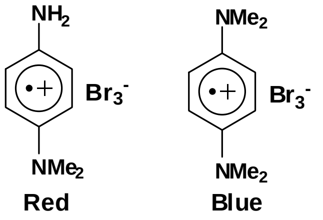
Baran Group Meeting
10/03/2007

Cation Radical Cycloadditions

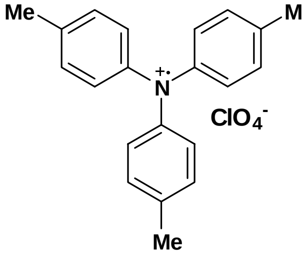
Shun Su

Introduction

- Stable cation radical salts were first isolated in 1879 (Wurster's Red and Blue).
- However, it was not until 1926 that the true nature of these salts as monomeric species possessing both an unpaired electron and a single unit of positive charge was decisively imputed by Weitz.
- Weitz also coined the terms 'cation radical' and 'aminium' ion.

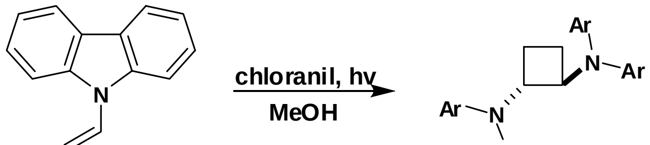


Wurster's Salts



Weitz' Aminium Salt

- In 1963, Labes et. al. surmised that the polymerization of *N*-vinylcarbazole (NVC) in acetonitrile induced by certain Wurster salts was, in fact, initiated by the NVC cation radical.
- Dimerization of NVC was disclosed in 1964 by Ellinger.
- The cation radical chain nature of the reaction was definitely established by Ledwith *et al* in 1968.
- DA dimerization of 1,3-cyclohexadiene under γ-radiolysis was disclosed in 1964; the radical chain nature of the reaction was identified in 1969.



Ellinger, 1964

Nathan L. Bauld *Tetrahedron* **1989**, *45*, 5307 and ref there in.

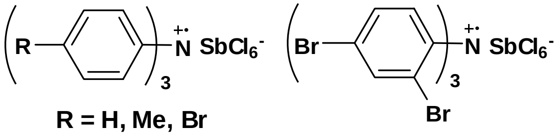
Generation of Cation Radicals:

$$S \xrightarrow{-e} S^{+\bullet}$$

Various methods may be applied to facilitate the remove of one electron from HOMO level: a) Chemical method; b) Photochemical method; c) Electrochemical oxidation; d) Radiolytic oxidation.

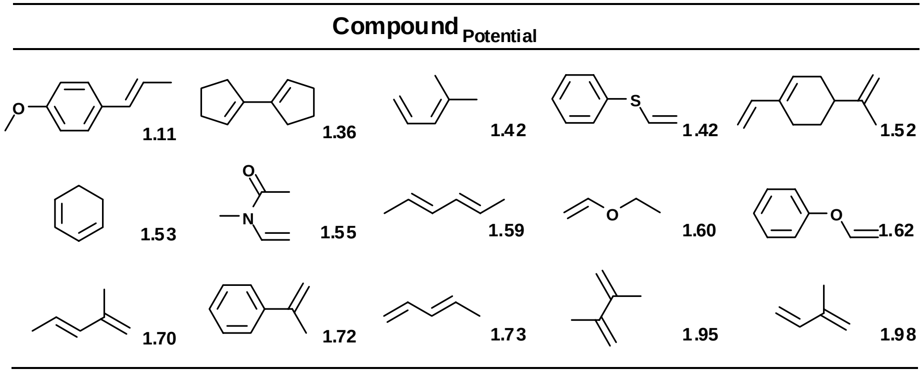
a) Chemical Method

A chemical one electron oxidant having suitable oxidation potential to match the potential of the substrate is chosen and react in inert solvent (e.g. CH_2Cl_2, MeCN). Due to the radical chain character of the reaction, only catalytic amount (e.g. 5-10%) of oxidant is need.



$Fe(Phen)_3(PF_6)_3$ $NO^+PF_6^-$
$Cp_2Fe^+BF_4^-$

Half-Wave Oxidation Potentials
(Ag/Ag^+ vs SCE, MeCN, Irreversible)



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b) Photochemical Method:

This process involves the excitation of a suitable sensitizer to its excited state followed by quenching of excited sensitizer by substrate leading to the formation of substrate cation radical and sensitizer anion radical.

Sensitized Electron Transfer

$$\mathbf{Sens} \xrightarrow{h\nu} [\mathbf{Sens}]^{*} \xrightarrow{\mathbf{S}} \mathbf{S}^{+\cdot} + [\mathbf{Sens}]^{-\cdot} \xrightarrow{\mathbf{BET}} \mathbf{S} + \mathbf{Sens}$$

Electron Transfer by Charge Transfer Excitation

$$\mathbf{D} + \mathbf{A} \rightleftharpoons [\mathbf{D},\mathbf{A}] \xrightleftharpoons{h\nu} [\mathbf{D}^{+\cdot}, \mathbf{A}^{-\cdot}]$$

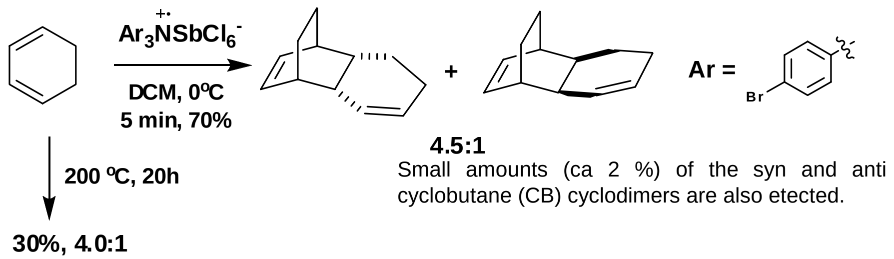
c) Electrochemical Oxidation:

Substrate is oxidized at the electrode interface at its oxidation potential, resulting in the direct formation of the corresponding cation radical.

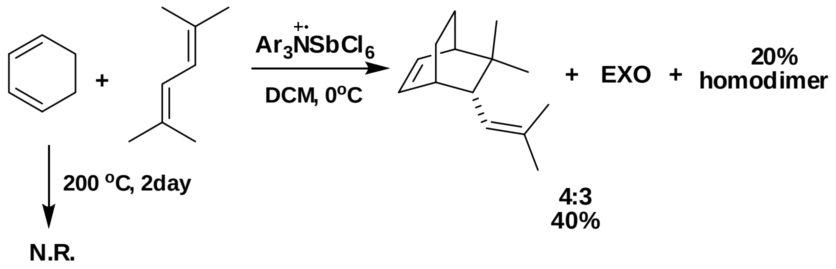
d) Radiolytic Oxidation:

Substrate in a cryogenic matrix is exposed to gamma ray (Normally ^{60}Co as source).

Radical Cation Diels-Alder Reaction



Small amounts (ca 2 %) of the syn and anti cyclobutane (CB) cyclodimers are also etected.



Bauld *et. al. JACS* **1981**, *103*, 718.

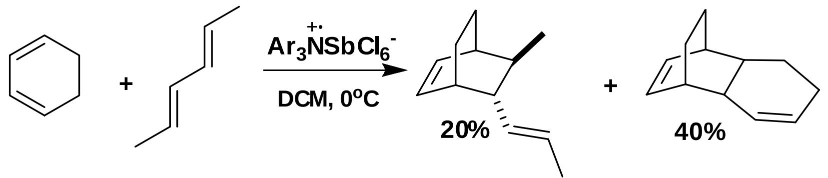
- A typical DA reaction is not efficient unless the dienophile is substantially electron deficient.
- Reactivity umpolung of electron rich diene *via* cation radical formation provides an effective and direct remedy for the absence of electron deficiency in the dienic system.

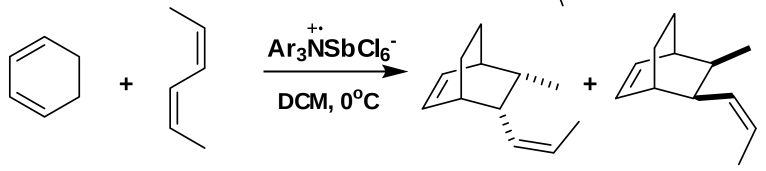
Terminology:

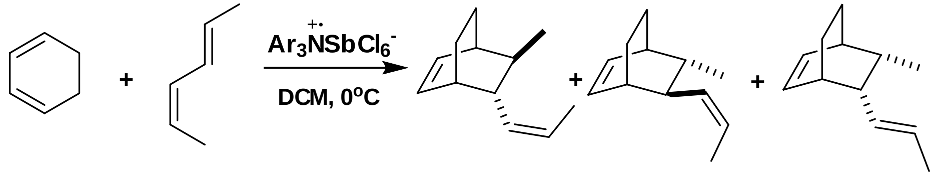
- Caticophile: neutral component which react with cation radical
- Caticogen: neutral component which generate cation radical
- Caticogenicity: the ability to generate cation radical (assumed to parallel the half-wave potential of the caticogen)
- Caticophilicity: assumed to parallel π basicity or neucleophilicity.

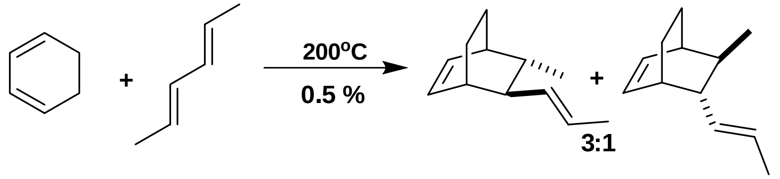
Cation Radical Cycloadditions

Stereochemical Outcome:







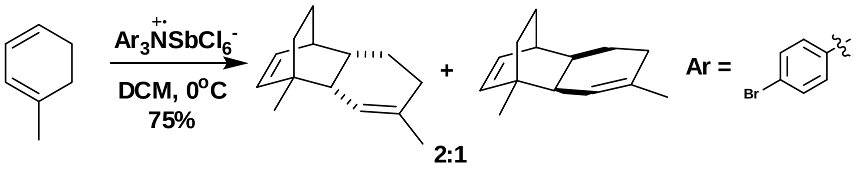


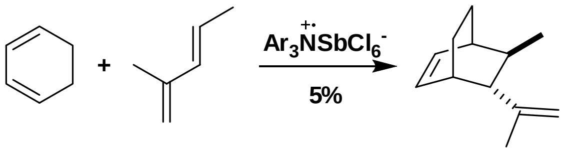
Complete suprafacial stereospecificity was observed.

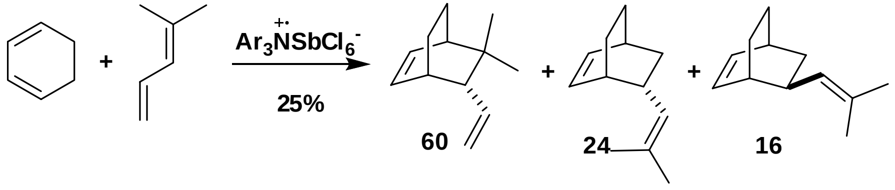
It was believed that the cation radical DA inherently has an extremely high endo stereoselectivity as a consequence of 1) low reaction temperature; 2) the electron deficient nature of the dienophile provides strong secondary orbital interaction in the transition state for endo addition, which closely parallel the situation exists for the Lewis acid catalyzed DA.

Bauld *et. al. JACS* **1982**, *104*, 2665.

Regiospecificity & Chemoselectivity:

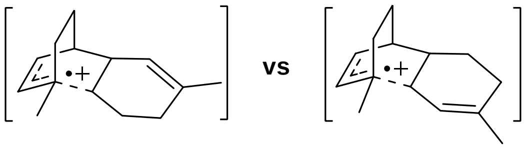






Three factors may control the selectivity:

1) Steric effect; 2) Maximum stabilization of the bisallylic transition state; 3) *Charge effect*



Bauld *et. al. JACS* **1982**, *104*, 2665.

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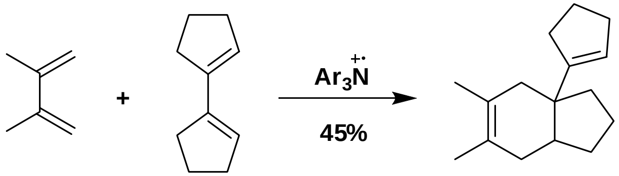
Acyclic Diene Components:

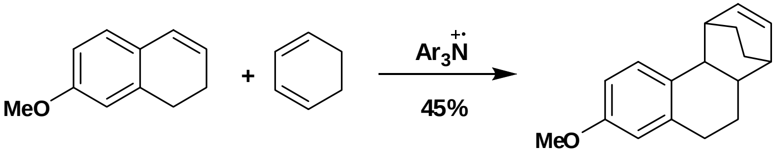
Dienic component in the cation radical DA need not be cyclic, however substantial *s-cis* contents is necessary. Simple acyclic diene such as 1,3-butadiene, isoprene, piperylene, and 2,4-hexadienes are not efficient as diene component.



Reynold *Dissertation at the University of Texas Austin* **1988**

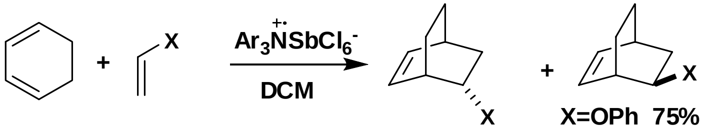
Styrene as Dienophiles:

Styrenes are often sufficiently caticogenic to participate in the cation radical DA, normally in the dienophilic role. Certain substrates can also assume the dienic role in the cyclodimerization.



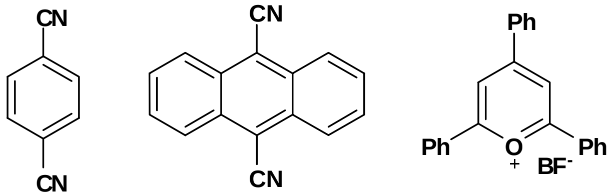
Electron Rich Alkenes:

These substrates are moderately caticogenic but extraordinarily caticophilic. Cycloaddition to acyclic dienes is predominantly cyclobutane (CB) periselective.



X=OPh 75%
X=SPh 68%

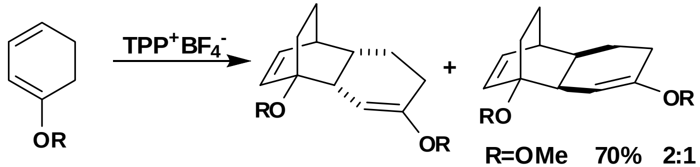
Photosensitized Electron Transfer (PET) Initiation:



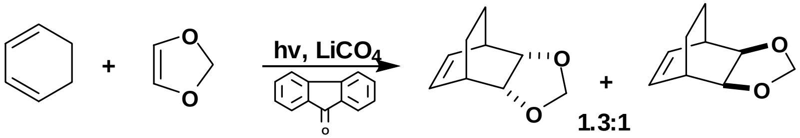
DCB **DCA** **TPP**

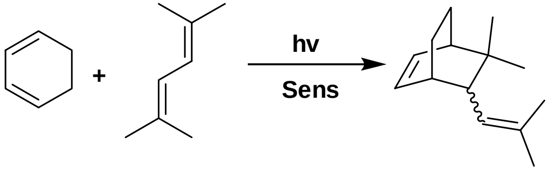
Compared to aminium salt condition:

- PET condition provides similar results with a wide variety of substrates.
- Especially advantageous in the case of cycloadditions involving very sensitive functionalities.
- However, cation radical lifetimes are limited by back electron transfer when cycloadditions are exceptionally slow (e.g. sterically hindered substrate).



R=OMe 70% 2:1
R=OAc 20%





Sens=DCB 0%
$Sens=TPP^+$ 34%

Bauld *et. al. JACS* **1987**, *109*, 4960;
Matty *et. al. J. Chem. Soc. Chem. Commun.* **1985**, 1088.

Cation Radical Cycloadditions

Several Issues to be Addressed:

Reaction mechanism

Chemical Initiation:

initiation $R + Ar_3N^{+\cdot} \rightleftarrows RH^{+\cdot} + Ar_3N$

cycloaddition $R^{+\cdot} + R' \longrightarrow P^{+\cdot}$

propagation 1 $P^{+\cdot} + Ar_3N \longrightarrow P + Ar_3N^{+\cdot}$

propagation 2 $P^{+\cdot} + R \longrightarrow P + R^{+\cdot}$

PET Initiation:

initiation $Sens + hv \longrightarrow Sens^{*}$

$Sens^{*} + R \longrightarrow Sens^{-} + R^{+\cdot}$

cycloaddition $R^{+\cdot} + R' \longrightarrow P^{+\cdot}$

propagation $P^{+\cdot} + R \longrightarrow P + R^{+\cdot}$

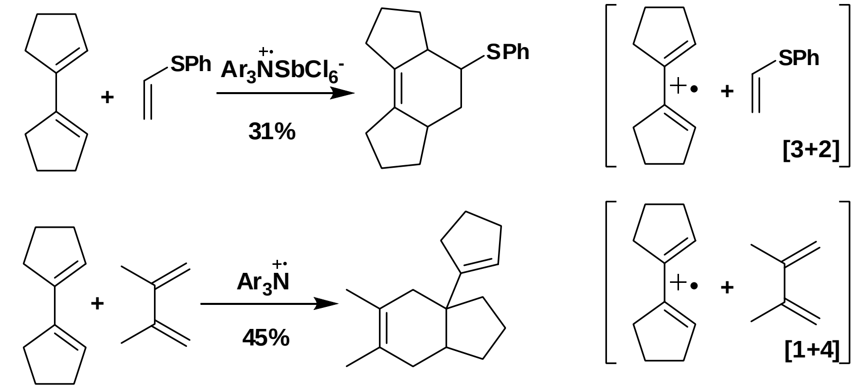
termination $Sens^{-\cdot} + P^{+\cdot} \longrightarrow Sens + P$

Stepwise vs Concerted Pathway:

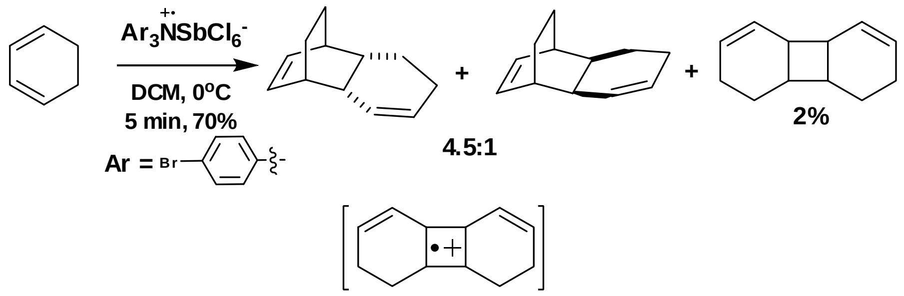
Based on extensive stereochemical investigations of various pericyclic reaction, it's more likely the reaction proceed in a concerted manner. However, many exceptions exist.

Role selectivity:

The majority of efficient radical DA cross reactions which had been observed involved systems in which the dienophile is more caticogenic than the diene, the extraordinarily high caticophilicity of cyclic ([4+1] type). However, [3 + 2] cycloadditions are also well established.



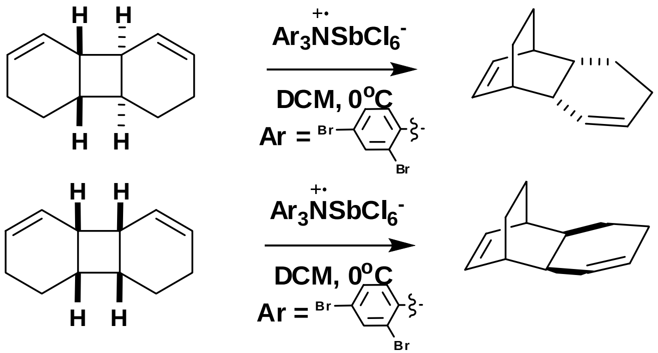
Direct DA vs Vinylcyclobutane Rearrangement:



Bauld *et. al. Phy. Org. Chem.* **1989**, *2*, 57.

Cation Radical Cycloadditions

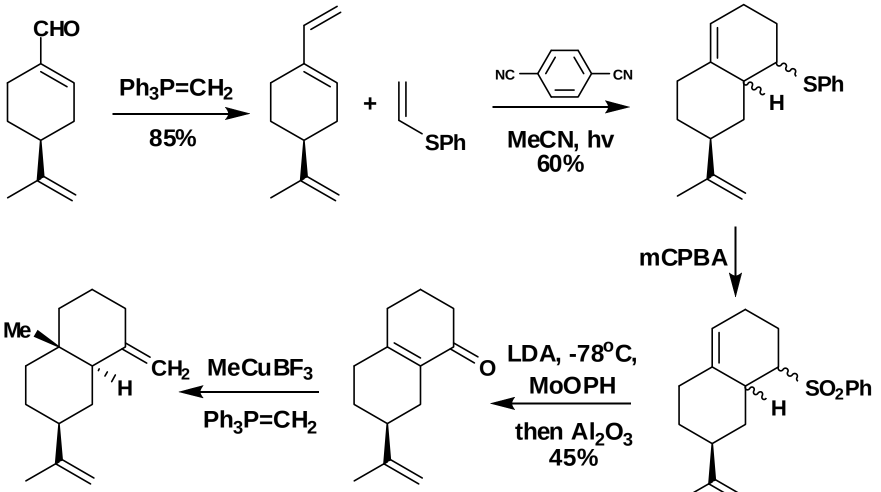
Direct DA vs Vinylcyclobutane Rearrangement:



Brief Summary:

1) Typical conditions: [$Ar_3N^{+\bullet}$/DCM/0ºC] or [2,4,6-triphenylpyrylium fluoroborate/MeCN/Pyrex/rt].
2) For a successful DA, diene components should either be cyclic or, if acyclic, have *s-cis* conformational populations.
3) The dienophile typically is of one of three basic structural types : conjugated diene, styrene, orelectron rich alkene.
4) Utilizing dienophiles which are more caticogenic than the diene component is preferred for a selective DA.
5) Caticogenicity can be assessed on the basis of oxidation potentials or ionization potentials; Caticophilicity is considered to be affected by ability to stabilize thebisallylic cation radicaloid transition state, steric hindrance toward bond formation, *s-cis* conformationcontent and so on.

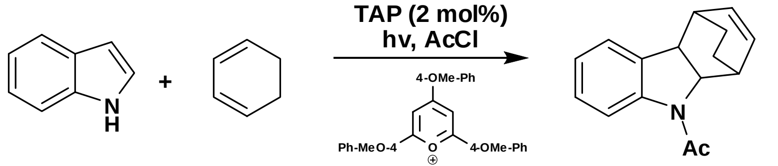
Synthetic Applications:



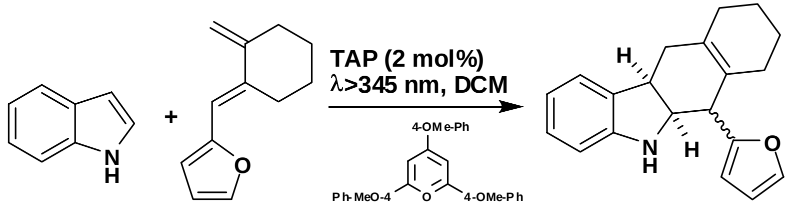
(-)-β-selinene

molybdenum pentoxide/pyridine/HMPA complex

Bauld *et. al. JACS* **1989**, *111*, 1826.



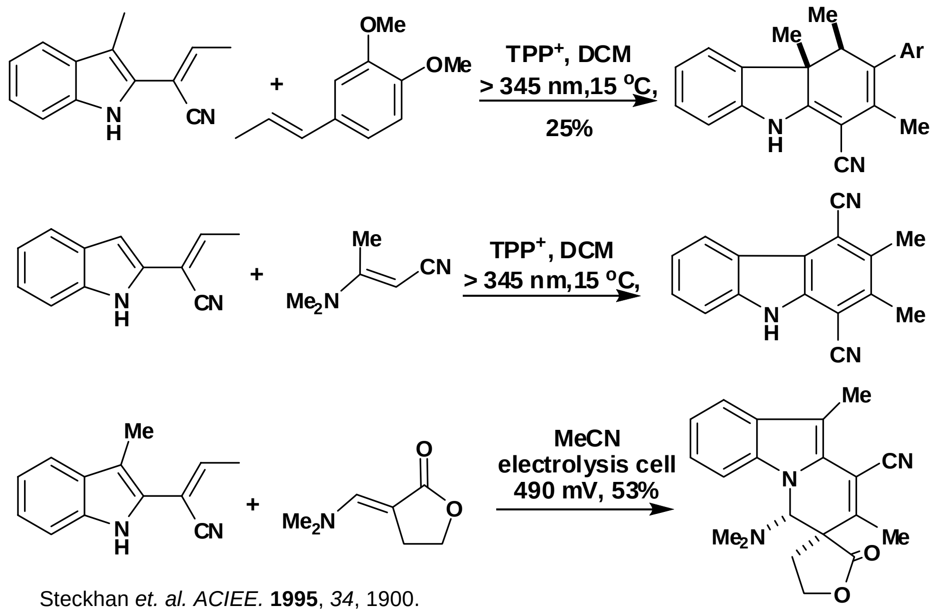
70% endo/exo = 3.3:1



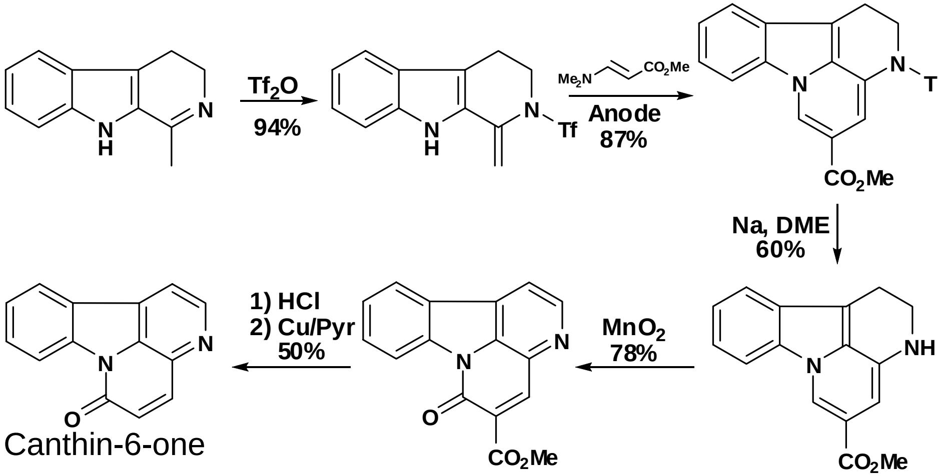
46% 2:1 anti:syn

Steckhan *et. al. Chem. Eur. J.* **1995**, *5*, 2859.

Cation Radical Cycloadditions

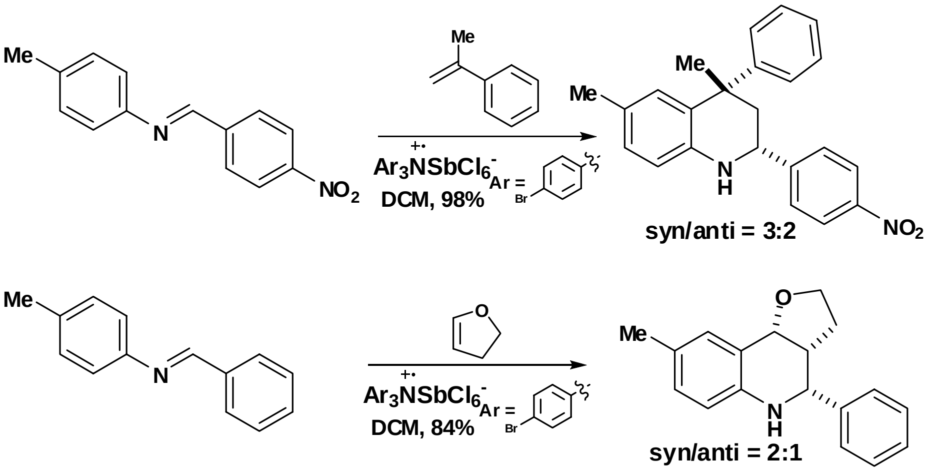


Steckhan *et. al. ACIEE.* **1995**, *34*, 1900.

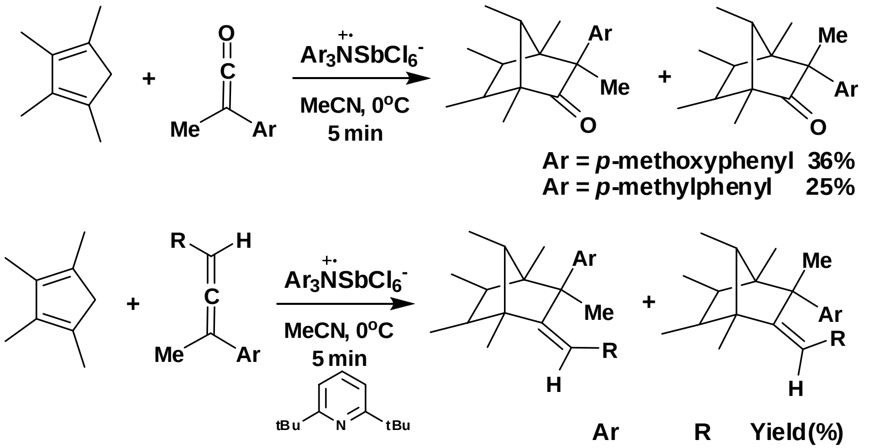


Canthin-6-one

Steckhan *et. al. Tetrahedron Lett.* **1999**, *40*, 7075.



Liu *et. al. Synlett.* **2003**, *40*, 1707.

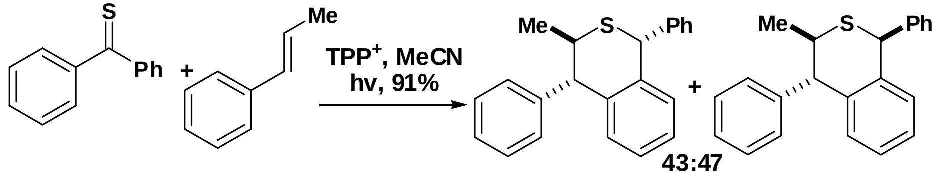


Ar = *p*-methoxyphenyl 36%
Ar = *p*-methylphenyl 25%

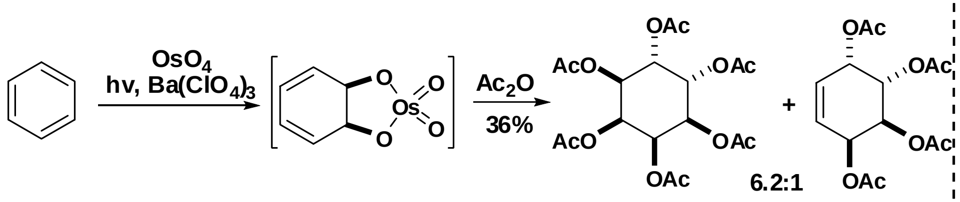
Ar	R	Yield(%)	
4-MeOPh	H	67	13
4-MePh	H	46	12
4-MeOPh	Me	63	09

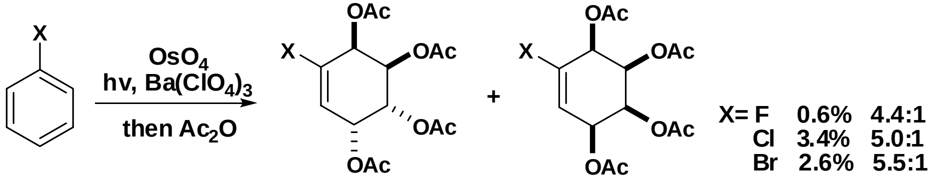
Schmittel *et. al. ACIEE.* **1991**, *30*, 999; *JACS.* **1993**, *115*, 2165.

Cation Radical Cycloadditions



Miranda *et. al. Org. Lett.* **2007**, *9*, 3587.

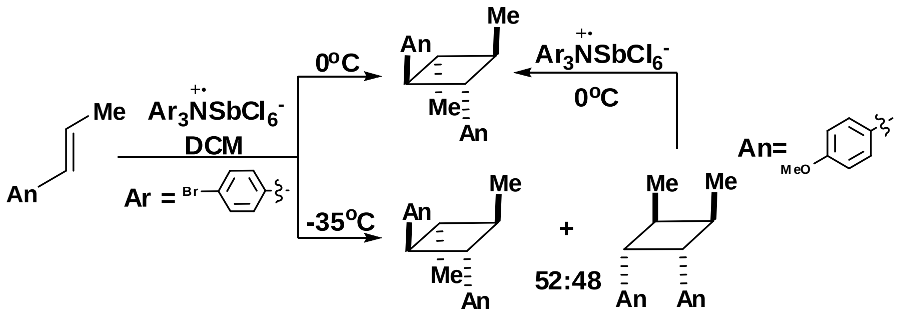




X= F	0.6%	4.4:1
Cl	3.4%	5.0:1
Br	2.6%	5.5:1

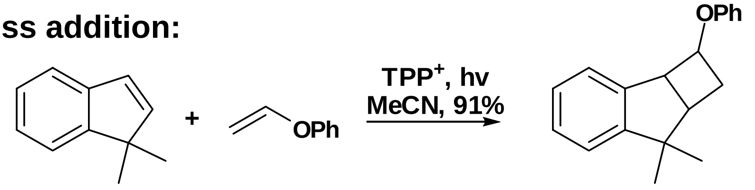
Motherwell *et. al. ACIEE.* **1995**, *34*, 2031.

Cation Radical Cyclobutanation



Bauld *et. al. JACS* **1986**, *108*, 6189.

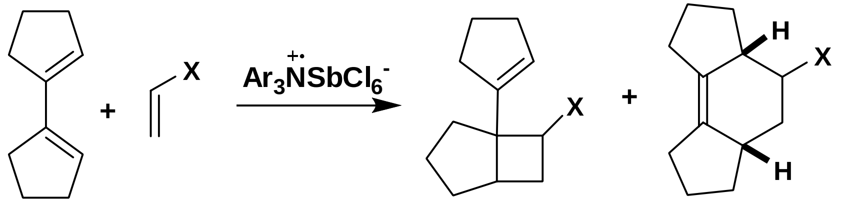
Cross addition:



40:60 syn:anti

Farid *et. al. J. Chem. Soc., Chem. Commun.* **1973**, 677.

Cross addition with conjugated dienes:



X = NAcMe	100	0
OEt	98	2
OCH_2CH_2Cl	97	3
OPh	82	18
SPh	69	31

Bauld *et. al. ibid* **1984**, *106*, 2730.

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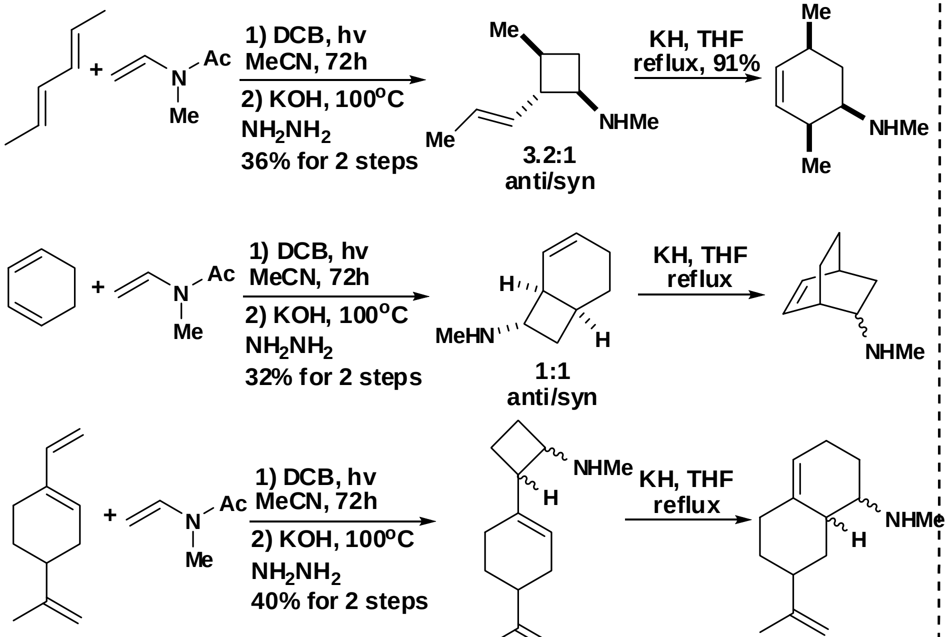
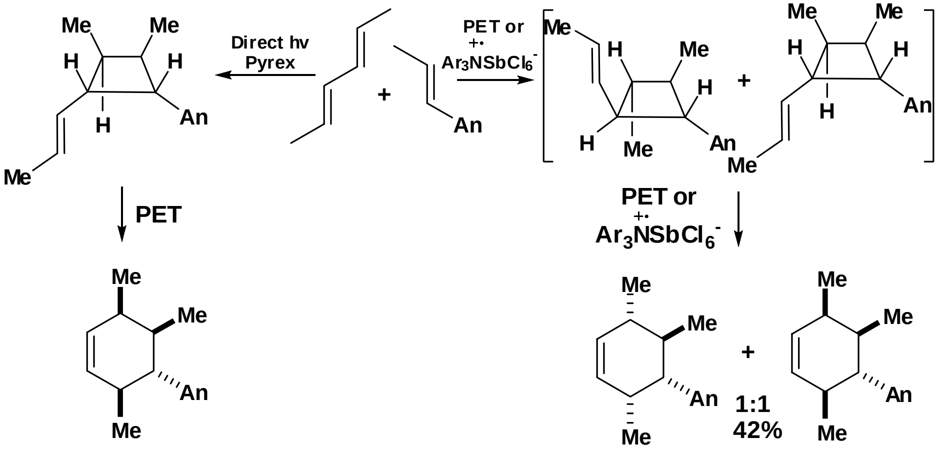
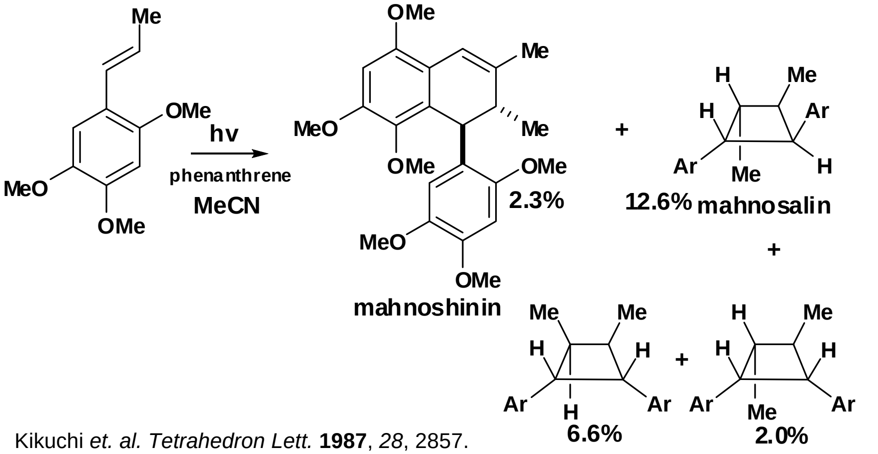
VCB Rearrangement:



Bauld *et. al. JACS* **1988**, *110*, 8111.

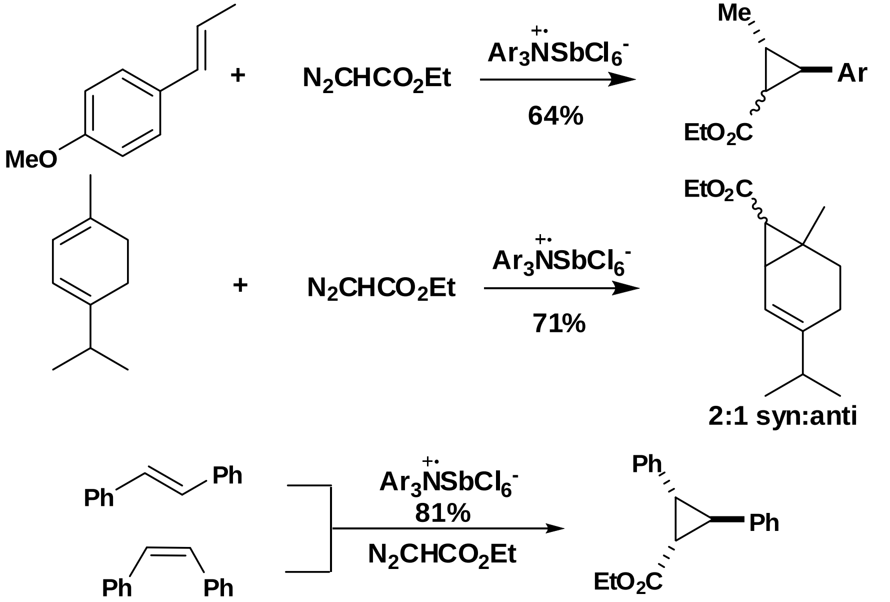


Bauld *et. al. Tetrahedron* **1986**, *42*, 6189.



Kikuchi *et. al. Tetrahedron Lett.* **1987**, *28*, 2857.

Cyclopropanation



Bauld *et. al. JACS* **1986**, *108*, 4235.

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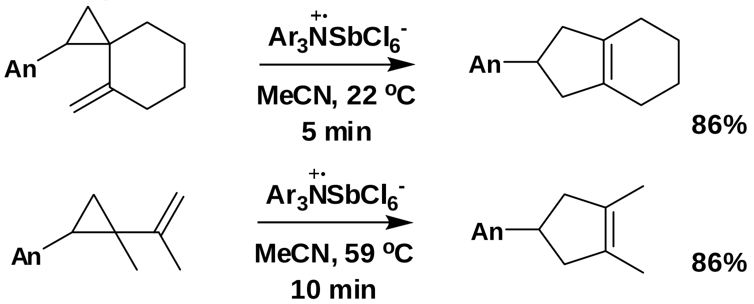
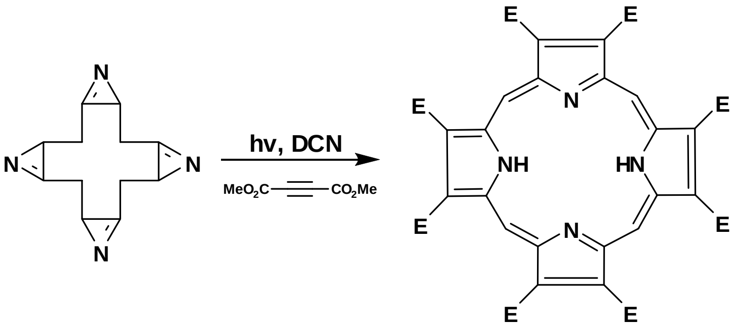
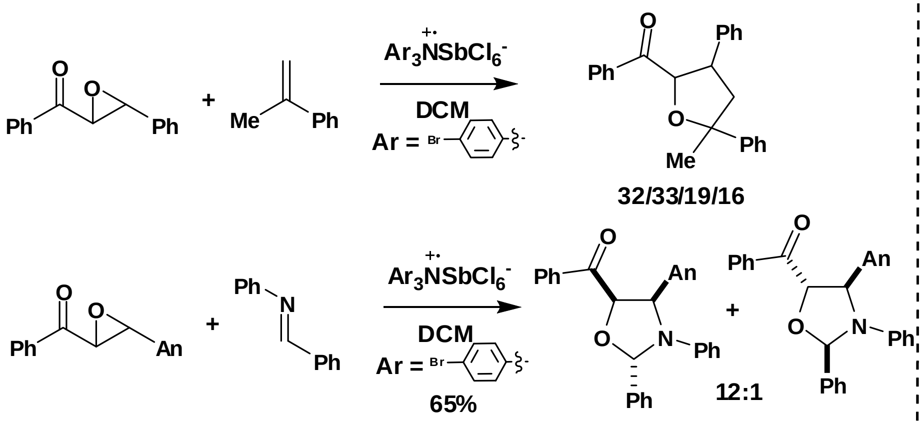
VCP Rearrangement



Colon *et. al. ibid* **1988**, *110*, 2324.



Mattay *et. al. Chem. Ber.* **1993**, *126*, 543.



Liu *et. al. Synlett.* **2004**, 251; **2005**, 161.