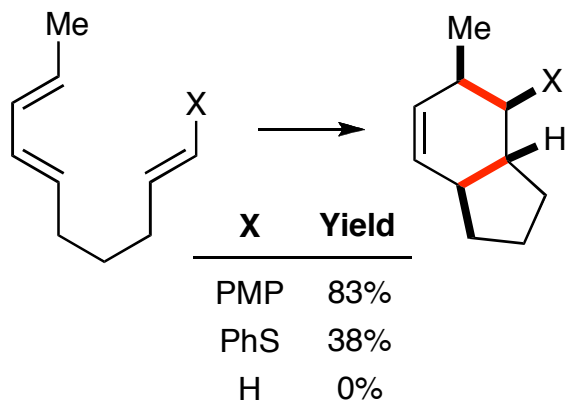
CHD = 1,3-cyclohexadiene

conditions:
 $\text{Ar}_3\text{N}^+\text{SbCl}_6^-$
 $\text{CH}_2\text{Cl}_2, 0^\circ\text{C}$

Steric Effects

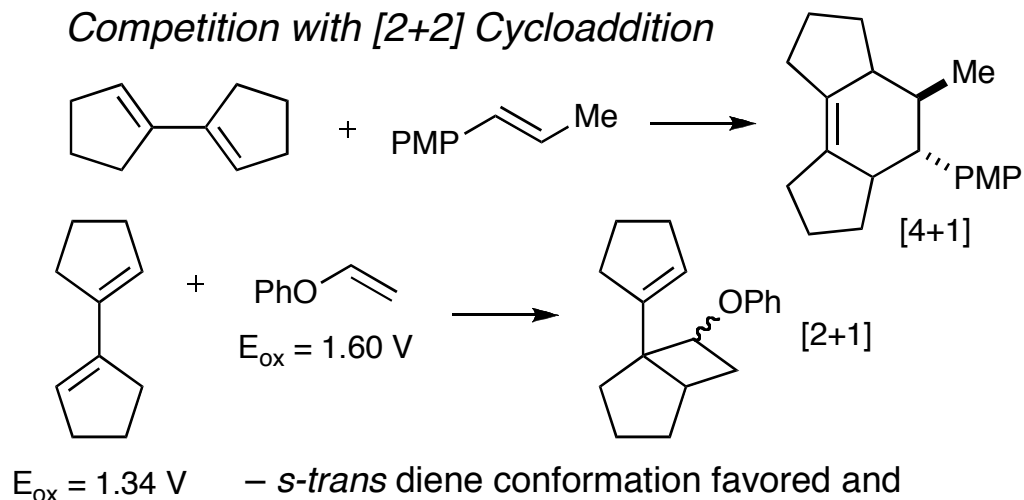


Electronic Effects



Harirchian, B.; Bauld, N.L. *Tetrahedron Lett.* **1987**, 28, 927–930.

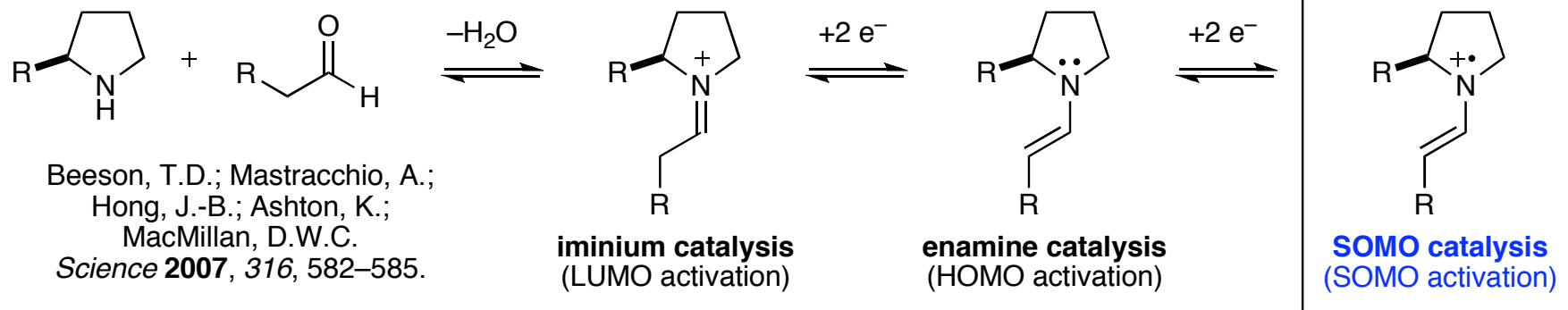
Competition with [2+2] Cycloaddition



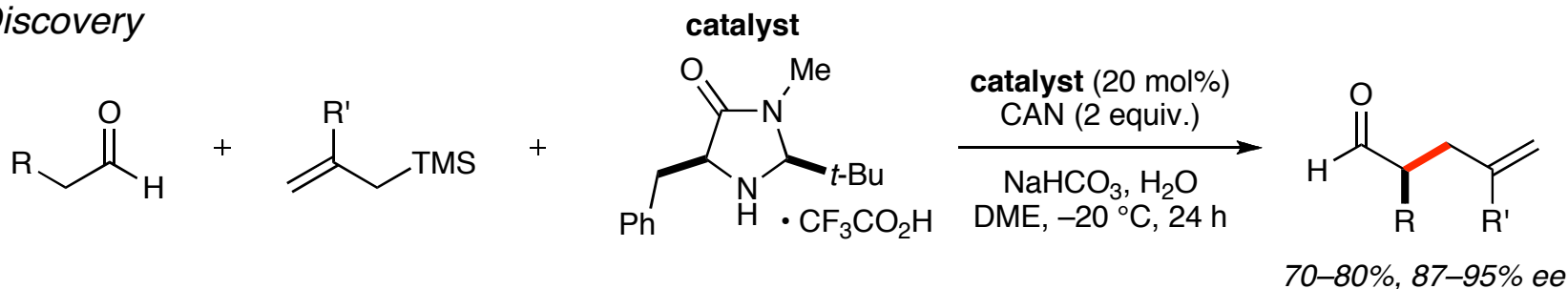
Kim, T.; Pye, J.; Bauld, N.L. *J. Am. Chem. Soc.* **1990**, 112, 6285–6290.

Radical Cations: SOMO Catalysis

New Mode of Organocatalysis



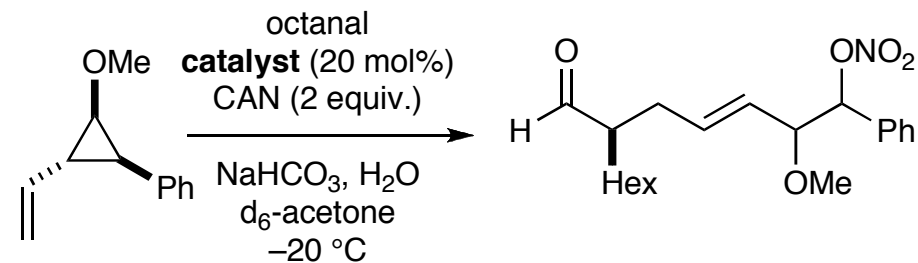
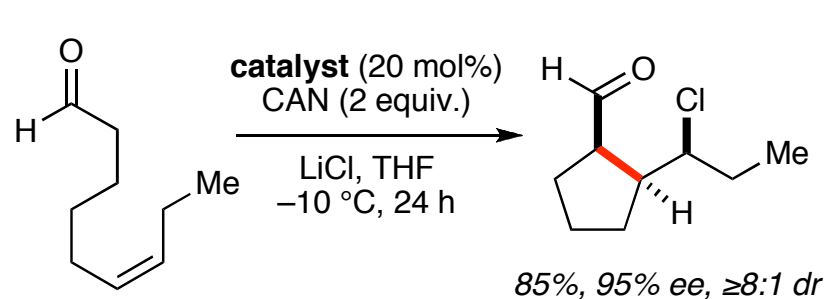
Discovery



Evidence for Radical Cation Intermediates

– intramolecular cyclization of unsaturated RCHOs

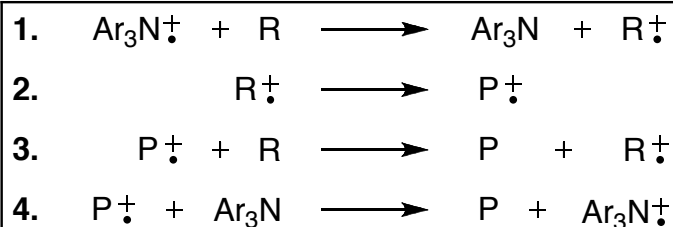
– Newcomb radical clock experiment



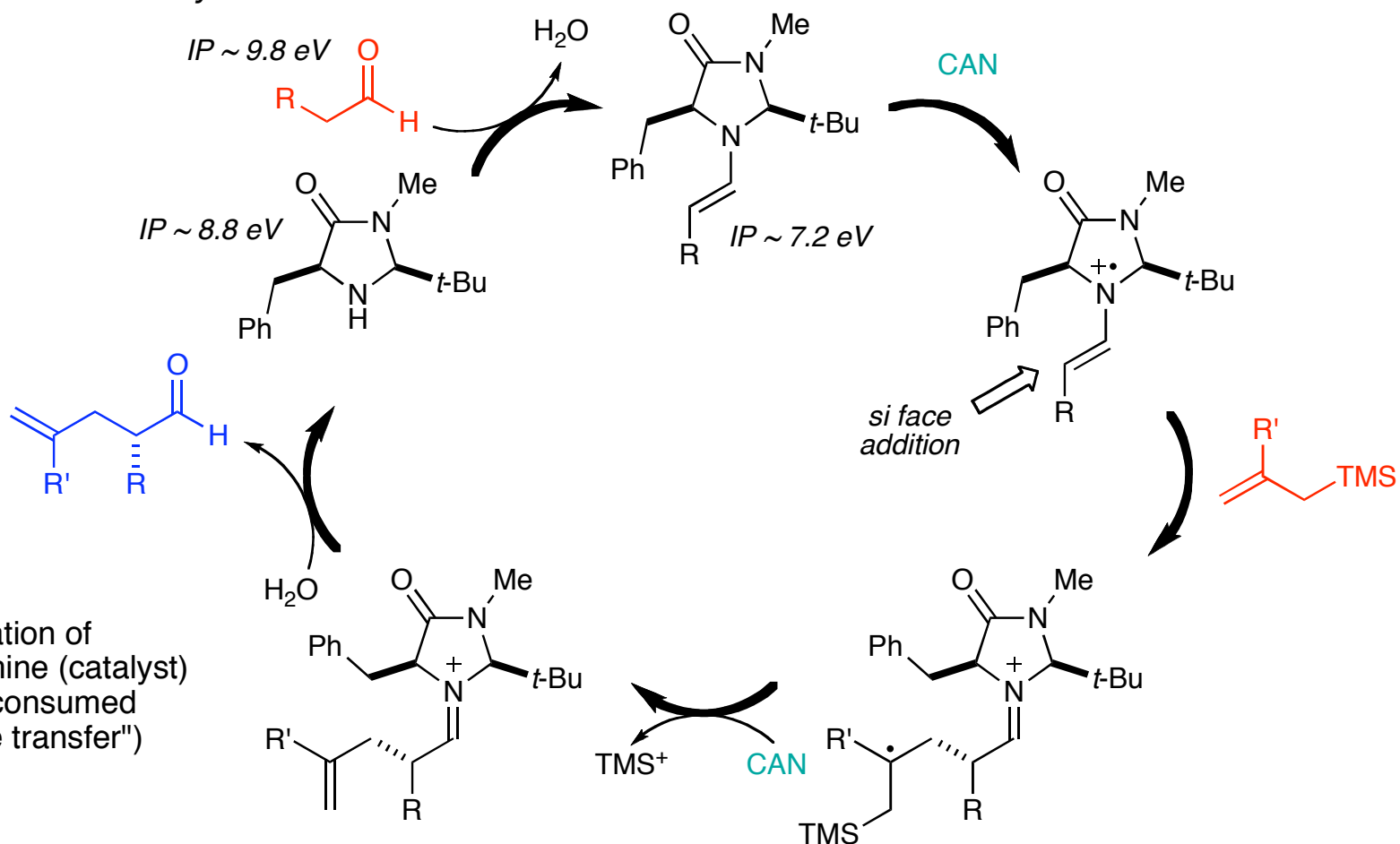
Radical Cations: SOMO Catalysis Mechanism

Radical Chain vs. Aminium Salt Catalysis

- difference is in mechanism of hole transfer
- radical chain (1,2,3) and catalysis (1,2,4)
- regeneration of oxidant (catalyst)



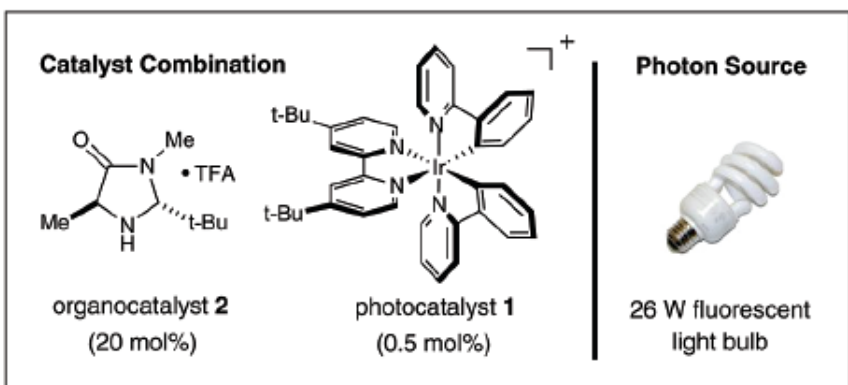
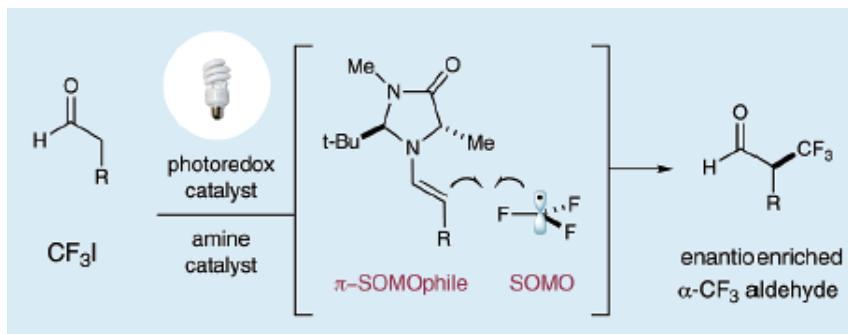
MacMillan SOMO Catalysis



- regeneration of chiral amine (catalyst)
- oxidant consumed (no "hole transfer")

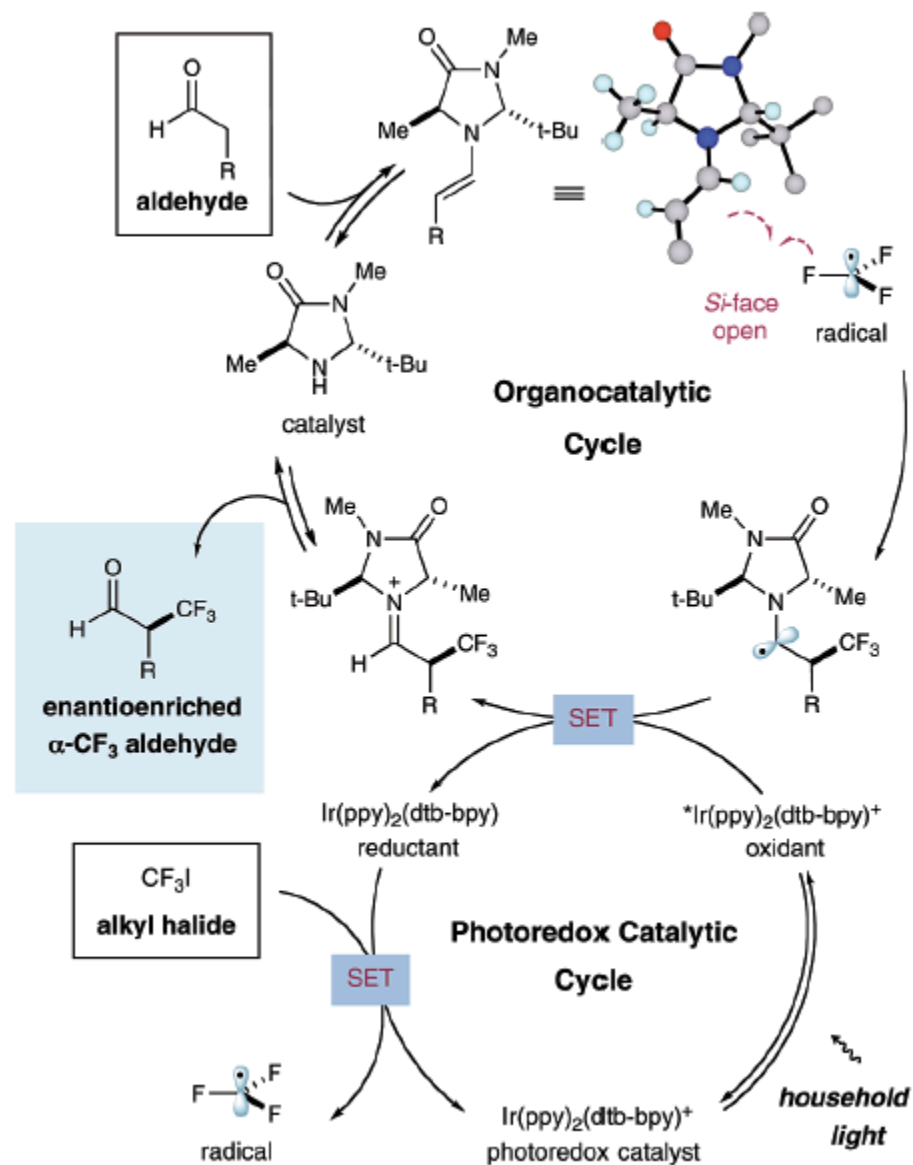
Radicals: Photoredox Catalysis Mechanism

Overall Reaction

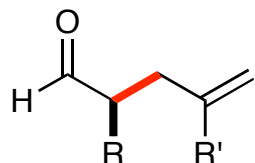
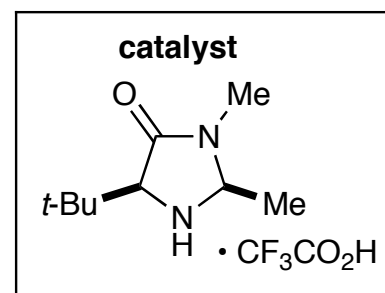
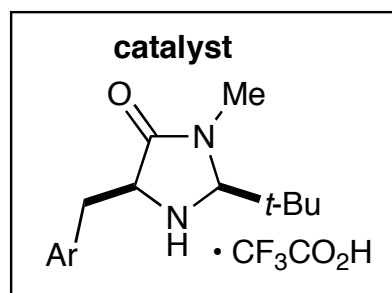


- regeneration of chiral amine (catalyst) coupled to regeneration of oxidant
- no radical cations involved

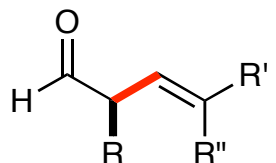
Nicewicz, D.A.; MacMillan, D.W.C.
Science **2008**, *322*, 77–80.
 Nagib, D.A.; Scott, M.E. MacMillan, D.W.C.
J. Am. Chem. Soc. **2009**, *131*, 10875–10877.



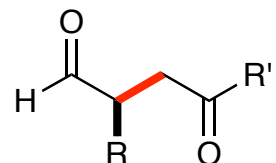
Radical Cations: SOMO Catalysis Applications



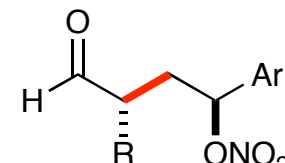
70–80%, 87–95% ee



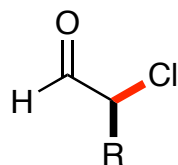
61–93%, 89–96% ee



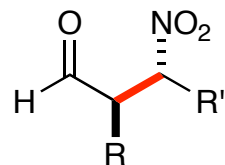
55–92%, 86–96% ee



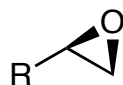
81–94%, 89–97% ee



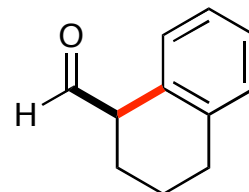
75–95%, 91–96% ee



53–84%, 80–97% ee
≤9:1 dr



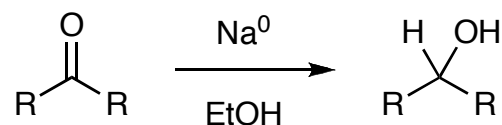
73–92%, 93–95% ee



61–96%, 58–98% ee

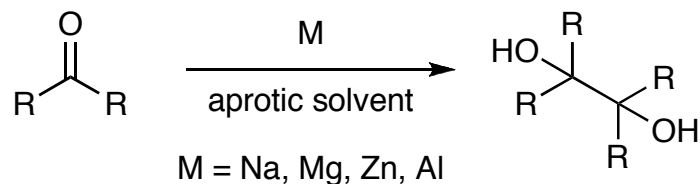
Radical Anions: Ketyl Radical Anion

Bouveault-Blanc Reduction



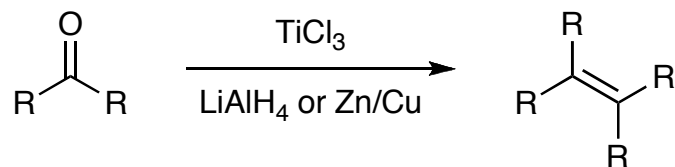
– rapid *in situ* protonation with NH_4Cl suppresses dimer byproducts

Pinacol Coupling



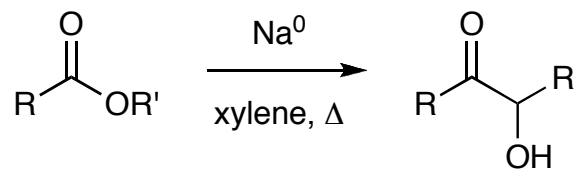
– rapid and irreversible if M forms strong covalent bonds with oxygen
– reversible for simple aromatic ketyls due to electrostatic repulsion

McMurry Reaction



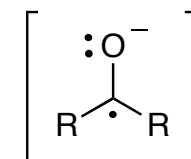
– pinacol isolable if conducted at low temperatures

Acyloin Condensation

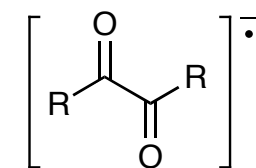


– trap enediolate with TMSCl to prevent ester condensations

common
intermediate

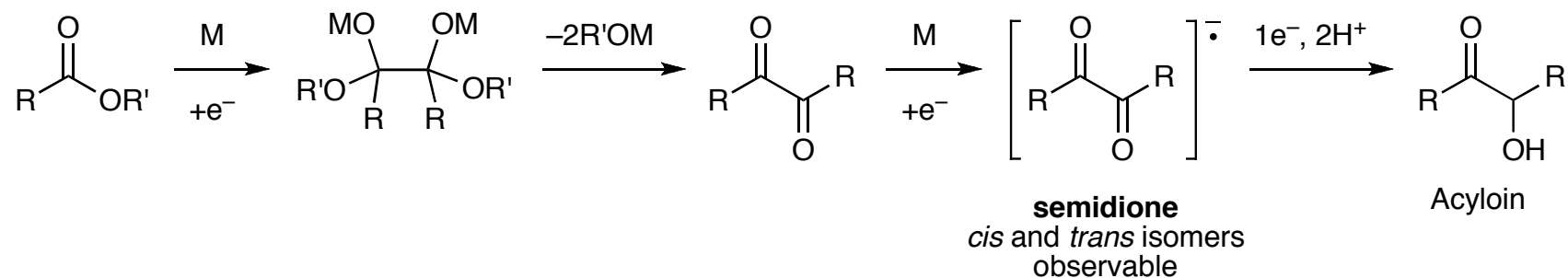
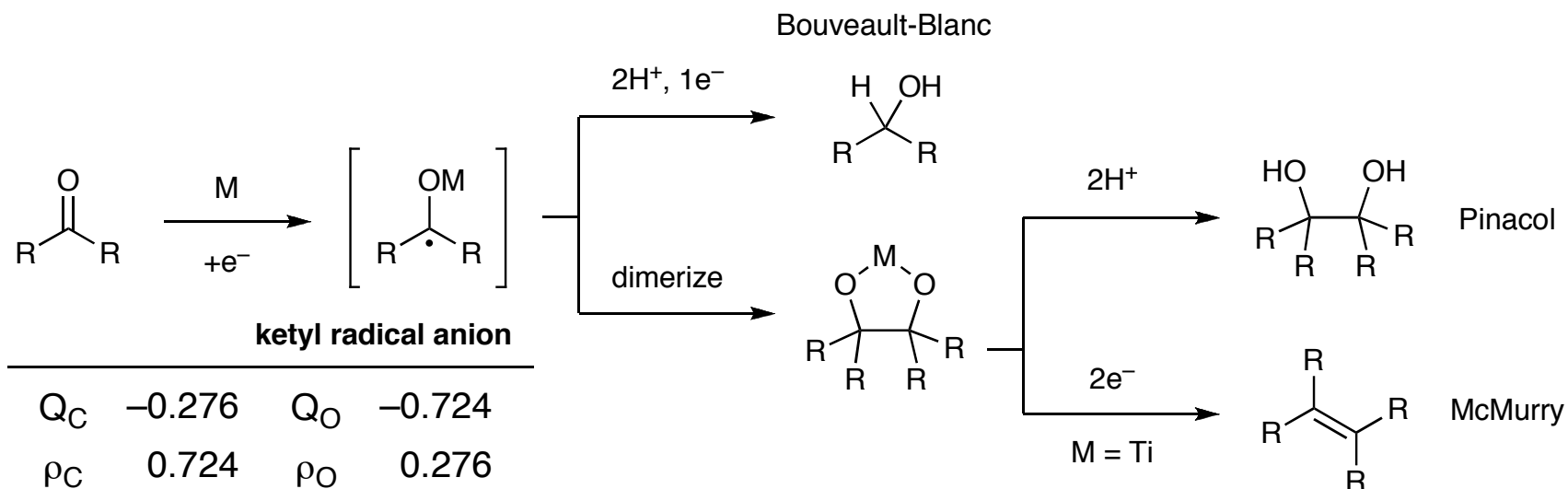


ketyl radical anion

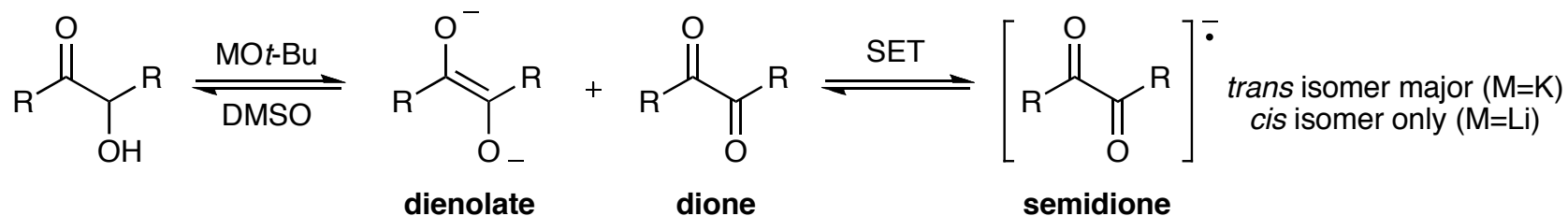


semidione

Radical Anions: Ketyl Radical Anion Mechanisms

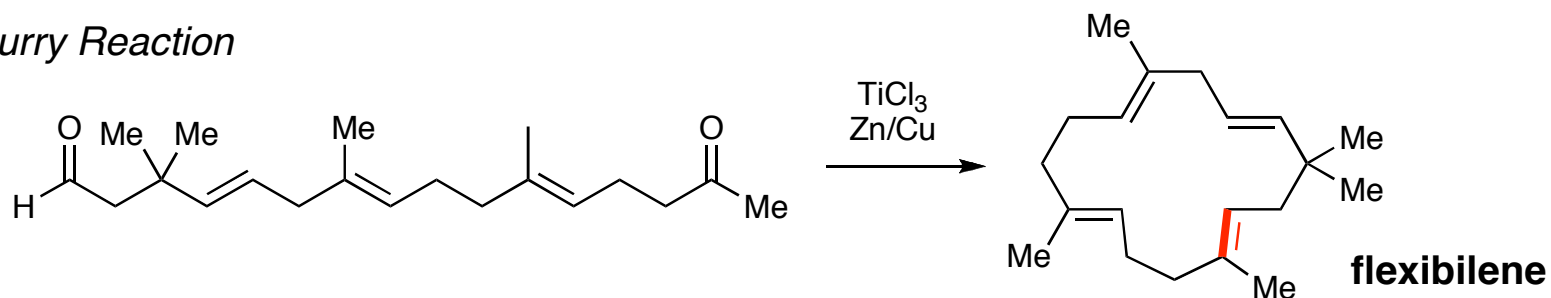


Comproportionation

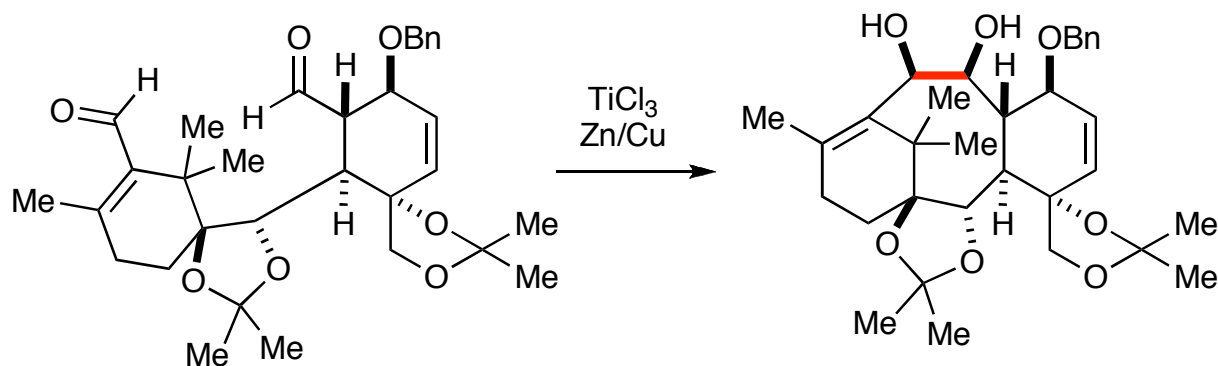


Radical Anions: Ketyl Radical Anion Applications

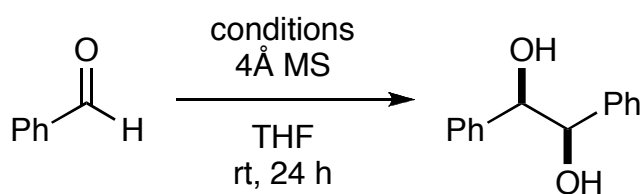
McMurry Reaction



Pinacol Coupling

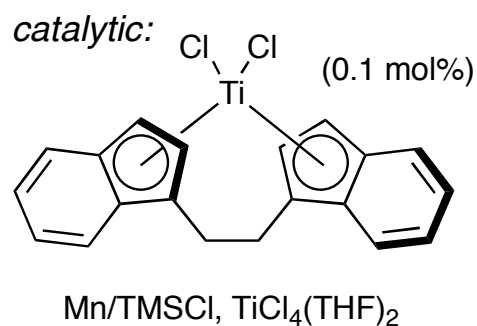


– attempts at enantioselectivity

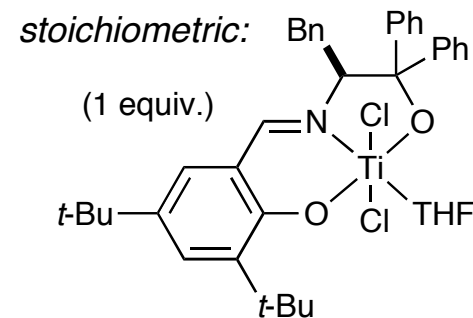


Issues:

- 1) relative and absolute stereocontrol
- 2) production inhibition (catalysis)



7:1 *dl*:*meso*, 60% ee



>95%, 49:1 *dl*:*meso*, 91% ee

>95%, 49:1 *dl*:*meso*, 91% ee