Department CMIC
Lecture 5b – FR5b

POLITECNICO DI MILANO

Free-Radicals:
Chemistry and Biology

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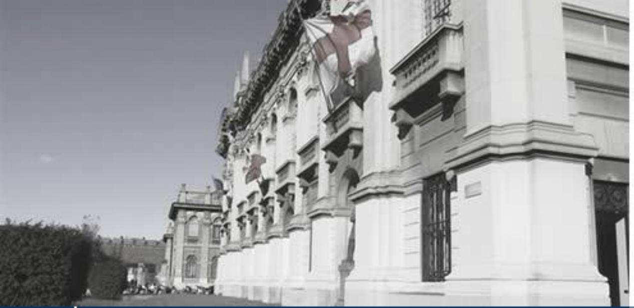
http://iscamap.chem.polimi.it/citterio/education/free-radical-chemistry/

Content



POLITECNICO DI MILANO

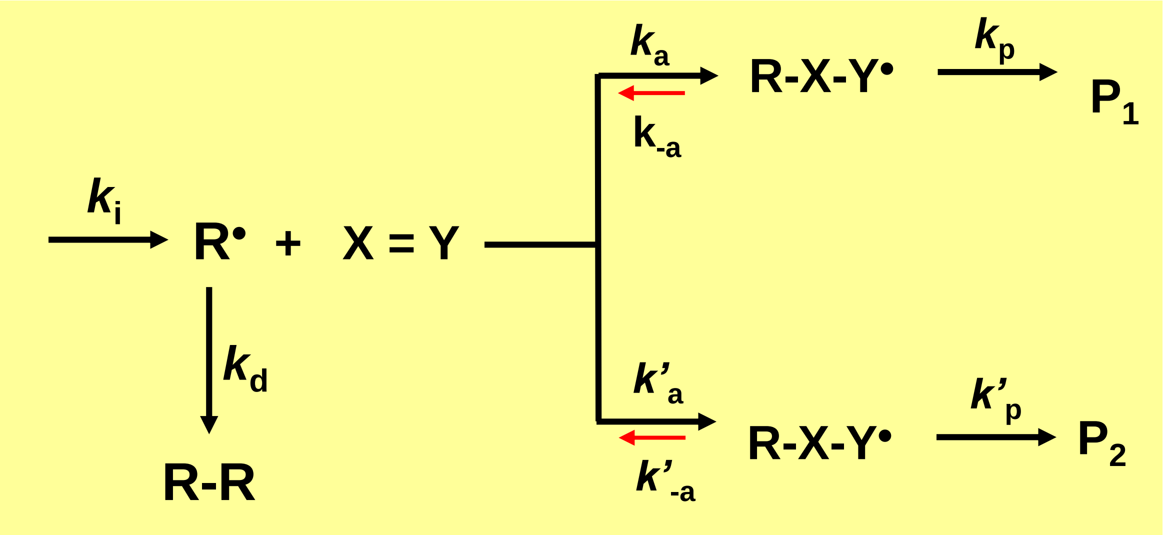
Synthetic Applications: Addition to Multiple Bonds

Prof. Attilio Citterio
Dipartimento CMIC “Giulio Natta”

Synthetic Applications of Radical Reactions

- T. Perchyonok, I. N. Lykakis, Al Postigo Streamlining *Free Radical Green Chemistry*, RCS, 2011.
- M. D. Forbes Ed. "*Carbon-Centered Free Radicals and Radical Cations: Structure, Reactivity, and Dynamics*", Wiley 2010.
- F. A. Carey, R. J. Sundberg "*Free-Radicals*" in Advanced Organic Chemistry, Springer Ed., pp 965-1071, 2008
- S. Z. Zard "*Radical Reactions in Organic Synthesis*", Oxford, 2004.
- Parsons, Blackwell "*An Introduction to Free Radical Chemistry*", Oxford, 2000.
- M.J. Perkins, "*Radical Chemistry: The Fundamentals*", OUP No. 91, 2000
- W.B. Motherwell and D. Crich "*Free Radical Chain reactions in Organic Synthesis*",, Academic Press, 1992.
- B. Giese, "*Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*", Pergamon Press, Oxford, 1986.
- D.P. Curran, "*The Design and Application of Free Radical Chain Reactions in Organic Synthesis*", *Synthesis,* 1988, 417 and 489.

Radical Addition to Unsaturated Systems



Competitive investigations

Reactivity : **Irreversible Process** $(k_i, k_d, k_a, k'_a, k_p, k'_p)$

Reversible Process $(k_i, k_d, k_a, k'_a, k_p, k'_p)\ k_{-a}, k'_{-a}$

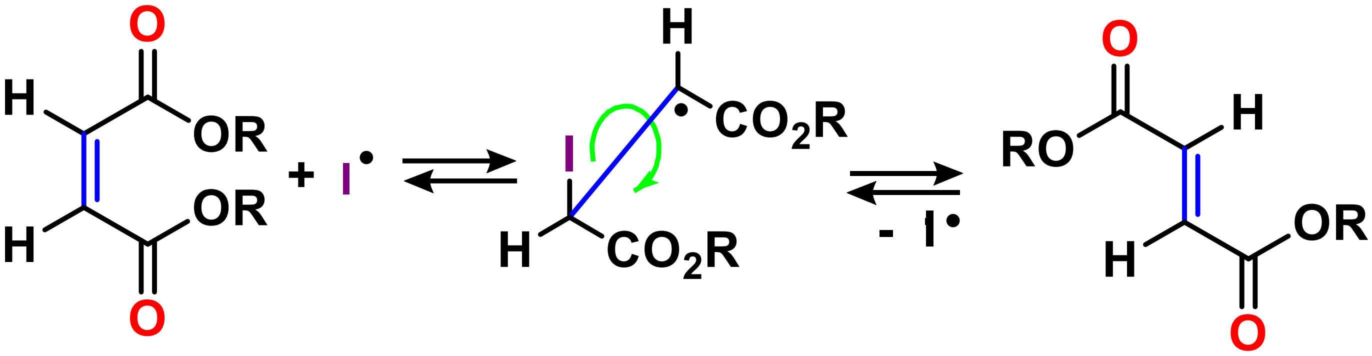
Regioselectivity: k_a / k'_a

Substrate Selectivity : k_a/k_d e k'_a/k'_d

Stereochemistry: A) Spatial relationship between substituents on R and X/Y in the bond

B) Spatial relationship between the formed bond and SOMO orbital.

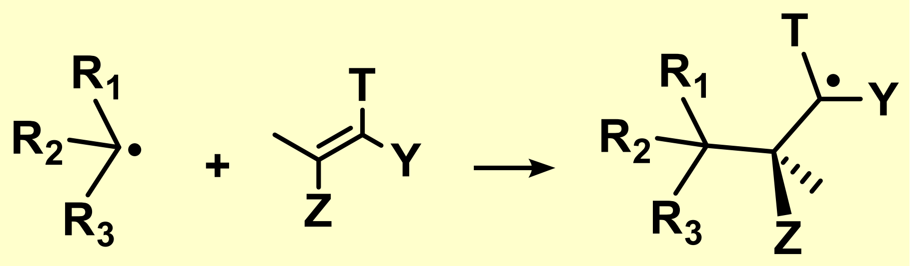
Radical *cis-trans* Isomerization of Alkenes



- The final product sensitive to the presence of *cis* isomer (1% - pasty product)
- Lower temperature to reduce *cis* isomer (0.5% I_2, 80 °C, hν (visible, 100 watt), 1 h).
- in lab the *trans* is isolated by slow addition of hexane to the mixture
- The process was developed adding hexane at 50°C in several hours
- The process work at 2000 L scale but at 10.000 L: pasty crystals
- Solution: ppt. hexane at 55 °C (recycling the iodine from hexane).

T (°C)	$R_{trans/cis}$
30	13.6
80	11.9
120	10.8
180	8.9

Peculiarity of Carbon Centered Free Radical Addition to Olefins (C=C)



Substituent Effects:

R_1, R_2, R_3 induce polar and conjugative effects :

electron-donor groups* - *<u>nucleophilic radicals</u>

electron-withdrawing groups* - *<u>electrophilic radicals</u>

conjugated groups* - *<u>stabilized radicals</u>

induce relevant steric effects

when all R are bulky* - *<u>persistent radicals</u>

induce significant conformational effects

R = electronegative atoms* - *<u>non planar radicals</u>

Z induces moderate polar and remarkable steric effects

Y,T induce only important polar effects:

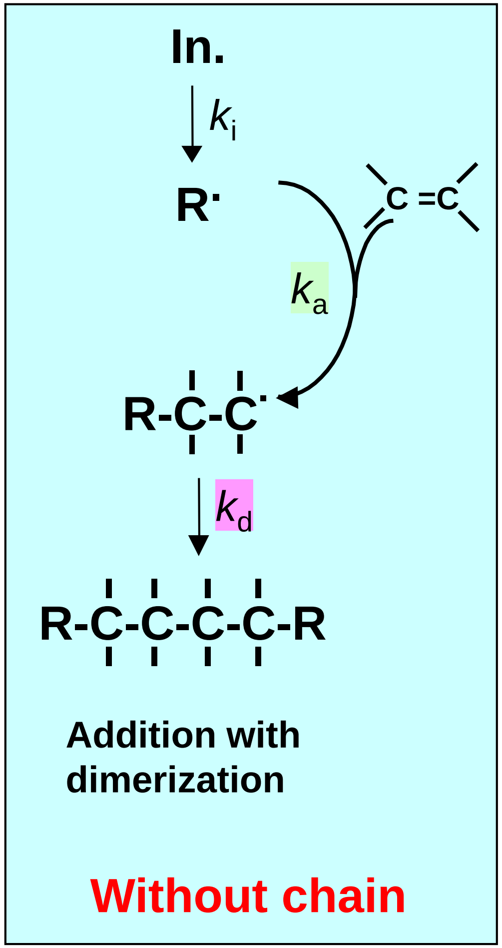
<u>nucleophilic radicals</u>* → *electron-poor olefins

<u>electrophilic radicals</u>* → *electron-rich olefins

Some More Considerations on Radical Addition to Olefins

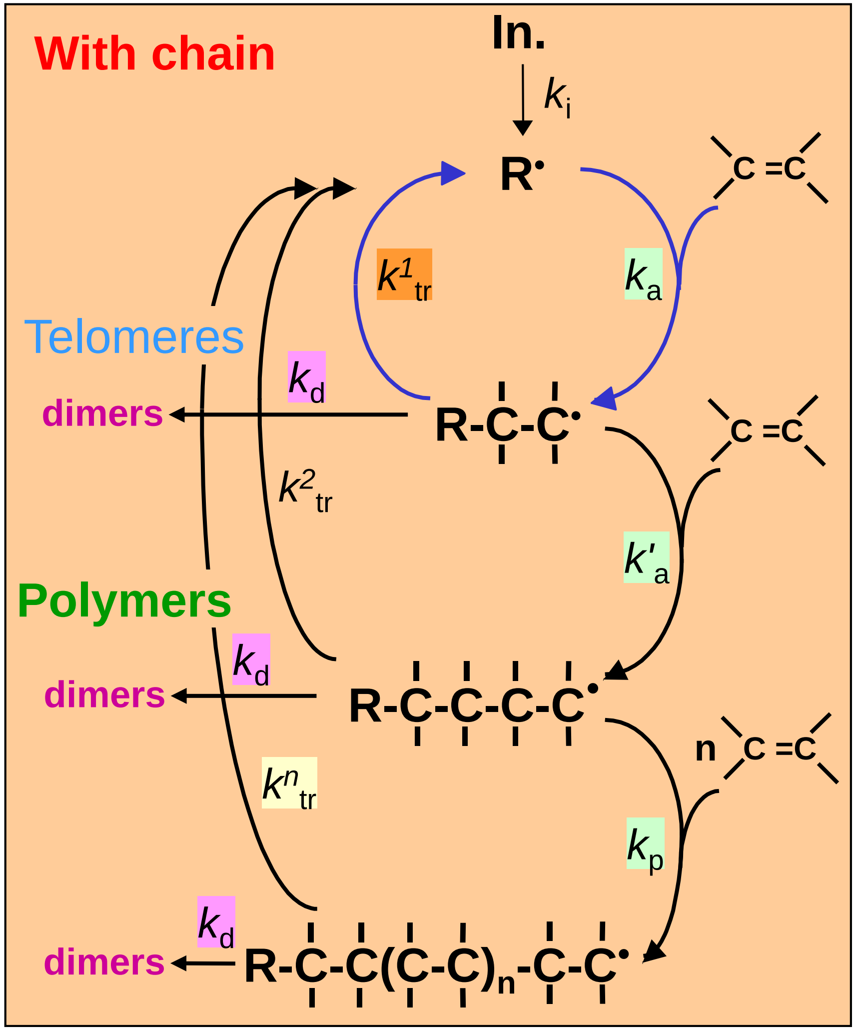
- Frequently the process is reversible; the positional and substrate selectivity are controlled by the fate of adduct radicals (k_p)
- The regioselectivity is mainly determined by steric effects (addition to terminal C), in the absence of reversibility (high k_p) .
- Sensitivity to substrate and radical conformation (stereo-electronic effects, electronegative atoms)
- The stabilization of adduct radical ($^{\bullet}CR_2$-Y) is determinant only if Y is a strongly conjugating group (Ar, S, etc.)
- Generally the process is exothermic and fast ($k_a > 10^2$ $M^{-1}\cdot s^{-1}$) and shows an early transition state (can be investigated using the Frontier Orbital Theory).

Inhibited Radical Additions and Radical Mono- and Poly-Additions



Addition with dimerization

Without chain



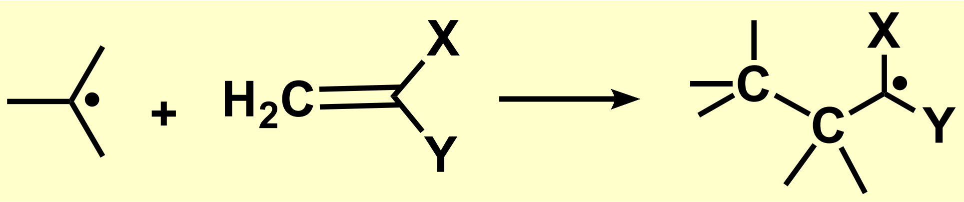
— Mono- or Direct Addition

Rate Propagation Constants in the Polymerization of Vinyl Monomers

Monomer	k_p ($M^{-1}\cdot s^{-1}$) (60°)	log A ($M^{-1}\cdot s^{-1}$)	E_{att} ($kcal\cdot mole^{-1}$)
Acrylamide	18.000[a]	-	-
Vinyl Chloride	12.300	6.5	3.7
N,N-Dimethyl Acrylamide	11.000[b]	-	-
Vinyl Acetate	3.700	8.4	7.3
Methyl Acrylate	2.090	8.0	7.1
Acrylonitrile	1.960	-	-
Methyl Methacrylate	734	7.0	6.3
Styrene[c]	145	6.7	7.3
Butadiene	100	8.1	9.3
Isoprene	50	8.1	9.8

[a] at 25°C. [b] at 50°C. [c] Also reported k (60°)= 176; logA = 7.0, e E_{att} = 7.8

Absolute Rate Constant for the Addition at 25°C of Carbon Radicals to Olefins

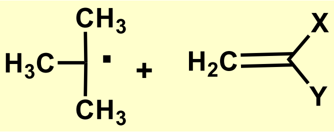


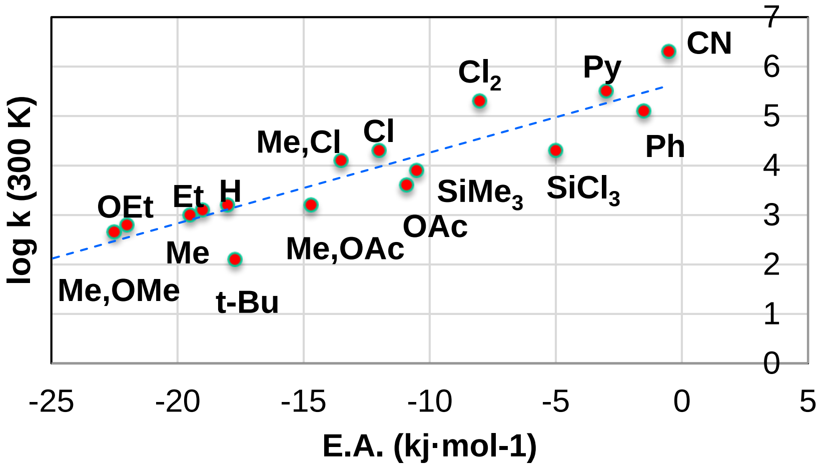
X, Y	*k*	*k*	*k*/10^3	*k*	*k*/10^3	*k*	*k*
	$(CH_3)_3C^{\bullet}$	$(CH_3)_2C^{\bullet}OH$	$NCCH_2^{\bullet}$	$(CH_3)_2C^{\bullet}OH$	$(CH_3)_2CCOOCH_2^{\bullet}$	$HOCH_2^{\bullet}$	$PhCH_2^{\bullet}$
H, OEt	**390**	**108**	**43**	**320**	**150**	**180**	**14**
Me, OMe	**220**	**82**	**35**	**1080**	**140**	**33**	**-**
Me,OCOMe	**1700**	**79**	**52**	**4850**	**88**	**680**	**-**
H, Ph	**13200**	**2410**	**380**	2.2×10^6	**1900**	2.3×10^4	**1300**
Cl, Cl	**35000**	**603**	**33**	2.15×10^5	**270**	5.3×10^4	**550**
H, COOMe	**-**	**367**	**110**	$> 10^7$	**490**	7.1×10^5	**450**
H, CN	2.4×10^6	**2020**	**110**	$> 10^8$	**540**	1.1×10^6	**2200**
H, CHO	**-**	**1200**	**25**	**-**	**380**	2.1×10^6	**-**

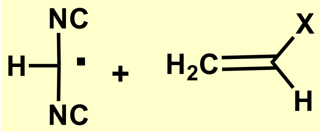
H. Fisher, Landolt-Börnstein, New Ser. Vol. 18a-e (1995)

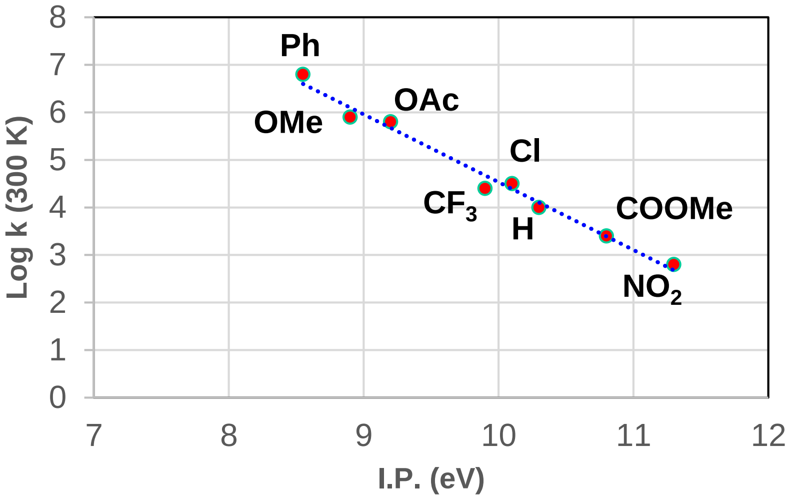
General Trends of Rates

- **For nucleophilic 1°, 2° and 3° alkyl radicals k_a is proportional to EA**
- **For alkyl radicals substituted by electron-donor groups (very nucleophilic) k_a is roughly proportional to EA**
- **For alkyl radicals substituted by electron-withdrawing groups (electrophilic) k_a is proportional to IP**
- **Benzyl and allyl radicals (nucleophilic) react inefficiently owing to stabilization.**

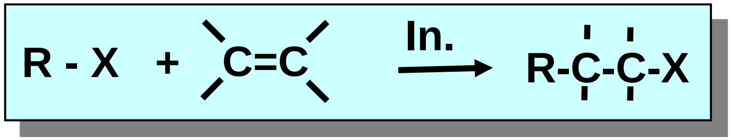




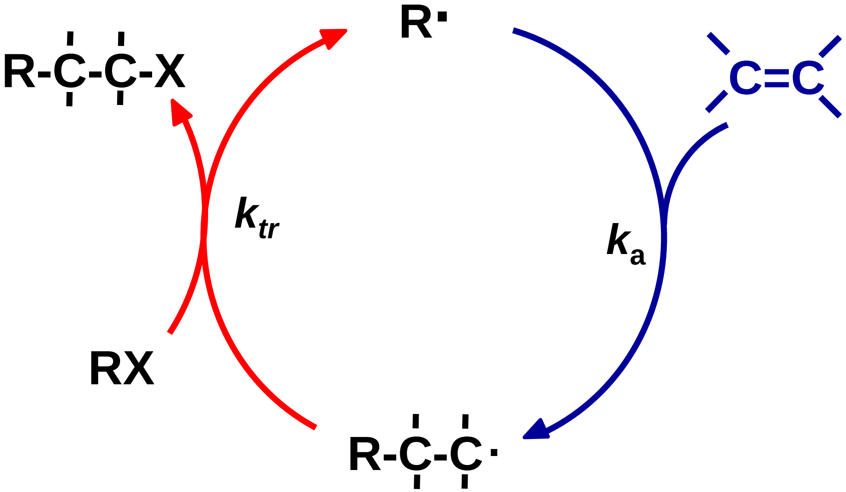




Direct (Simple) Addition



$$R - X + C{=}C \xrightarrow{In.} R{-}C{-}C{-}X$$

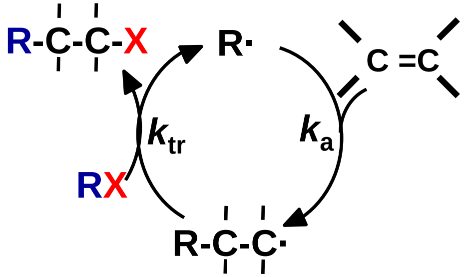


- **THERMINAL OLEFINS**
- **THERMINAL ACETYLENES**
- **CYCLOALKENES**
- **Internal olefins/acetylenes**

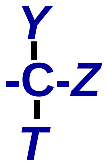
R-X can be quite structurally different (but needs a k_{tr} sufficiently high to sustain the chain!) and frequently is used as solvent.

Substituents in the Direct Addition

X = H R = Halo, SR, PR_2, $P(OR)_2$, SnR_3, SiR_3, GeR_3



R =



$$R = -\overset{Y}{\underset{T}{C}}-Z$$

Y = NR_2, OR, SR, CN, COR, COXR, (R = H, Alkyl, Acyl) (X = O, S, N)

Z, *T* = H, Alkyl, COOR'

R = -C(*A*)=*B* *A* = H, Alkyl, COR, OR, NR_2, SR; *B* = O, NR_2

Vogel, *Synthesis*, 1970, 99. Sosnovsky, "*Free Radical Reactions in Preparative Organic Chemistry*" (Mc Millan, N.Y.) 1964. Walling, 1957. Giese, B. 1986. Curran 1992. Crich 1992.

X = Cl, Br, I R = H, Halogen, SR, SiR_3, NO, NO_2, SO_2R
R = $-C(Halogen)_nH_{3-n}$, $-CR_2COOR$, R_f

C.Walling, E.S. Huyser, *Org. React*., 1963, 13, 91. P. Martin. *Tetrahedron*, 1985, 41, 4057
R.Kh. Friedlina, *Synthesis*, 1977, 145 e *Russ. Chem. Rev*. 1984, 53, 222. Curran, 1994

X = BR_2 R = Alkyl

H.C. Brown, *J. Am. Chem. Soc*., 1970, 92, 710 e 3503. *Angew. Chem. I. E*., 1972, 11, 693..

Simple Chain Radical Additions (Atom Transfer)

A) Polyhalomethanes

$$\mathrm{RCH{=}CH_2 + {}^{\bullet}CCl_3 \rightarrow R\dot{C}(H){-}CH_2CCl_3}$$

$$\mathrm{R\dot{C}(H){-}CH_2CCl_3 + CCl_4 \rightarrow RCHClCH_2CCl_3 + {}^{\bullet}CCl_3}$$

The transfer shows the order: $\mathrm{CX_3}$-X > $\mathrm{CHX_2}$-X > $\mathrm{CH_2X}$-X > $\mathrm{CH_3}$-X
(X = halogen atom)

B) N-Haloamines

$$\mathrm{R'CH{=}CH_2 + R_2N^{\bullet} \rightarrow R_2N{-}CH_2\dot{C}(H)R'}$$

$$\mathrm{RA{-}CH_2\dot{C}(H)R' + R_2N{-}Cl \rightarrow RA{-}CH_2CHCl{-}R' + R_2N^{\bullet}}$$

C) Amines, Alcohols (X = O, NR")

$$\mathrm{R'CH{=}CH_2 + R\dot{C}(XH)H \rightarrow RCH(XH){-}CH_2\dot{C}(H)R'}$$

$$\mathrm{RCH(XH){-}CH_2\dot{C}(H)R' + RCH_2XH \rightarrow RCH(XH){-}CH_2CH_2R' + R\dot{C}(XH)H}$$

Simple Chain Radical Additions (Hydrogen Transfer)

D) Esters (X =COOR, Y = H, Cl, COOR, CN, etc.)

$$\mathrm{R'CH{=}CH_2 \;+\; R\dot{C}(X)Y \;\rightarrow\; RCXY{-}CH_2\dot{C}(H)R'}$$

$$\mathrm{RCXY{-}CH_2\dot{C}(H)R' \;+\; RCHXY \;\rightarrow\; RCHXY{-}CH_2CH_2R' \;+\; R\dot{C}(X)Y}$$

E) Mercaptans and Hydroperoxides

$$\mathrm{RCH{=}CH_2 \;+\; RS^{\bullet}\;(ROO^{\bullet}) \;\rightarrow\; R\dot{C}(H)CH_2{-}SR(OOR)}$$

$$\mathrm{R\dot{C}(H)CH_2SR(OOR) + RSH\;(ROOH) \;\rightarrow\; RCH_2CH_2SR(OOR) + RS^{\bullet}\;(ROO^{\bullet})}$$

F) Organometallic Hydrides (A = Alkyl-Hg, Sn, Ge, Si, etc.)

$$\mathrm{R'CH{=}CH_2 \;+\; RA^{\bullet} \rightarrow\; RA{-}CH_2\dot{C}(H)R'}$$

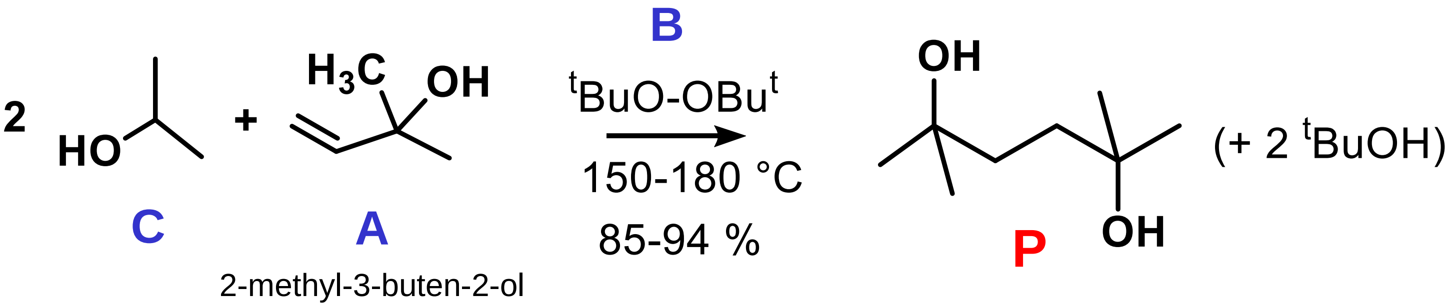
$$\mathrm{RA{-}\dot{C}H_2C(H)R' \;+\; RA{-}H \;\rightarrow\; RA{-}CH_2CH_2R' \;+\; RA^{\bullet}}$$

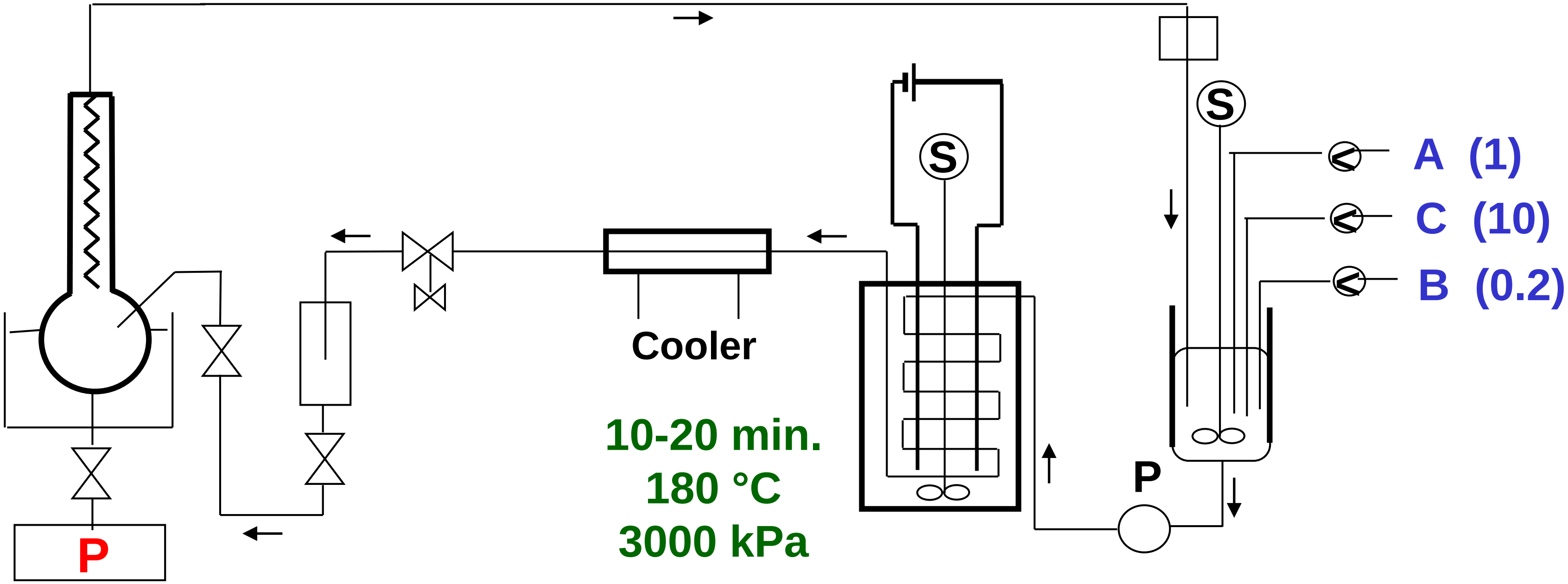
B) Aldehydes (ketons)

$$\mathrm{RCH{=}CH_2 \;+\; RCO^{\bullet} \rightarrow\; RCO{-}CH_2\dot{C}(H)R}$$

$$\mathrm{RCO{-}CH_2\dot{C}(H)R + RCHO \;\rightarrow\; RCOCH_2CH_2R \;+\; RCO^{\bullet}}$$

Continuous Synthesis of 2,5-Dimethylhexandiol



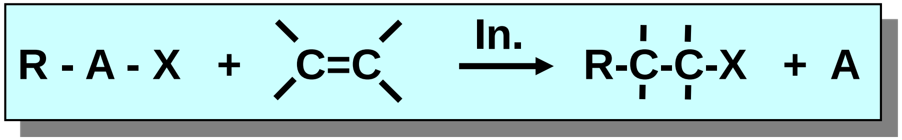


10-20 min.
180 °C
3000 kPa

97% pur., 85% sel.

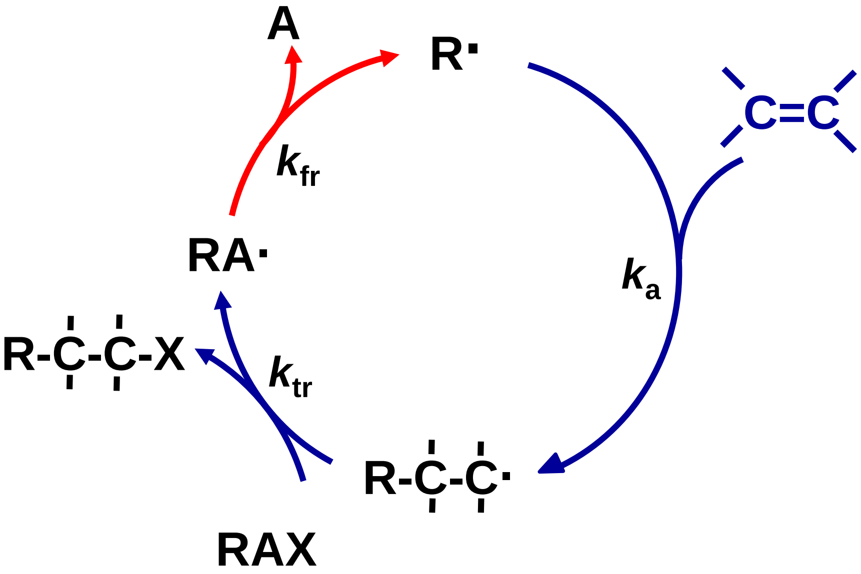
Peroxid-Chemie G.m.b.H., *U.S. Patent* US 5831134 (**1998**)

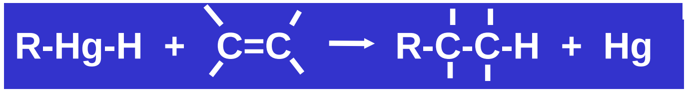
Synthetic Strategy
“Fragmentation/Addition”



$$\mathrm{R\text{-}A\text{-}X} + \mathrm{C{=}C} \xrightarrow{\mathrm{In.}} \mathrm{R\text{-}C\text{-}C\text{-}X} + \mathrm{A}$$

Based on fragmentation of weak bonds *alfa* to the radical center of precursor RAX before addition.

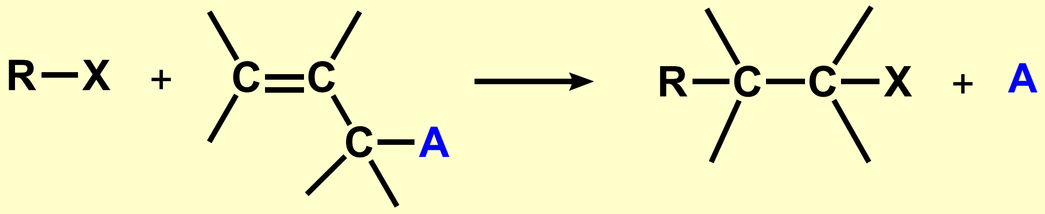


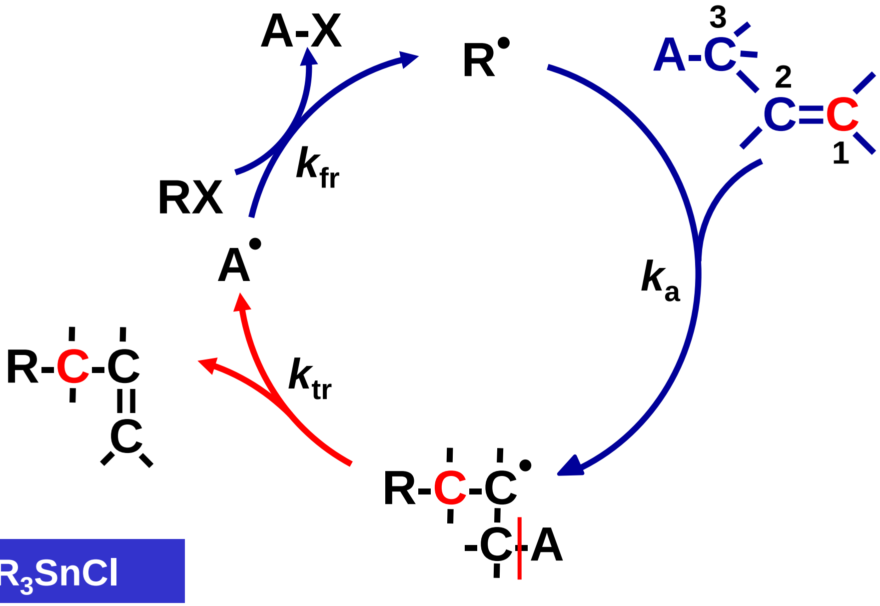


$$\mathrm{R\text{-}Hg\text{-}H} + \mathrm{C{=}C} \longrightarrow \mathrm{R\text{-}C\text{-}C\text{-}H} + \mathrm{Hg}$$

B. Giese, *Chem. Ber*. 1983, 116, 1240.
Angew. Chem. I.E. 1981, 20, 965.
Tetrahedron, 1985, 41, 4025.

Synthetic Strategy
“1-Addition/3-Fragmentation”



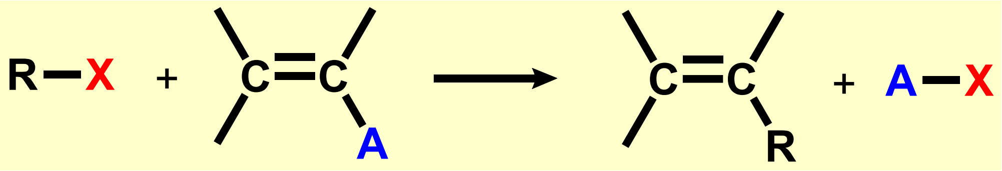


Based on fragmentation of weak bonds C-A (allylic) in *beta* position to the radical center after the addition to the olefin.

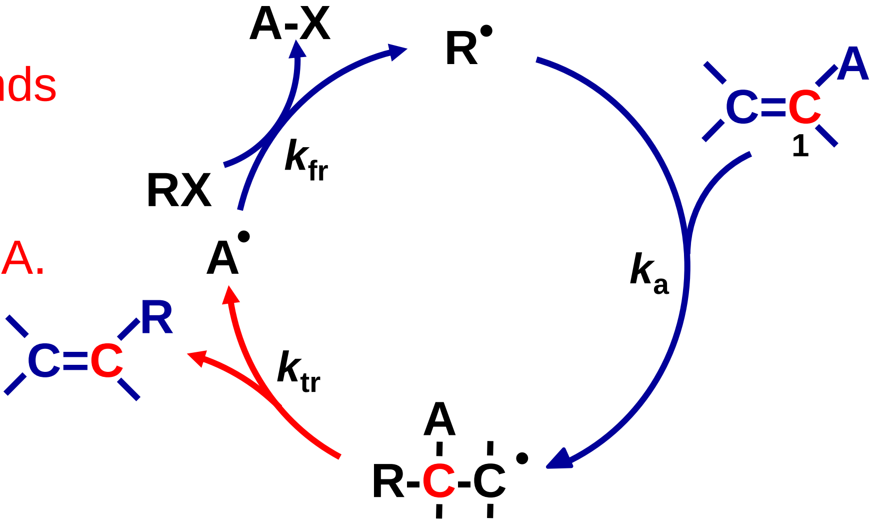
$R\text{-}Cl + CH_2{=}CH\text{-}CR_2\text{-}SnR_3 \rightarrow R\text{-}CH_2\text{-}CH{=}CR_2 + R_3SnCl$

G.E. Keck, Y. B. Yates *J. Am. Chem. Soc*. 1982, 106, 5829.
Tetrahedron, 1985, 41, 4079; Baldwin, *J. Org. Chem*. 1985, 25, 3211.

“1-Addition/1-Fragmentation”



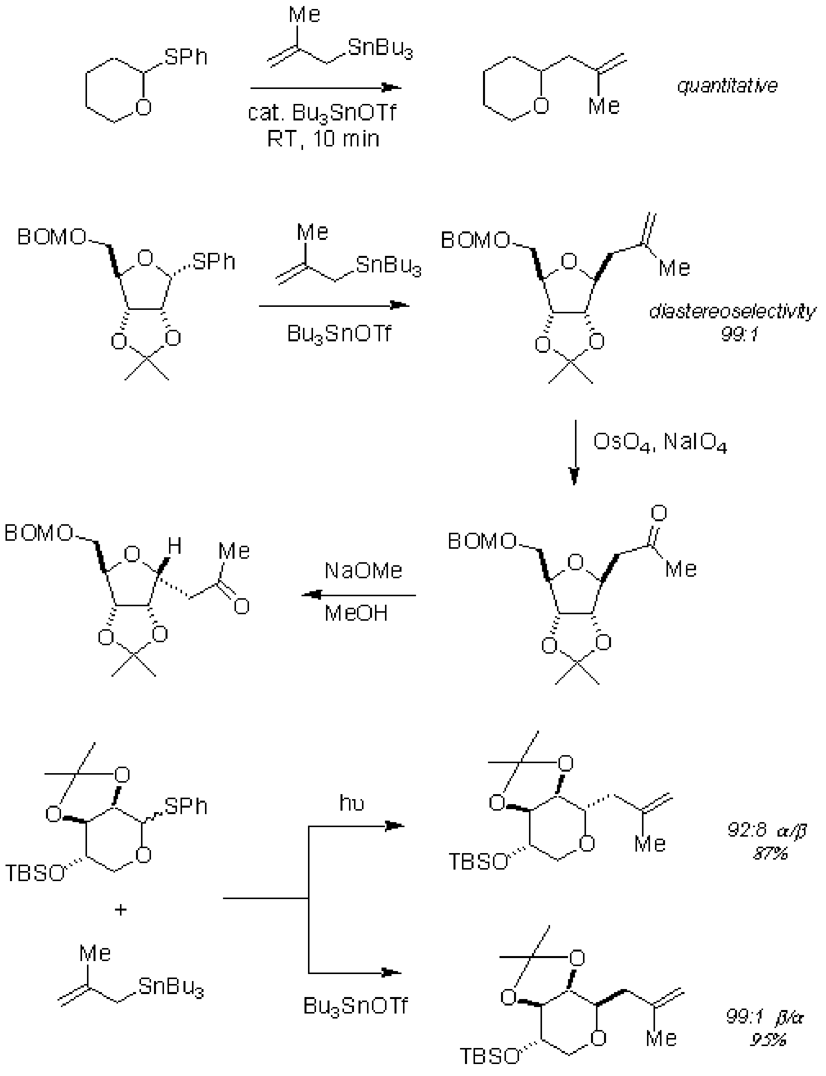
Based on fragmentation of weak bonds C-A in *beta* position to the radical center after addition to the olefin on carbon atom bearing the substituent A.

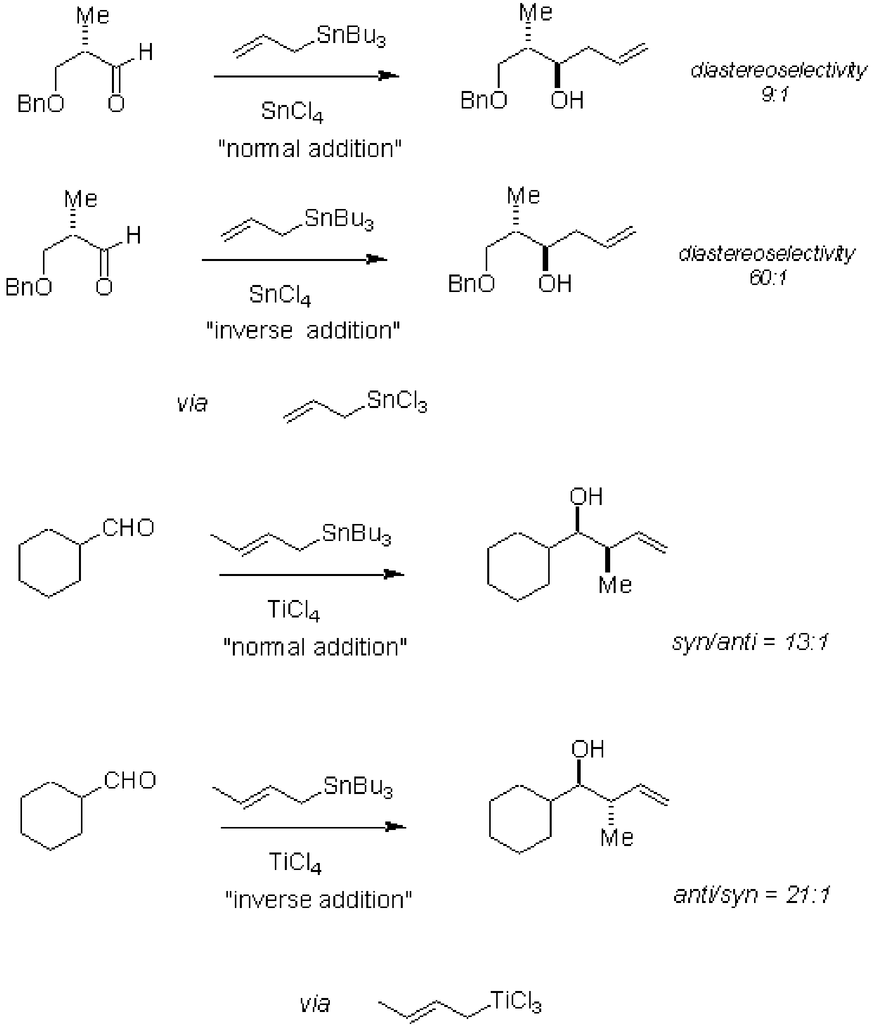


R-Br + ROOC-CH_2=CH-SnR_3 → ROOC-CH=C-R + R_3SnBr

Baldwin, *JCS Chem. Com*. 1983, 133.

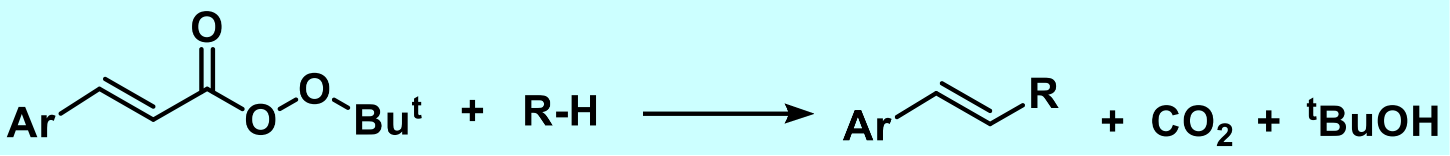
C-Glycosides and Trans Metalation Reactions





Example of 1-Addition/1-diFragmentation

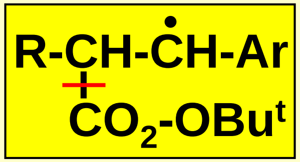
(Insertion of a styryl group on C-H bonds)



Radical Chain

$^{t}BuO^{\cdot}$ + R-H → $R^{\cdot}$ + $^{t}BuOH$

$R^{\cdot}$ + Ar-CH=CH-CO_3R' →

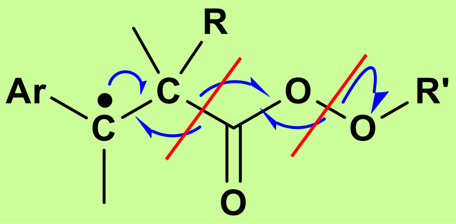


$$R\text{-}\underset{\displaystyle CO_2\text{-}OBu^t}{\cancel{CH}}\text{-}\dot{C}H\text{-}Ar$$

→ R-CH=CH-Ar + CO_2 + $^{t}BuO^{\cdot}$

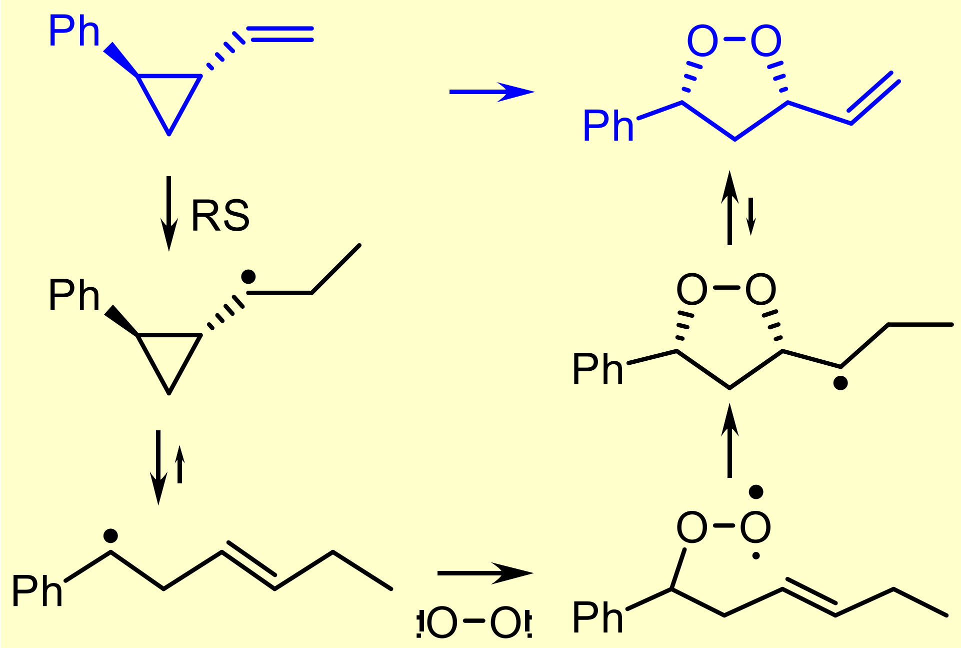
Radical (R)	Yield %
Cyclooctyl	78
2,3-adamantyl	88
$PhCH_2$	86
Dioxanyl	75
DMF	81
PhCO	45
2-THF	85
Polyethylene	75-85

Consecutive *beta* fragmentation of C-CO and O-O bonds.



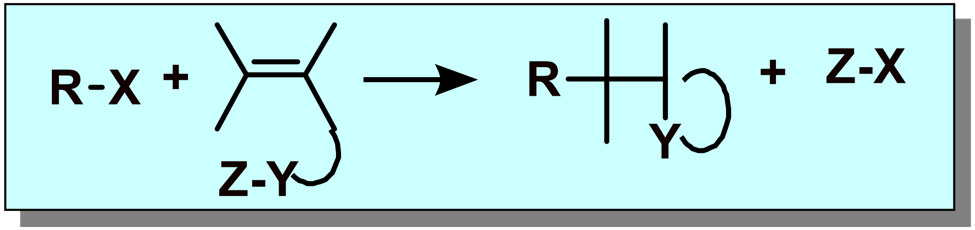
A. Citterio et al. unpublished results

Example of Insertion in Cyclopropane Ring

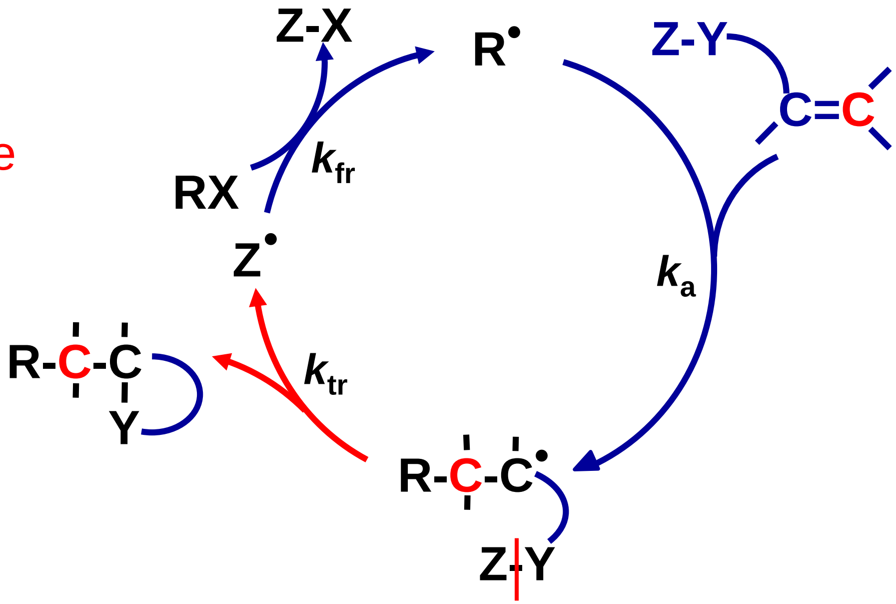


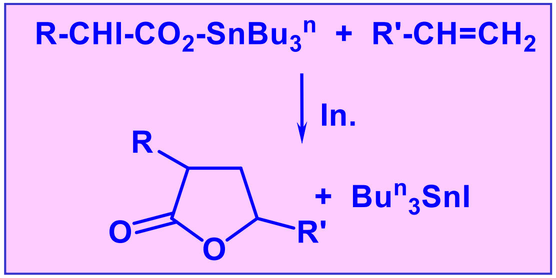
K.S. Feldman, *J. Am. Chem. Soc*. 1986, 108, 1328.
S.C. Shim, J. S. Song, *J. Org. Chem*. 1986, 108, 51 2817.

Synthetic Strategy “Addition/Displacement”



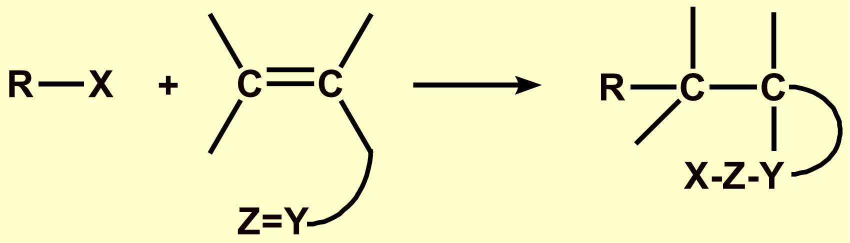
Based on the displacement of weak bonds in appropriate positions to the radical center after the addition to the olefin.



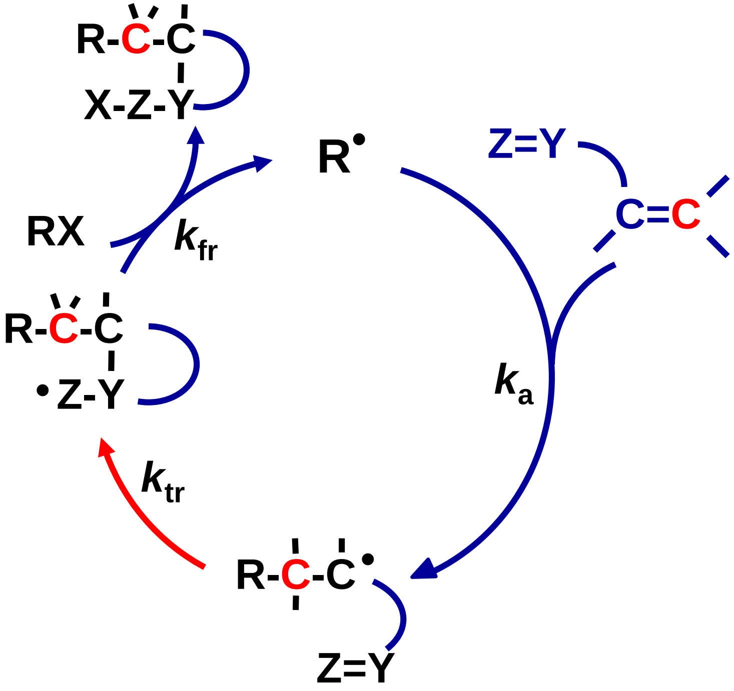


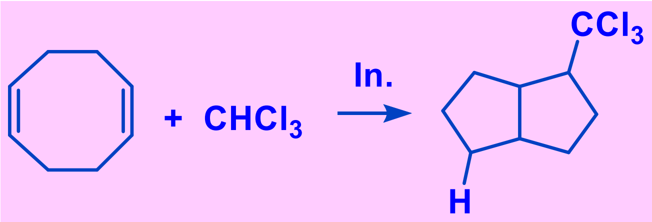
G.A. Kraus *Tetrahedron*, 1985, 41, 4039; For reactions on peroxide Z-Y bonds, see Maillard, *Tetrahedron*, 41, 4047 (1985).

Synthetic Strategy “Addition/Displacement”



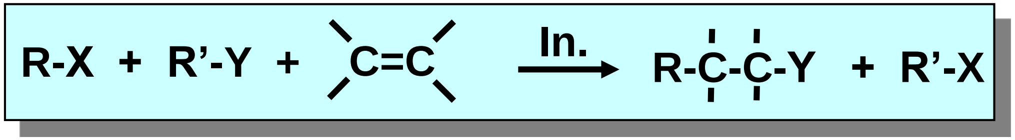
Based on “tandem” additions to unsaturated Z=Y systems at appropriate distance to the radical center of first addition.





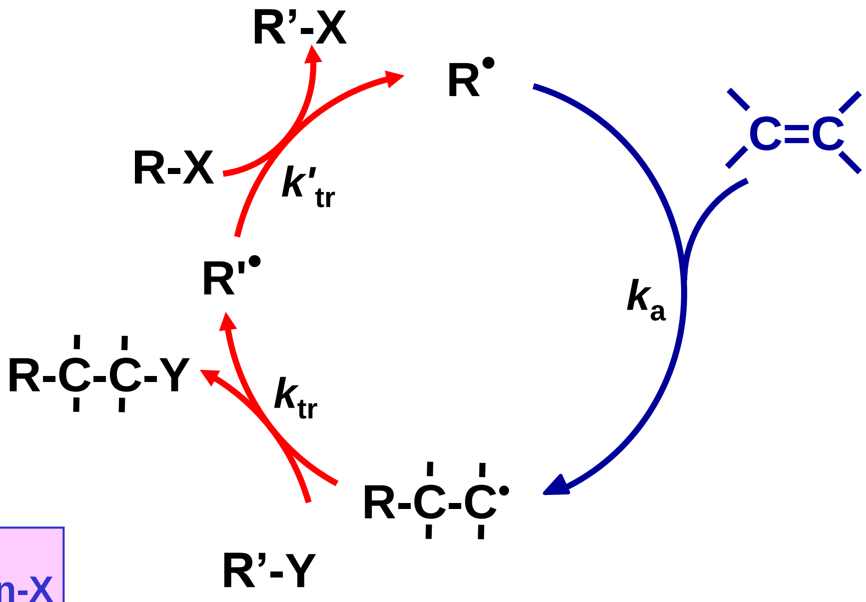
R. Dowbenko, *J. Am. Chem. Soc*. 1964, 86, 946.

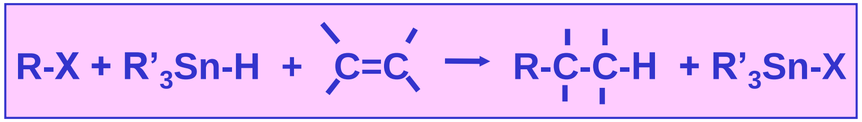
Synthetic Strategy “Assisted Addition”



$$\text{R-X} + \text{R'-Y} + \text{C=C} \xrightarrow{\text{In.}} \text{R-C-C-Y} + \text{R'-X}$$

Based on different thermodynamic stability of R’-X compared to R’-Y.



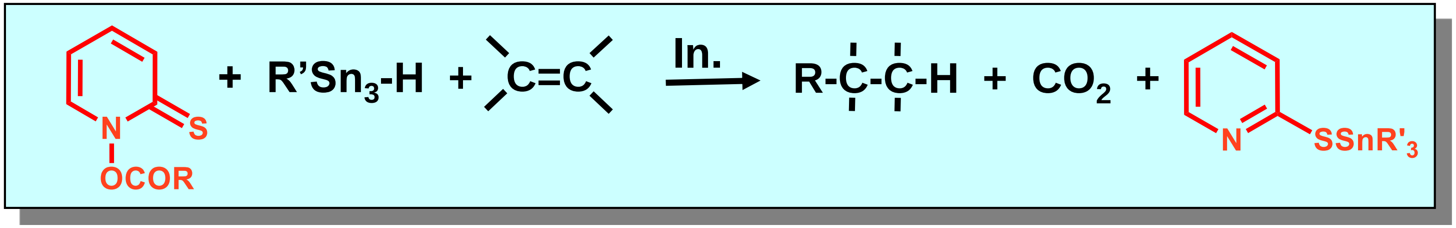


$$\text{R-X} + \text{R'}_3\text{Sn-H} + \text{C=C} \rightarrow \text{R-C-C-H} + \text{R'}_3\text{Sn-X}$$

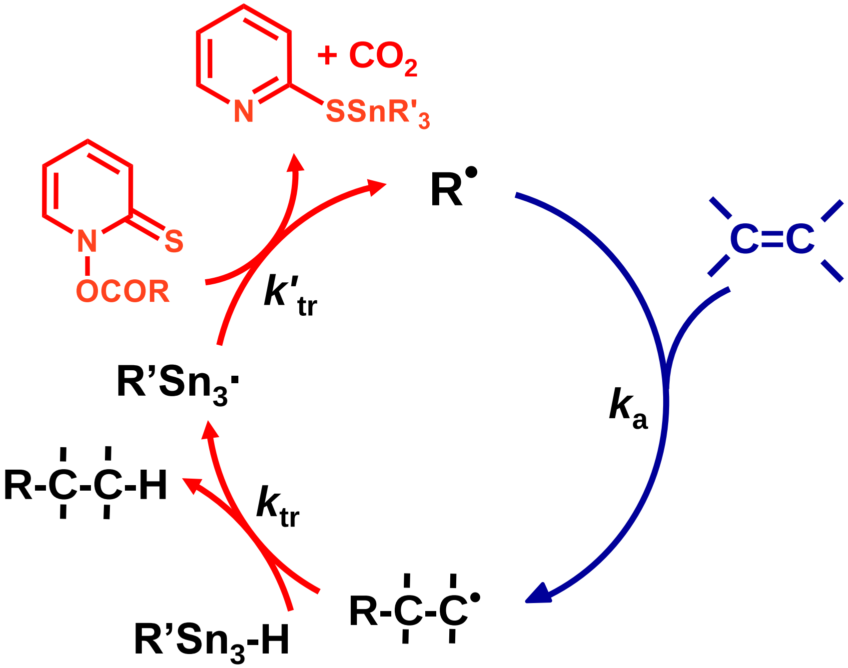
X = Cl, Br, I, SePh, SR, NO_2

H.G. Kuivila, *Synthesis*, 1970, 499; S.D. Burke, *J. Org. Chem*., 1982, 47, 3348,
N. Ono, *Tetrahedron*, 1985, 41, 4013.

Assisted Addition/Fragmentation

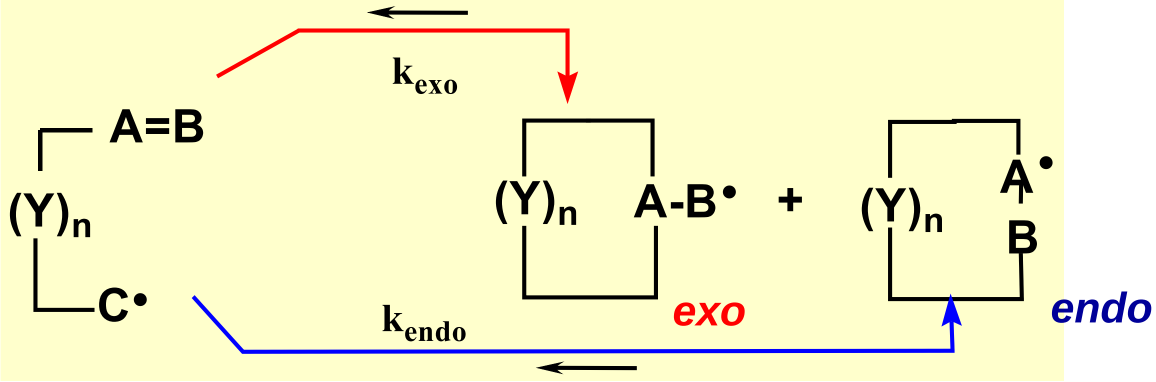


Based on the easy addition of radicals on thiocarbonyl group (C=S) and to consecutive fragmentation of α-oxyaminoalkyl radical induced by aromatization.



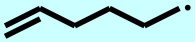
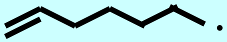
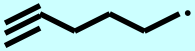
D.H.R. Barton, *Heterocycles*, 1984, 21, 1; *Pure Appl. Chem*., 1981, 53, 1081.
D. Colombani, *Prog. Polym. Sci*. 24 (1999) 425–480

Homolytic Cyclizations on Unsaturated Systems



exo = 1,n

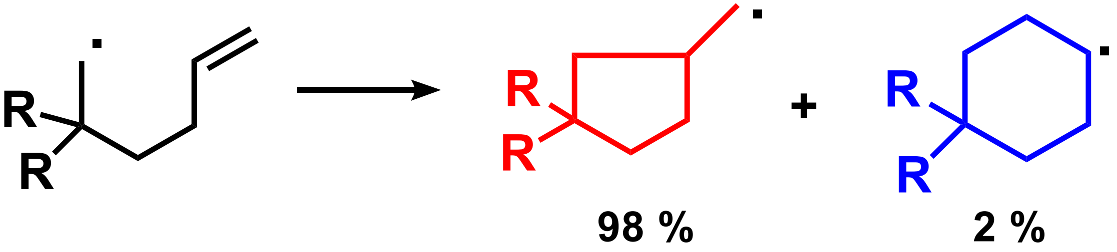
endo = 1,n+1

Radical	% *exo*	k_{exo} (s^{-1})	k_{endo} (s^{-1})
	100	1.8×10^4	-
	100	7×10^{-1}	-
	98	2.3×10^5	7×10^3
	85	1.1×10^4	1.9×10^3
	100	3×10^2	-
	100	4.6×10^4	-

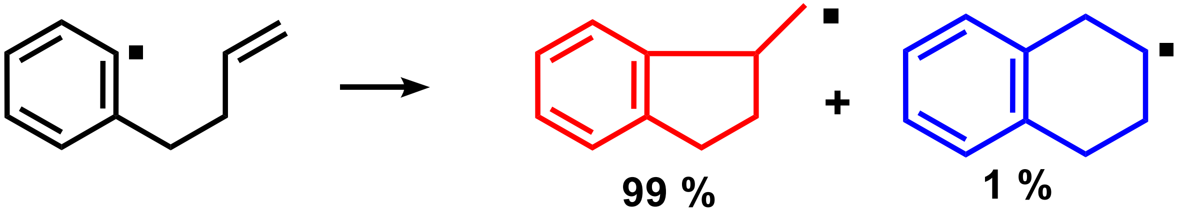
Rate constants (65°C) for ring closure of ω-alkenyl radicals

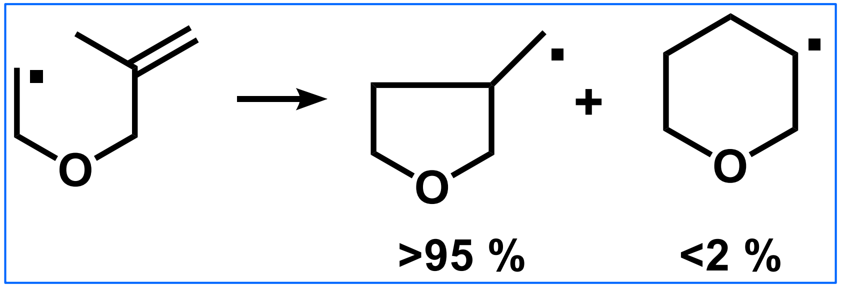
H. Fisher, *Landölt-Börnstein, New Ser. Vol 13 a-e* (1983-1985); A.L.J. Beckwith, K.U. Ingold, “*Rearrangements in ground and exited states*”, P. de Mayo Ed. Acad. Press. (1980).

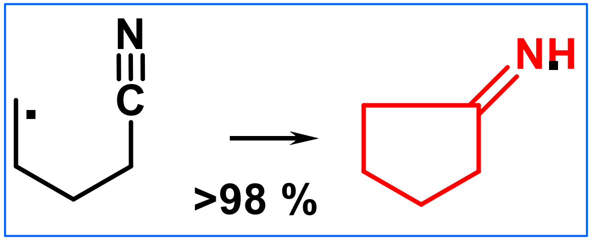
Regioselectivity in the 1,n-Cyclization

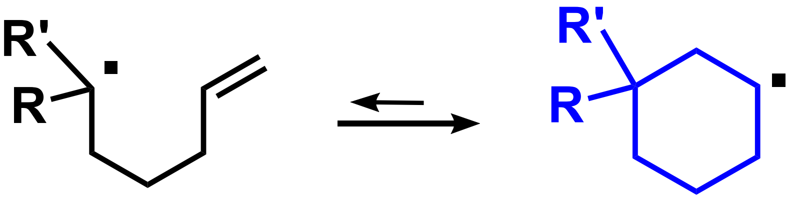


kinetic control







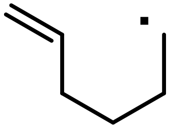
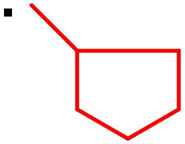
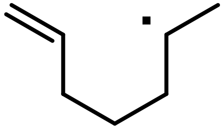
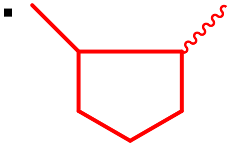
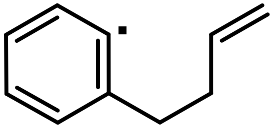
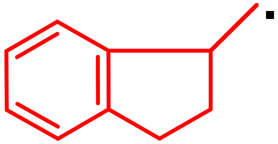
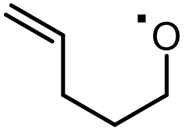
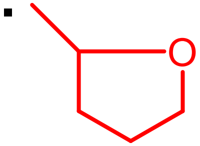
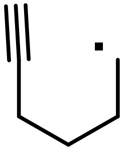
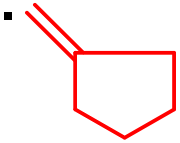
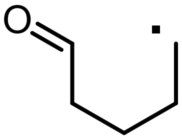
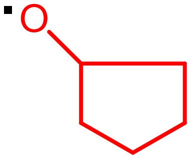


thermodynamic control

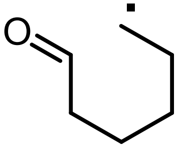
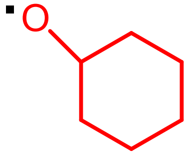
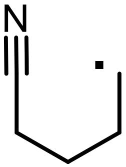
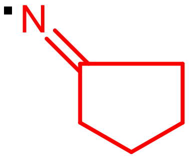
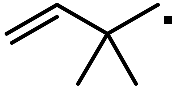
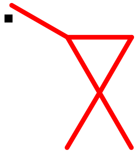
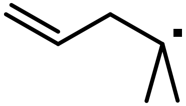
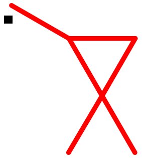
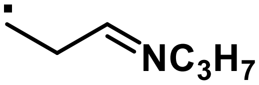
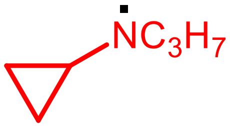
R = CO$_2$Et, R' = CN (>95%)

R = R' = CH$_3$(1%), *exo* (99%)

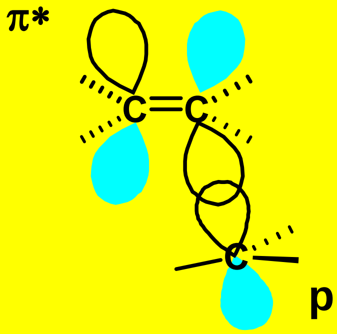
Cyclization-Opening Rate of Relevant Radicals (at 25 °C)

Initial radical	$\rightleftharpoons$ cyclized radical	k_c (s^{-1})	k_o (s^{-1})
		2.3×10^5	-
		1.0×10^5	-
		5×10^8	-
		6×10^8	-
		1×10^5	-
		8.7×10^5	4.7×10^8

Cyclization-Opening Rate of Relevant Radicals (at 25°C)

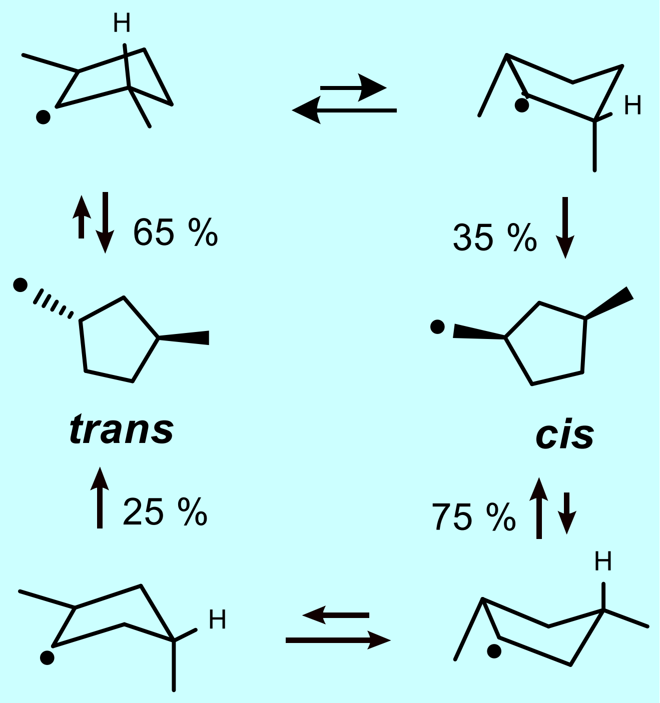
Initial radical	$\rightleftharpoons$	cyclized radical	k_c (s^{-1})	k_o (s^{-1})
			1×10^6	1.1×10^7
			4×10^3	-
			1.7×10^7	3×10^8
			$< 3\times10^4$	1.7×10^9
			-	2.5×10^7

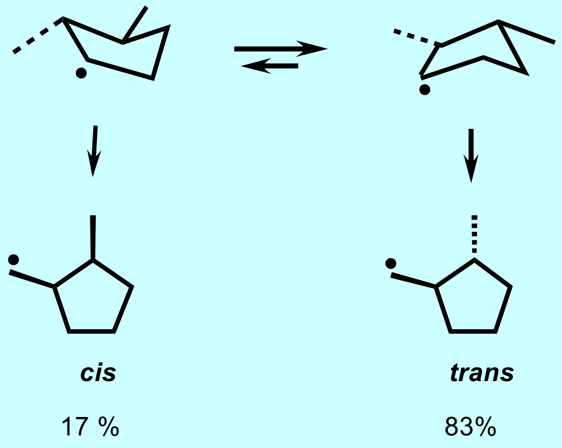
Substituent Effects on Stereochemistry



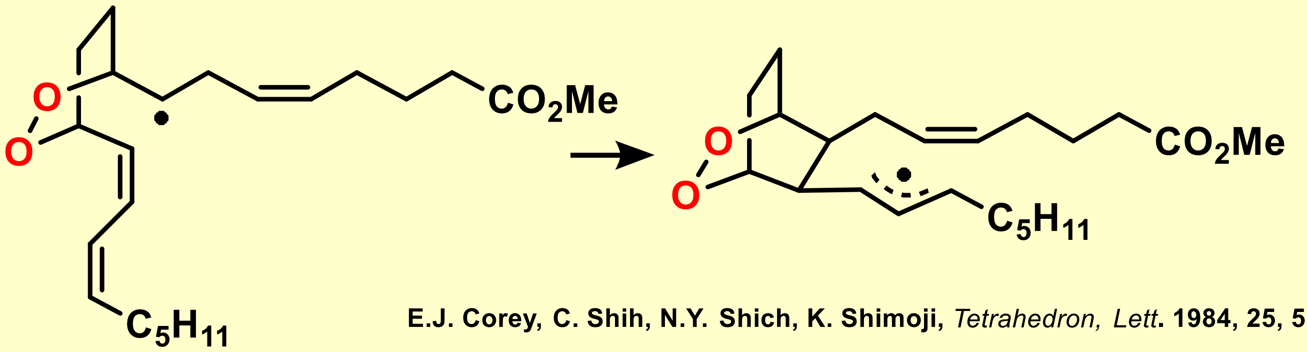
Transition State
(nucleophilic radical)

2- and 4- substituted 5-Hexenyl radicals afford *trans*-cyclopentanes, whereas the 1- e 3-sostituted afford *cis*-cyclopentanes.

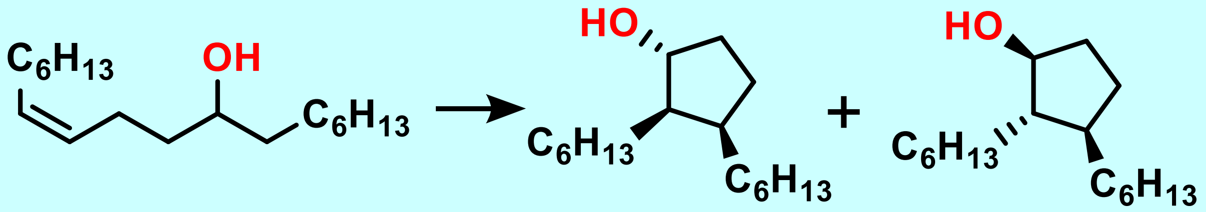




Examples of Radical Cyclization

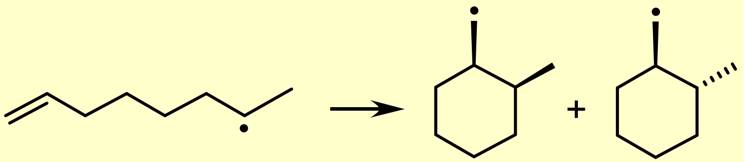


E.J. Corey, C. Shih, N.Y. Shich, K. Shimoji, *Tetrahedron, Lett*. 1984, 25, 5013.



D.G. Wujek, N.A. Porter,
***Tetrahedron*, 1985, 41, 3973**

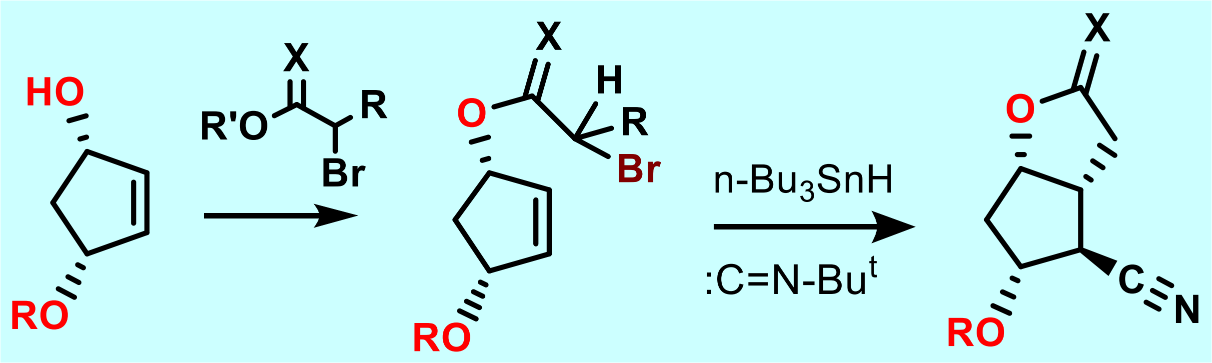
C_6H_6/H_2O 50 : 50
$C_6H_6/H_2O/Ts$ 70 : 30



73:27

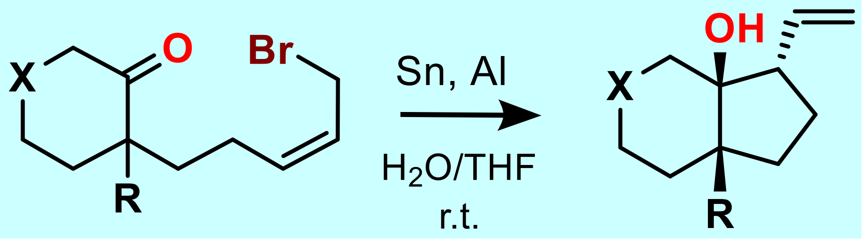
Curran *Synthesis* **1988**, 417,489,
Chem. Rev. **1991**, 91, 1,
Ramiah *Tet.* **1987**, *43*, 3541
Jorgensen *JOC* **1990**, *55*, 9

Stereo-chemical Control in Radical Cyclizations



G.Stork, P.M. Sher, H.-L.Chen, *J. Am. Chem. Soc*. 1986, 108, 6384; *Bull. Soc. Jpn*. 1988, 61, 149.

R = Me, X = H,OMe (60%)
R = Me, X = O (20 %)
R = THP, X = H,OMe (30%)

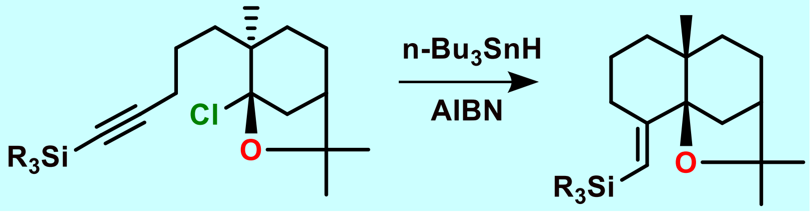


(80%)

Nokami, *Chem. Lett*., 1984, 21, 1;

Cyclization with Functionality Retention

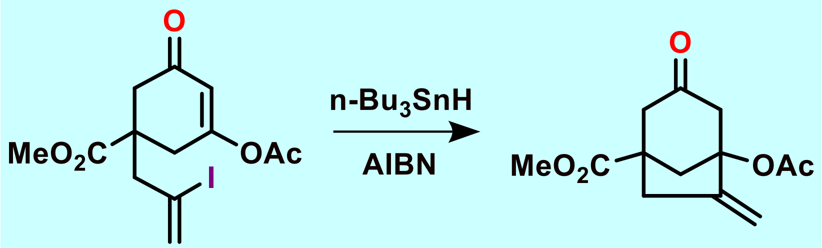
A) Reductive addition to acetyenic or allenic derivatives



G.Buchi, H.Wuest, *J.O.C*. 1979, 44, 546.
D.J.Hart, J.K.Choi, *Tetrahedron*, 1985, 3959.

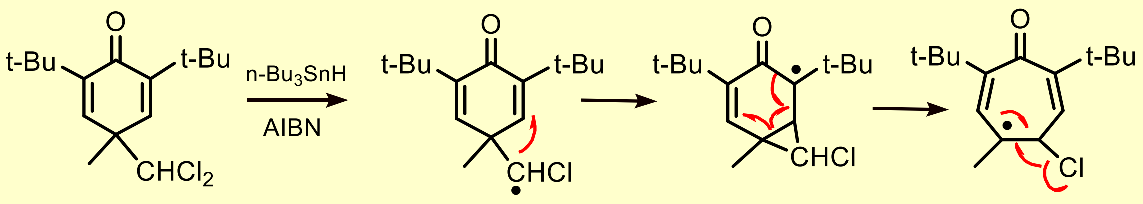
Mainly C-1,6 with bulky substituents

B) Reductive addition of vinyl radicals



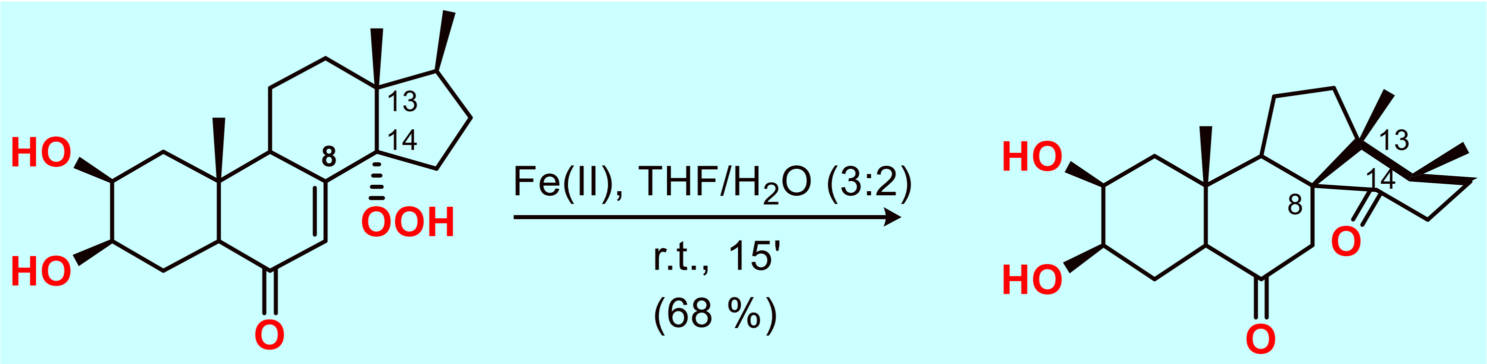
M.N. Marinovic, *Tetr. Lett*., 1984, 1871;
G. Stork, *J. A. C. S*.1982, 104, 2321

C) Reductive additions of haloalkyl radicals with rearrangement

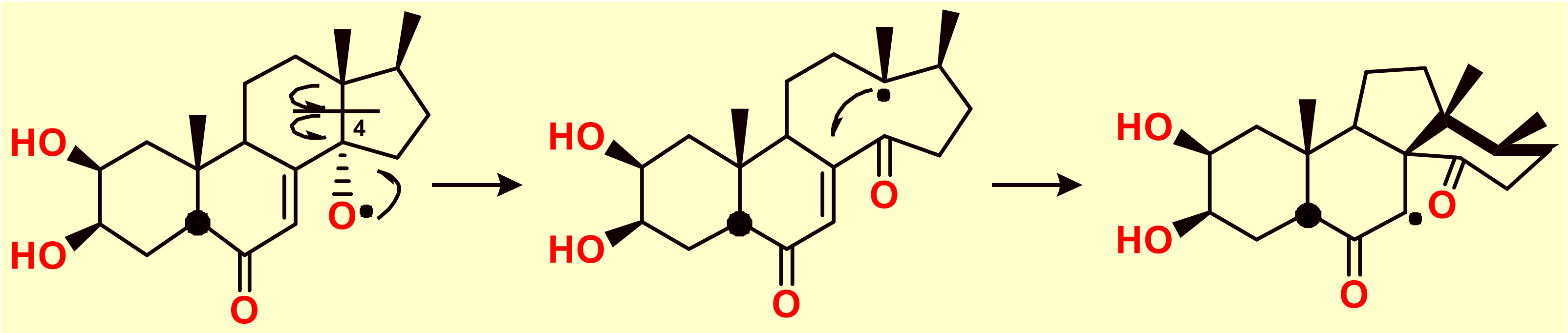


Barton, *Tetr. Lett.*,
1984, 2787.

Intramolecular Fragmentation/Addition

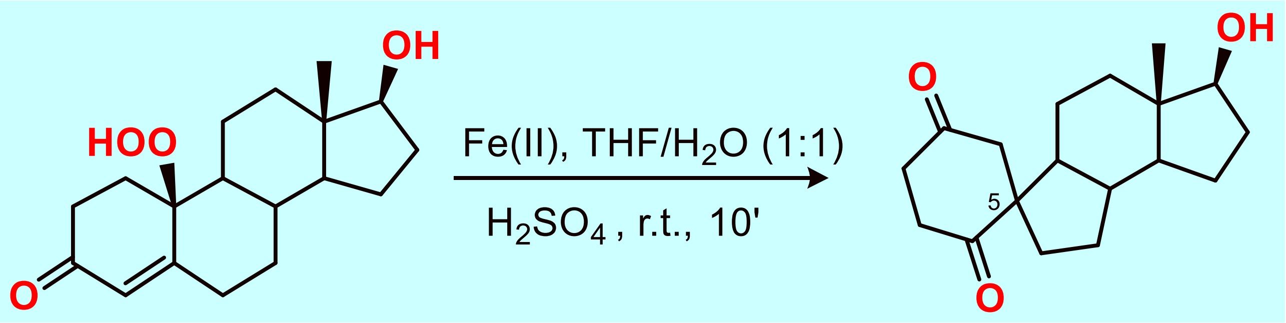


Fused ring rearrangements in the reduction of tertiary hydroperoxides.



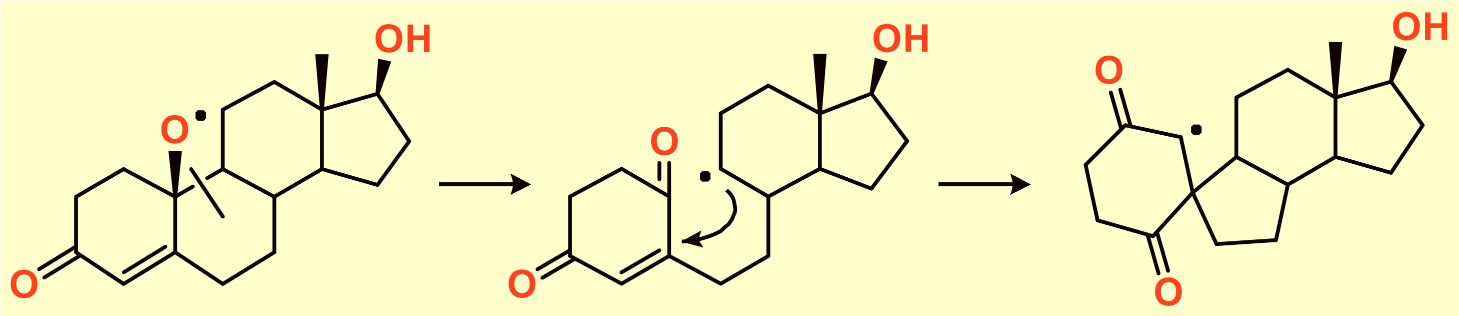
*A. Citterio, R. Santi** "Use of Homolytic Redox Processes in Organic Synthesis"
NATO ASI Series, C 260 (F. Minisci Ed.), Kluver, 187 (l989)

Intramolecular Fragmentation/Addition

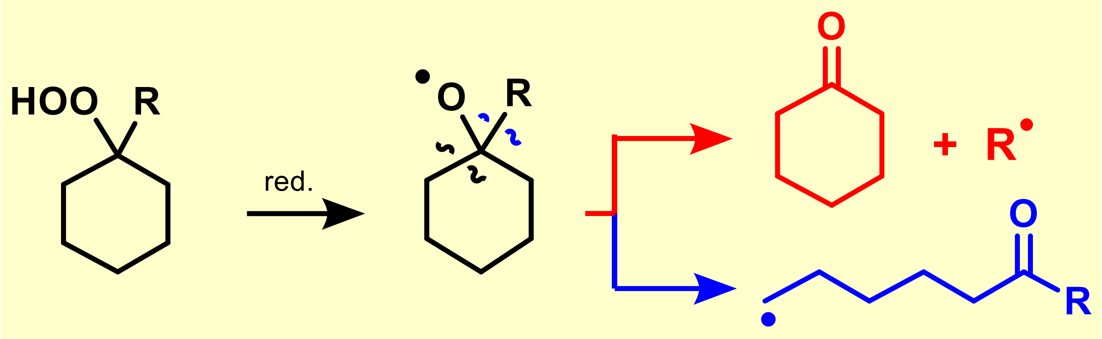


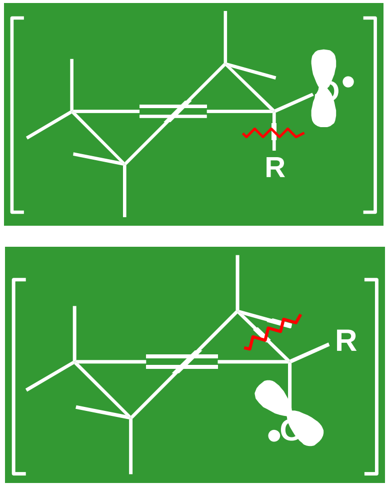
5R : 5S = 1:1 (65 %)

Selective beta-fragmentation, addition non stereo-selective

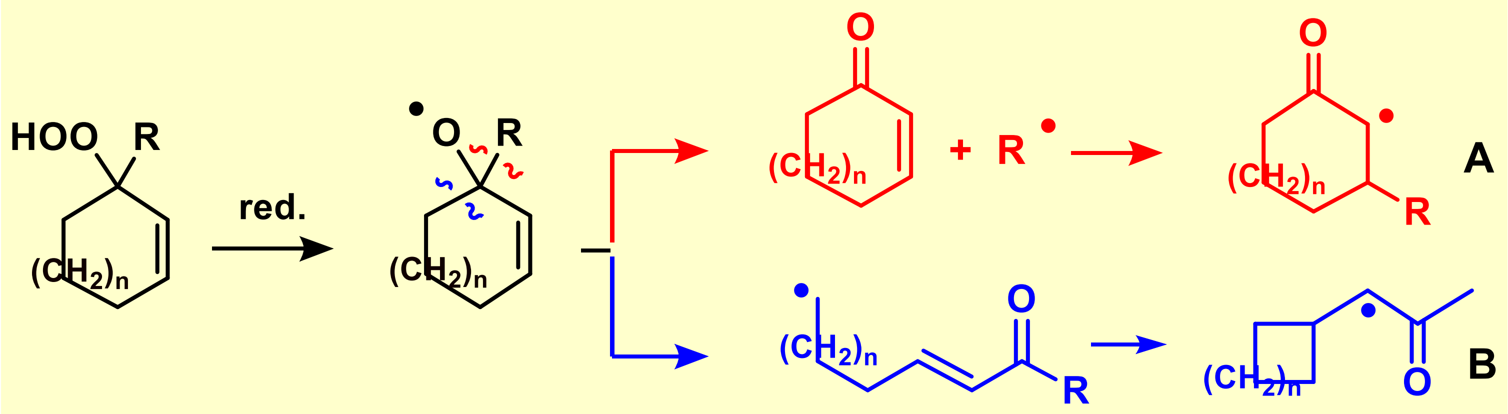


Stereo-selectivity in the Fragmentation of Tertiary and Allyl Hydroperoxides

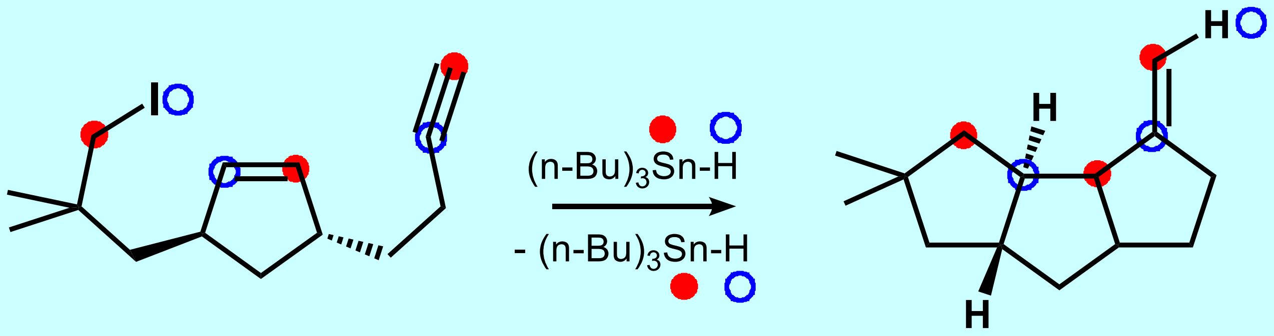




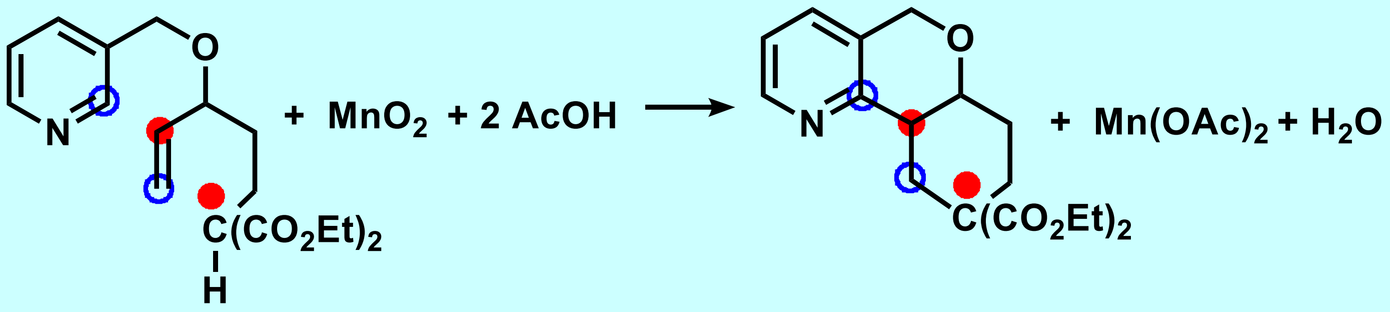
First path preferred or exclusive with bulky R.



Tandem Radical Cyclisations



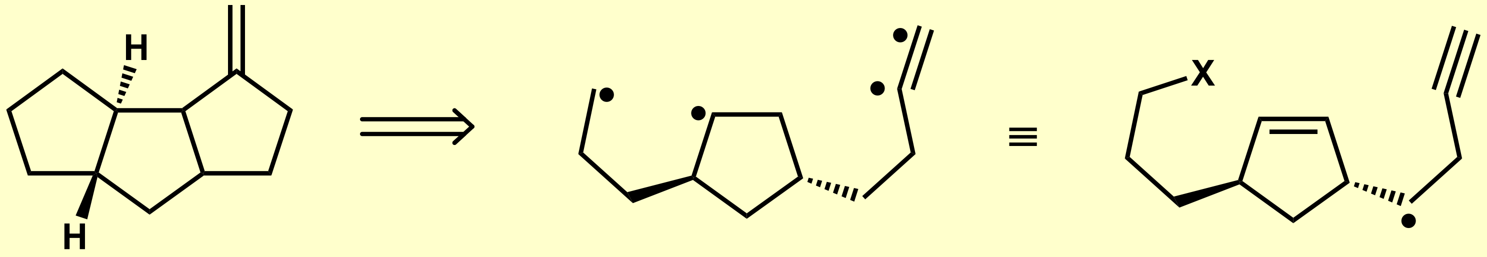
Curran, *Adv. Free Rad. Chem*. 1991, 1, 127



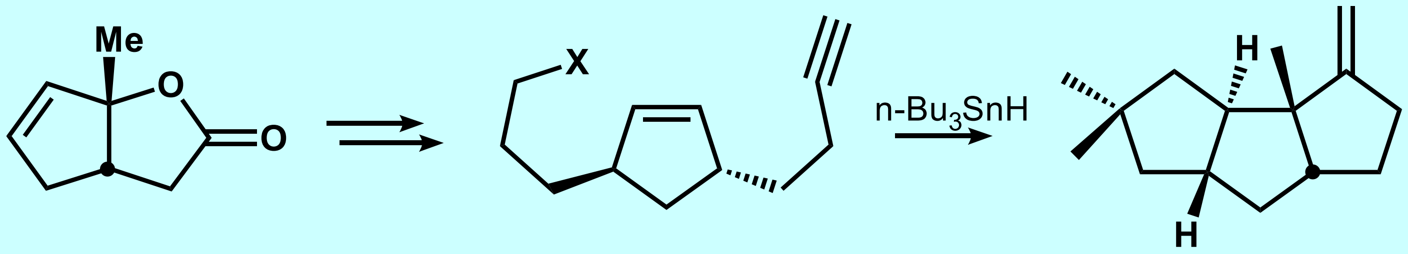
Citterio, *J. Org. Chem*. 57, 4250 (1992)
Snider, B. B. *Chem. Rev*., 96, 339 (1996)

Tandem Cyclization Design

Linear Triquinanes



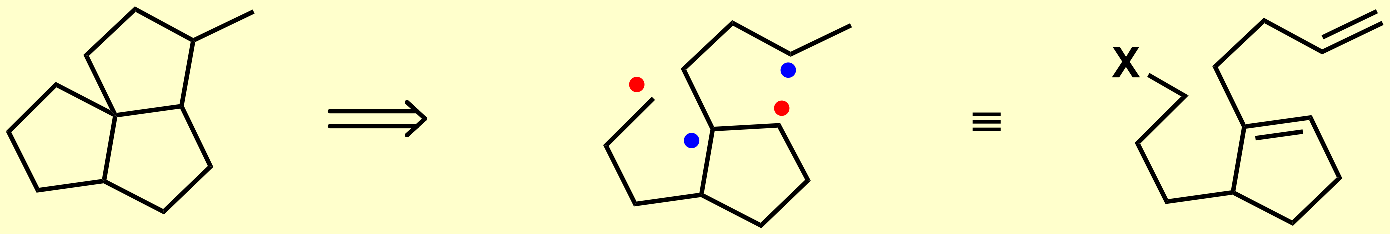
Synthesis of Irsutene



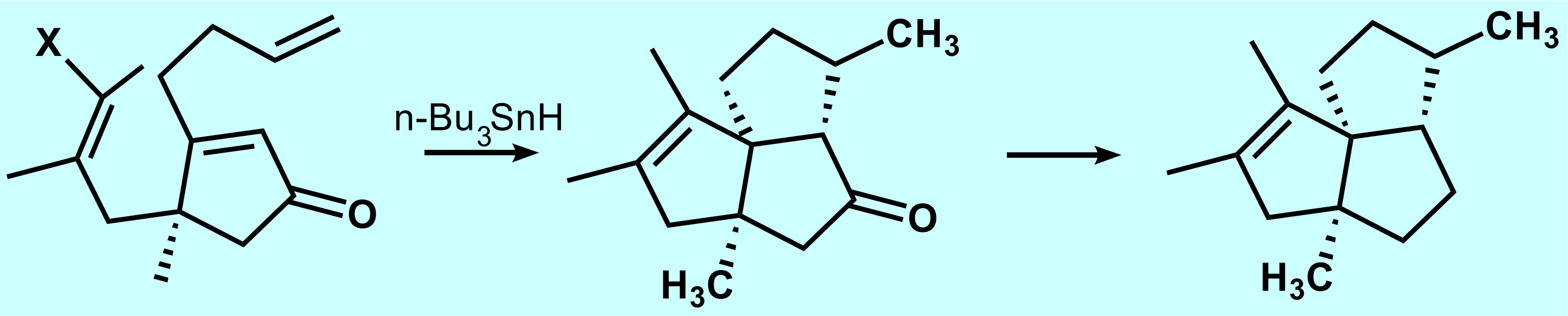
Curran, *Adv. Free Rad. Chem.* 1991, 1, 127

Tandem Cyclization Design

Angular Triquinanes

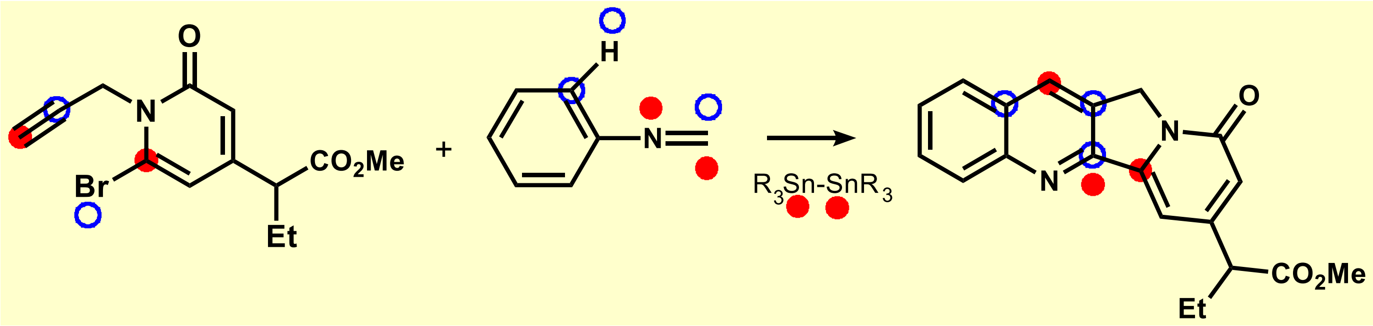


Synthesis of Silfiperfolene

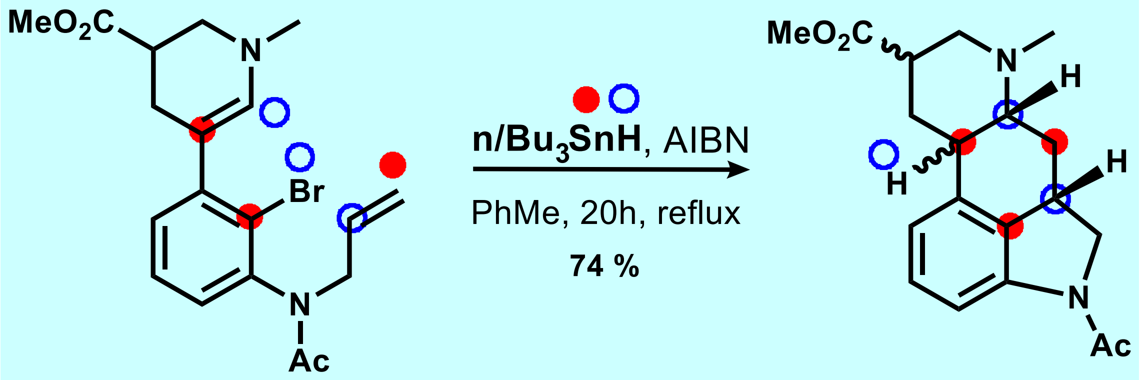


Curran, *Adv. Free Rad. Chem*. 1991, 1, 127

Tandem Radical Cyclisations

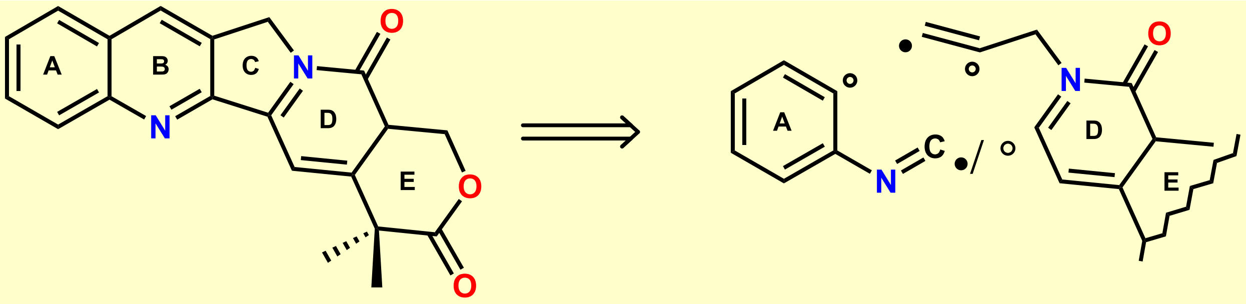


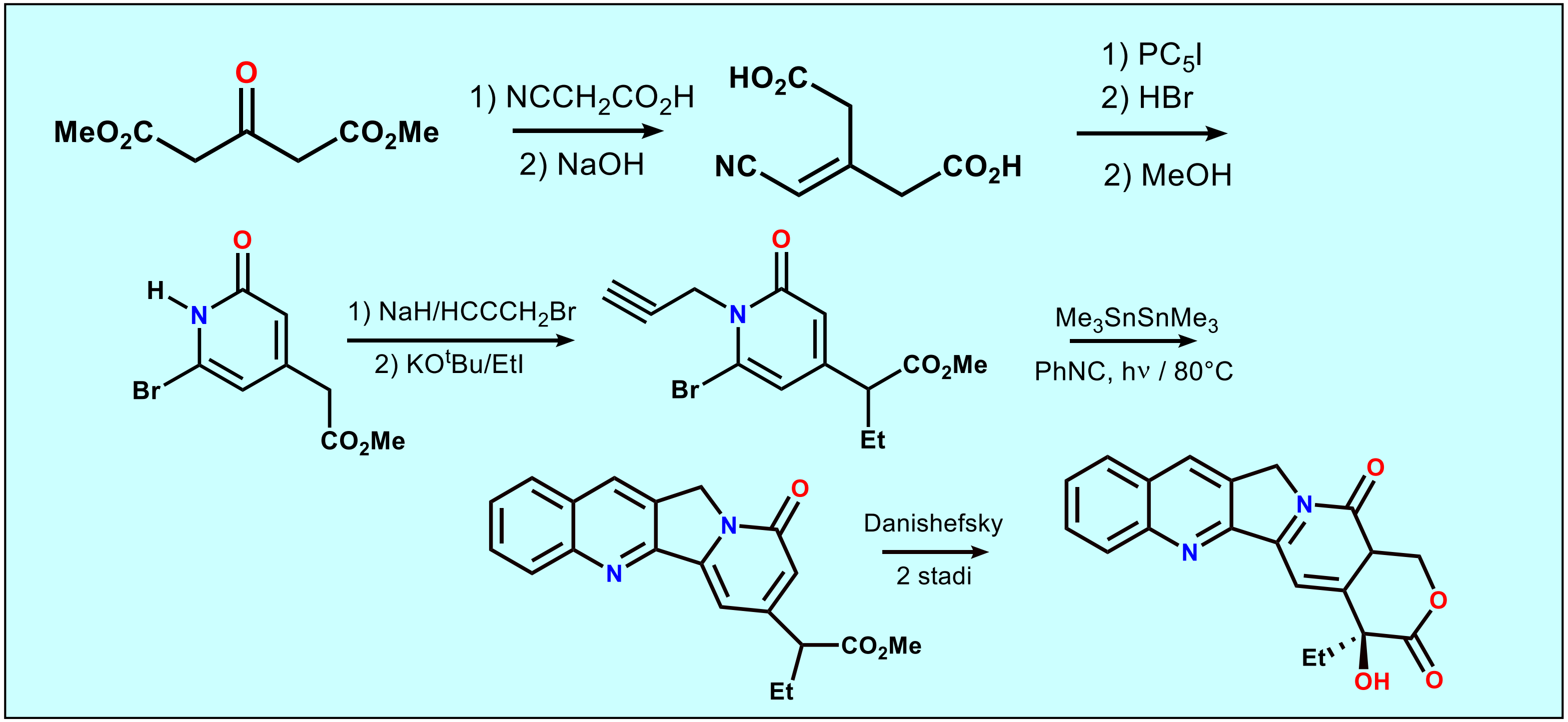
Curran (1992)



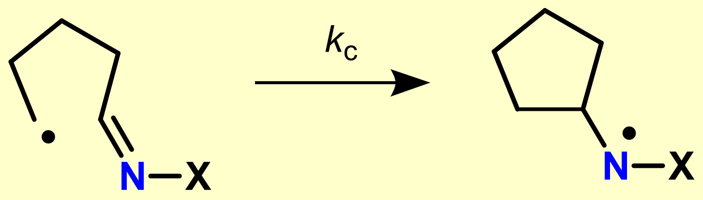
Parsons, *Synlett*, 357 (1993)

Synthetic Design of Camptotechin



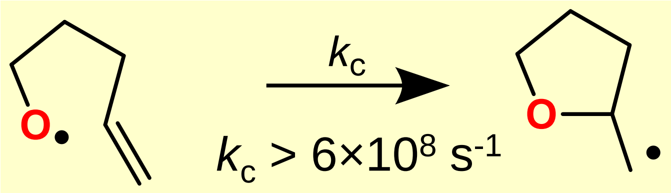


Cyclization of Oxygen-and Nitrogen-Centered Radicals

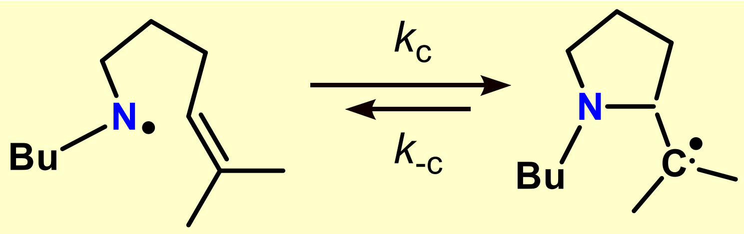


X=CH$_2$Ph	k_5 (s^{-1})	k_6 (s^{-1})
	6.2×10^6	6.7×10^5
OBn	4.2×10^7	2.9×10^6
NMe$_2$	7.6×10^7	3.1×10^6

$R_3C^{\bullet}$	$R_2\ddot{N}^{\bullet}$	$R\ddot{\underset{\cdot\cdot}{O}}^{\bullet}$
k_H ~ 3×10^6	8×10^4	2×10^8 M$^{-1}\cdot$s^{-1}



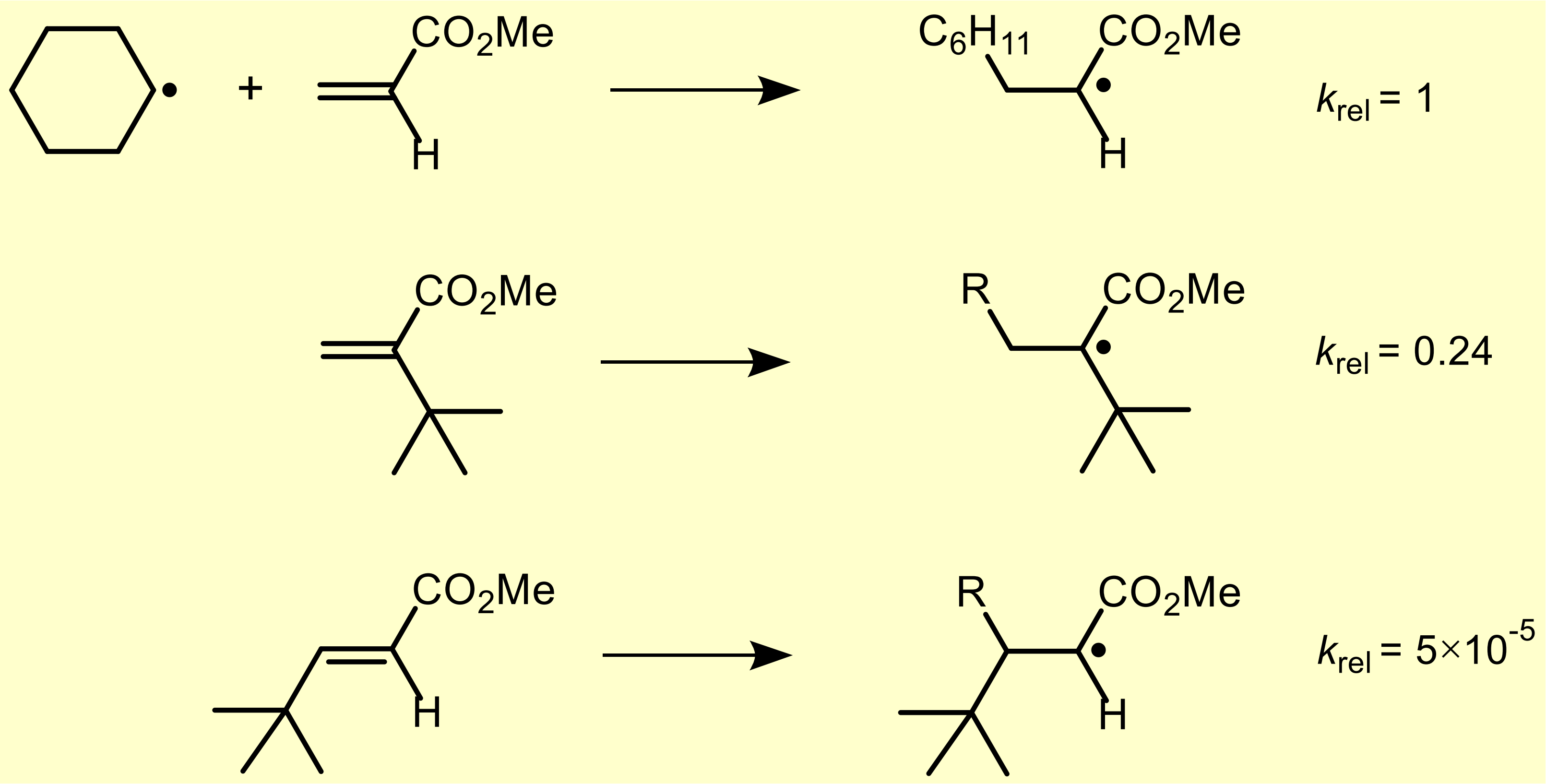
$k_c > 6\times10^8$ s^{-1}



$k_c \approx 3\times10^3$ s^{-1}

$k_{-c} \approx 7\times10^3$ s^{-1}

Steric Effect on Radical Addition



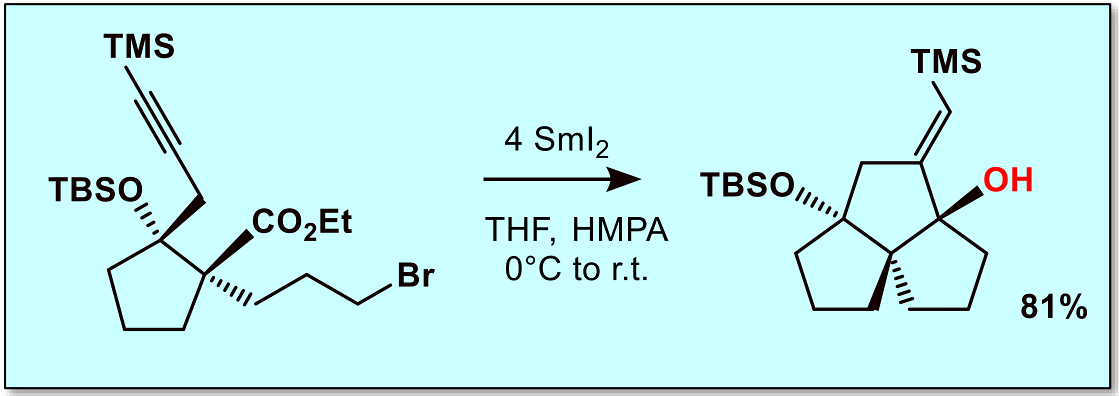
$k_{rel} = 1$

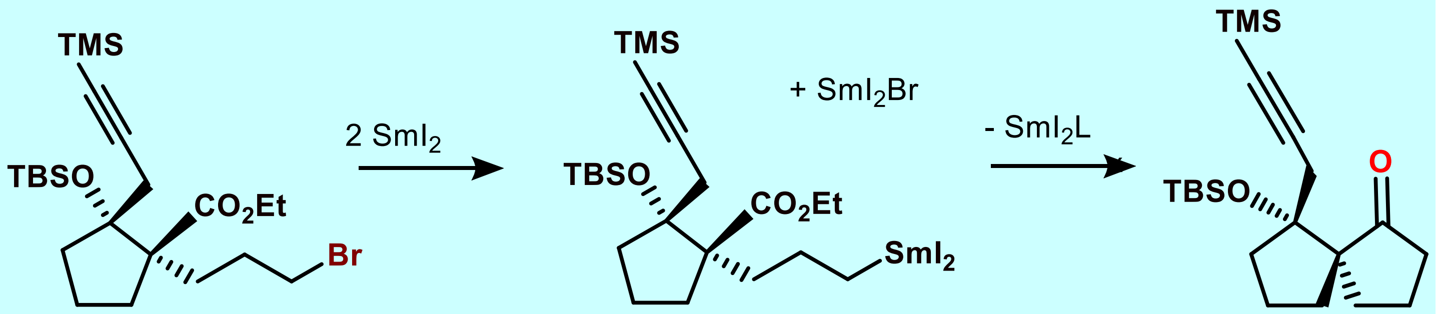
$k_{rel} = 0.24$

$k_{rel} = 5\times10^{-5}$

Samarium Diiodide Promoted Cyclization

- Tandem Anion/Radical - Step 1: The Samarium Barbier reaction gives a ketone:

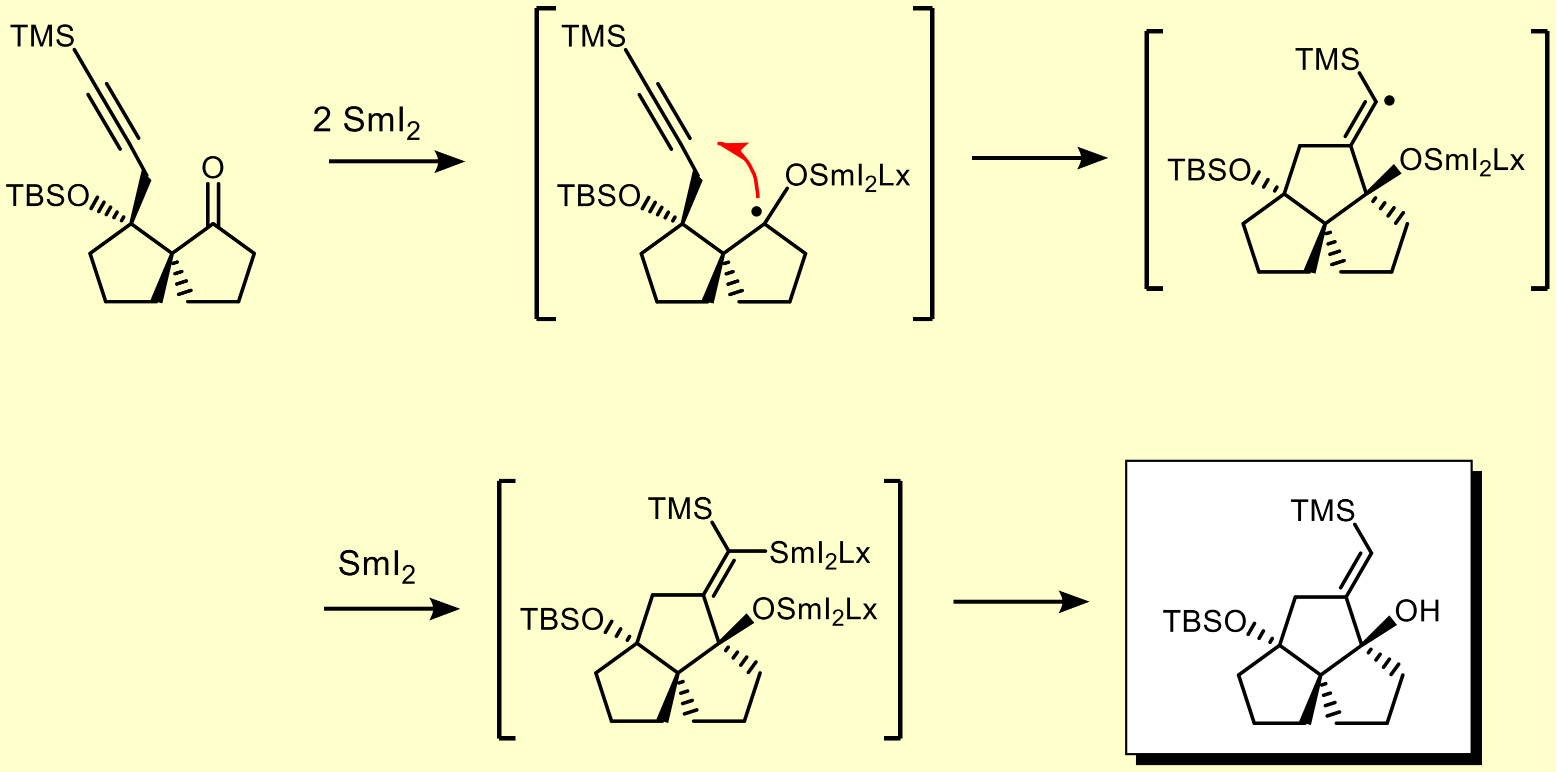




Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1996**, *118*, 4059-4071.

Samarium Diiodide Promoted Cyclization - 2

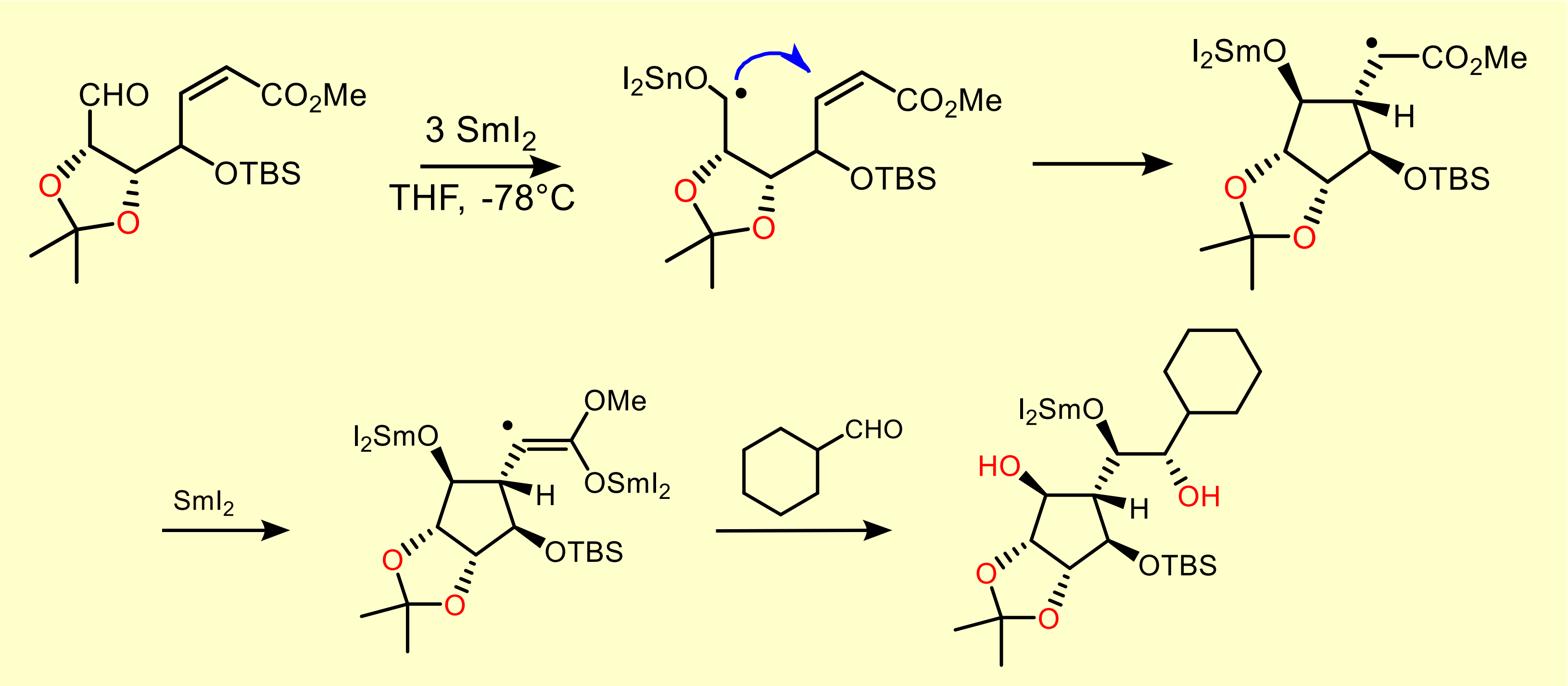
- Anion/Radical tandem- Step 2: The ketone gives a ketyl radical which cyclizes and is reduced.



Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1996**, *118*, 4059-4071.

Samarium Diiodide Promoted Cyclization - 3

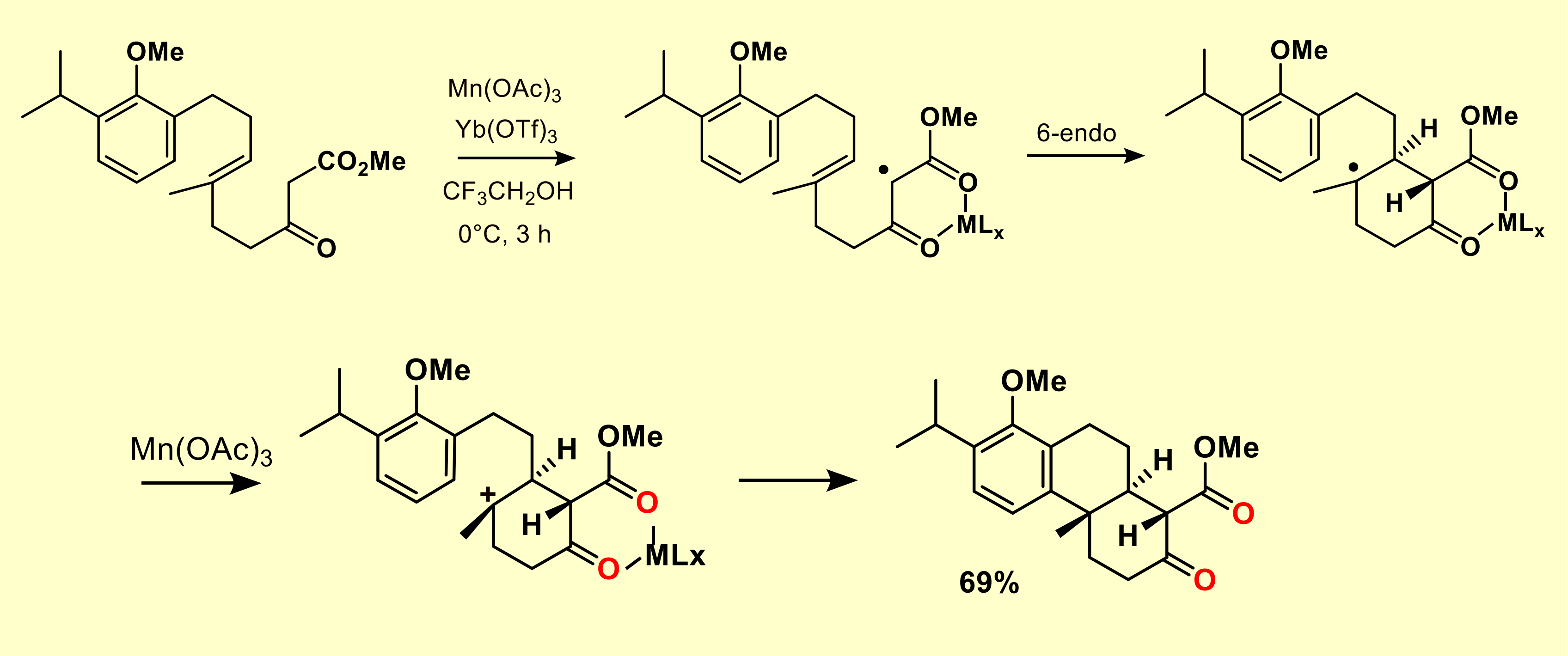
- Radical/Anion tandem: A ketyl radical cyclization followed by reduction to a reactive Sm-enolate.



Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1994**, *35*, 1627-1628.

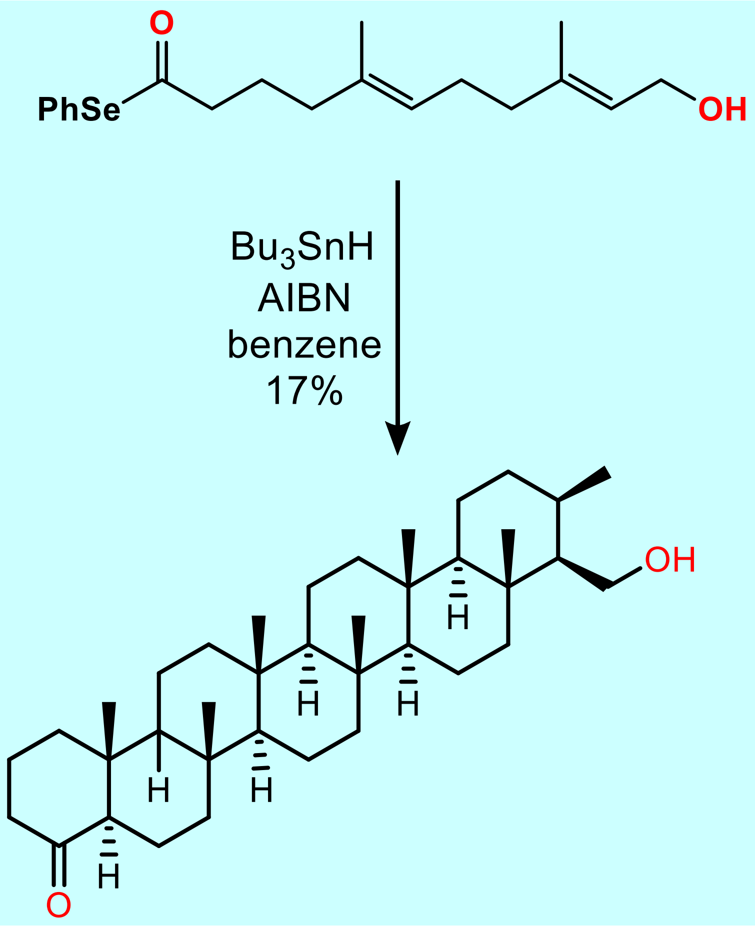
Manganese Radical/Cation Tandem

- Radical reactions of Manganese(III) Acetate terminate by conversion to a cation which can further react intramolecularly by electrophilic aromatic substitution:

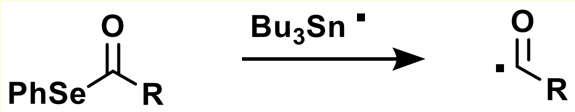


Yang, D.; Ye, X.-Y.; Xu, M. *J. Org. Chem.* **2000**, *65*, 2208-2217.

Tandem Radical Poly-Cyclisation



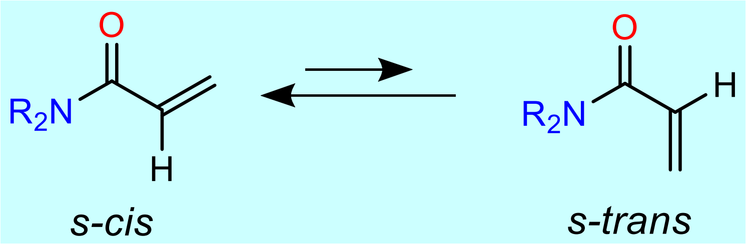
Via acyl radicals

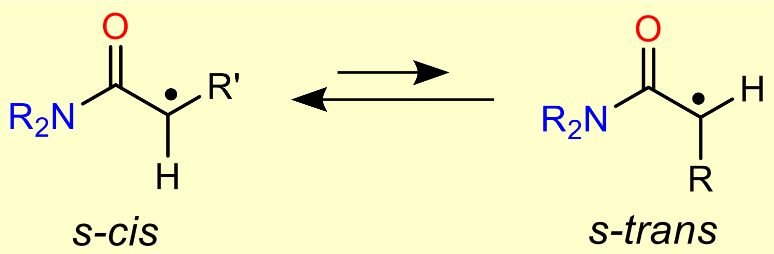


Pattenden, *J. Chem. Soc., Perkin Trans.* 1, **1999**, 843.

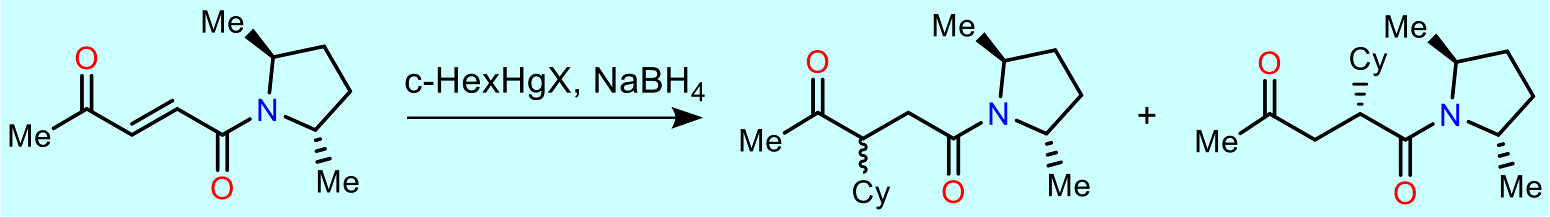
Early Efforts Toward Acyclic Stereochemical Control

- Amide groups were used to provide conformational control.





- C2-symmetric auxiliaries or dipole-dipole effects were used to fix the orientation of the auxiliary.



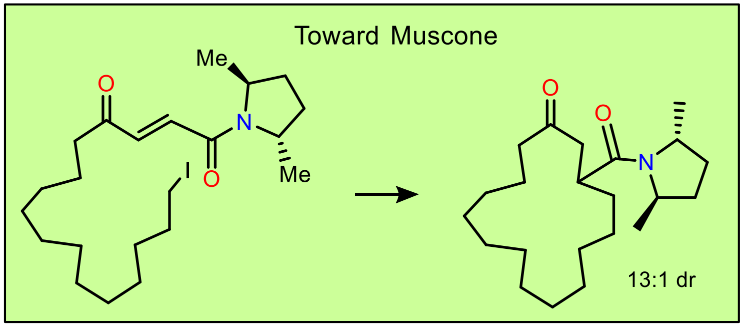
A : **B** = 1:1

A

dr: 60:40

B

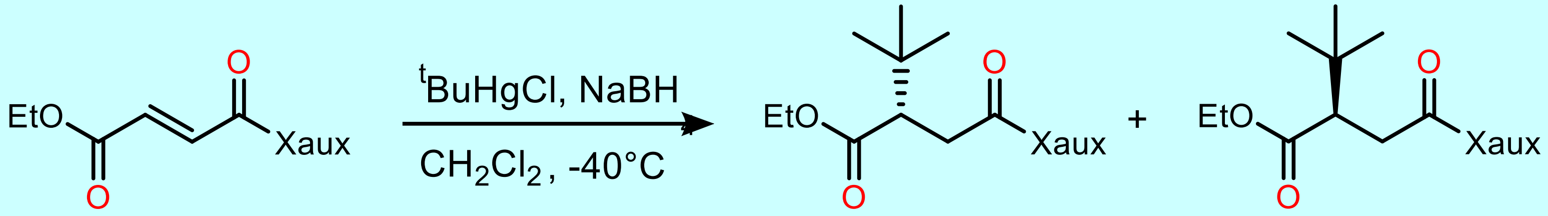
dr: 93:7



Porter, *JACS*, 1989, 111, 8309, 8311.

Early Efforts Toward Auxiliary-Based Control

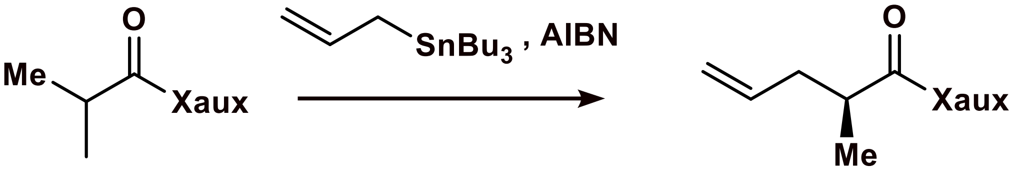
Curran, Rebek - auxiliary that can control β-stereoselectivity

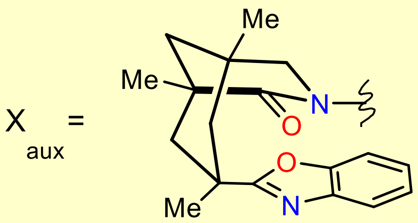


97 : 3

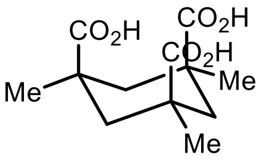
No α-addition was observed under these conditions

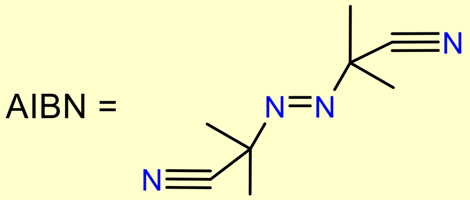
The auxiliary was also effective for radical allylation reactions.





Auxiliary Synthesized
in 7 steps from

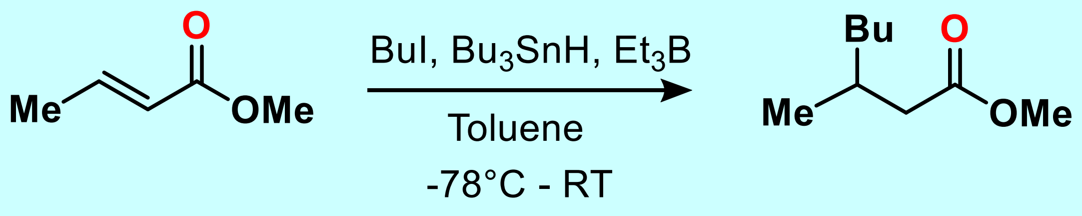




Curran, Rebek, *JACS*, 1992, 114, 7007.

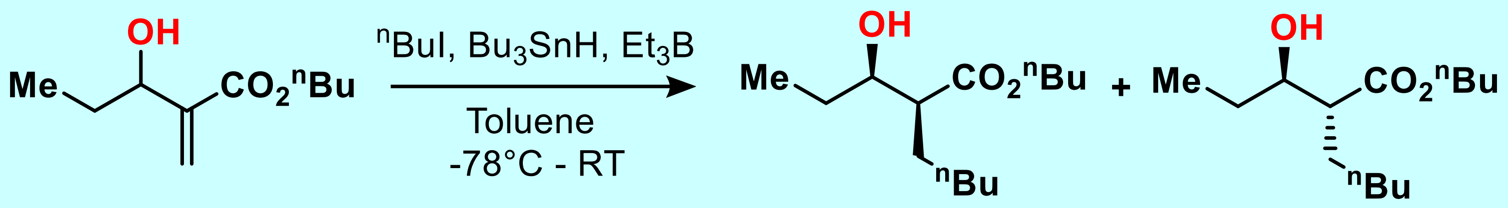
Lewis Acid-Enhanced Reactivity of Unsaturated Esters and Amides

- Lewis acids increase yields of conjugate additions

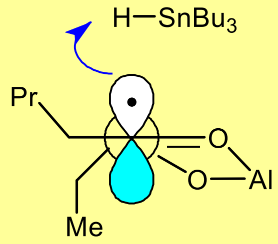


Lewis Acid	Yield (%)
None	< 1
$TiCl_4$	< 2
Et_2AlCl	18
$EtAlCl_2$	33

- Chelate control



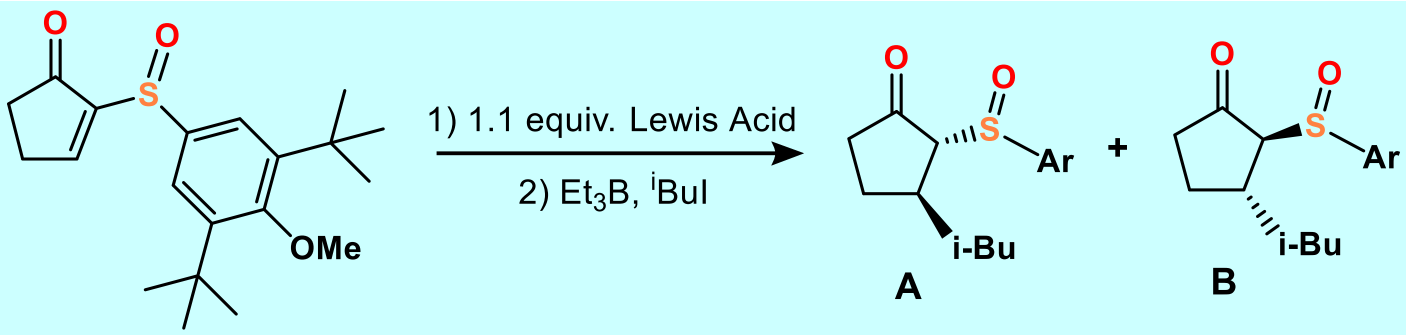
Via



Lewis Acid	Yield (%)	syn:anti
None	34	65:35
Et_2AlCl	76	87:13

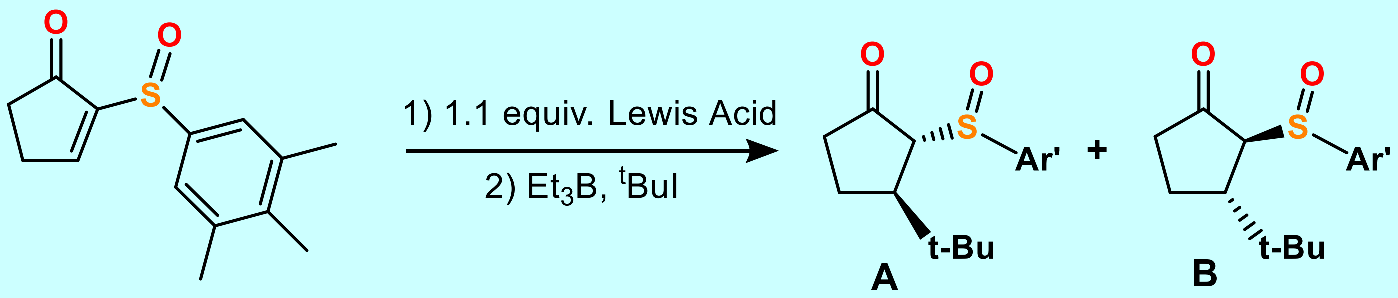
Sato, F. *J. Org. Chem*., 1995, 60, 3576.

Asymmetric Radical Addition to α-Sulfinylcyclopentenones



opposite enantiomers
of chiral auxiliaries

Lewis Acid	A : B
None	38 :62
$Ti(OPr)_4$	56:44
$TiCl_2(OiPr)_2$	91:8



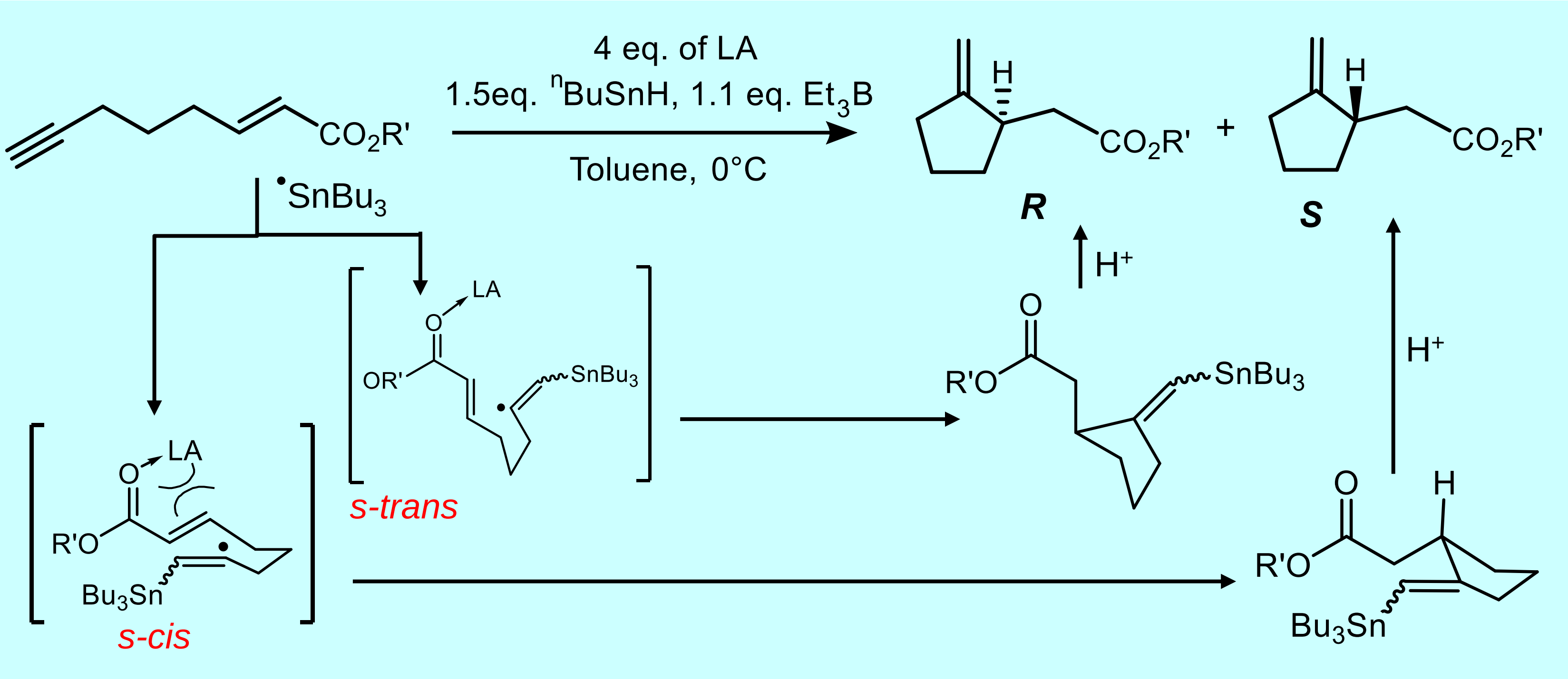
Auxiliaries can be cleaved with aluminum amalgam in THF/H_2O

Lewis Acid	A : B
None	98:2
$TiCl_2(OiPr)_2$	2:98

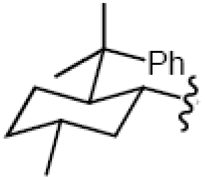
Toru, *JACS*, 1993, 10464; Toru, *JOC*, 1997, 7794

Lewis Acid Promoted Diastereoselective Radical Cyclization

- Coordination of Lewis acid controls *s-cis*/*s-trans* conformation of ester



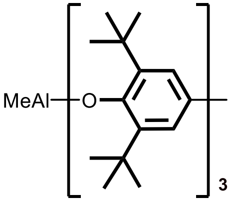
R* =



(-)-8-phenylmenthyl

Lewis Acid	A : B
None	67:33
BF$_3$	94:6
MAD	96:4

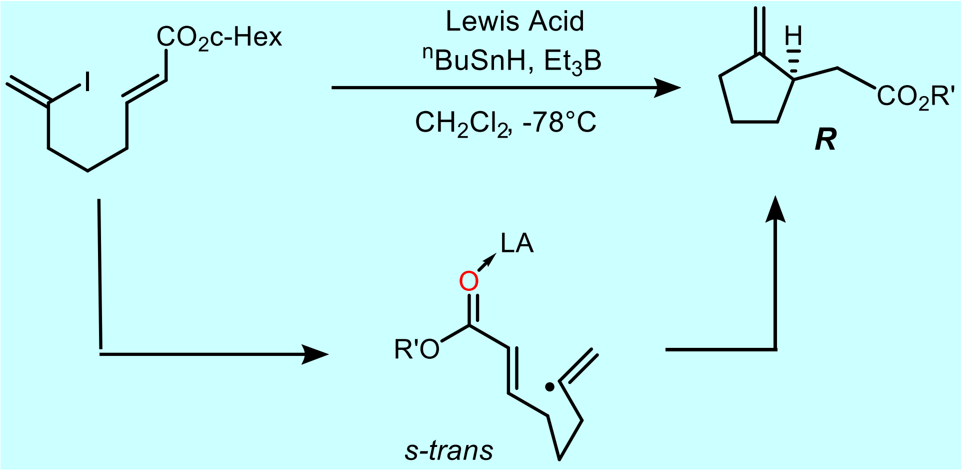
MAD =

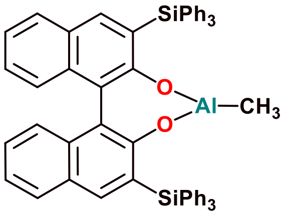


Nishida, *JACS*, 1994, 6455.

Enantioselective Lewis Acid Promoted Radical Cyclization

- First report of chiral Lewis Acid mediated radical cyclization

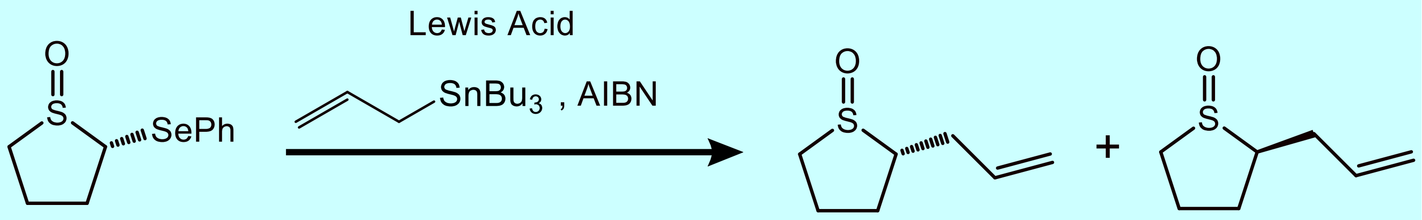


Lewis Acid	equiv.	ee (%)
(Binol)AlMe	**1**	**2**
	**1**	**12**
	4	**36**

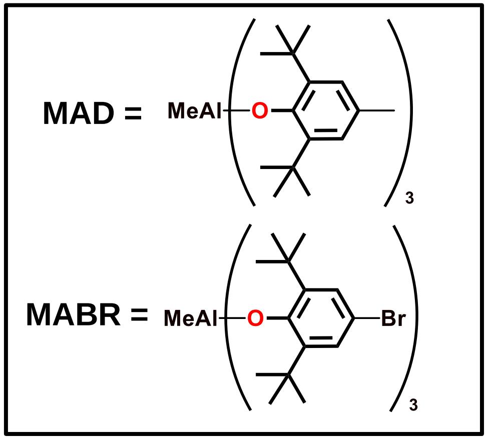
Reactions using the same Lewis Acid and the Weinreb amide provide the S-product in 26% ee.

Nishida, *Chem. Commun*., 1996, 579.

Allylation of α-Sulfinyl Radicals



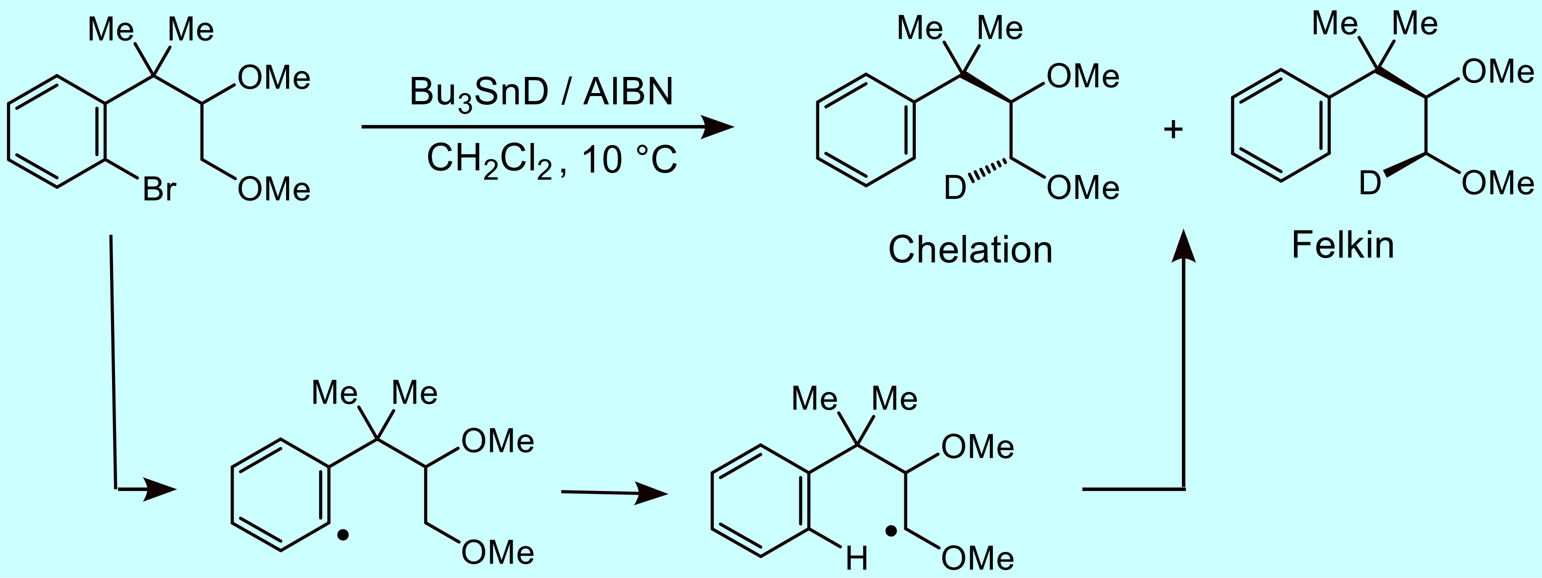
Solvent	Lewis Acid	*trans:cis*
propionitrile	--	77:23
propionitrile	$LiClO_4$	90:10
CH_2Cl_2	--	82:18
CH_2Cl_2	MAD (1)	98:2
CH_2Cl_2	MABR (1)	98:2
CH_2Cl_2	MABR (0,1)	90:10



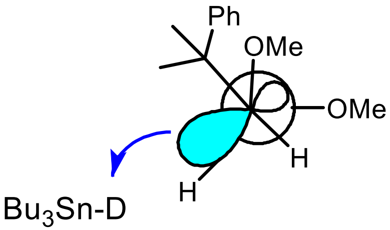
Selectivities were increased with the use of catalytic amounts of Lewis acid.

Renaud, *JACS*, 1991, 7803
Renaud, Curran, *JACS*, 1994, 3547

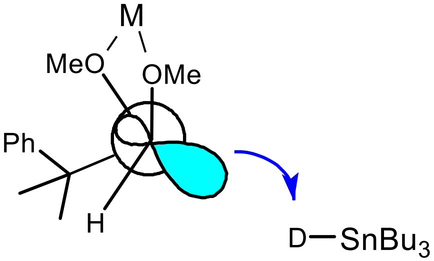
Stereo-selective Reactions of 1,2-Dioxysubstituted Radicals



<u>Felkin-Ann</u>



<u>Chelation Control</u>

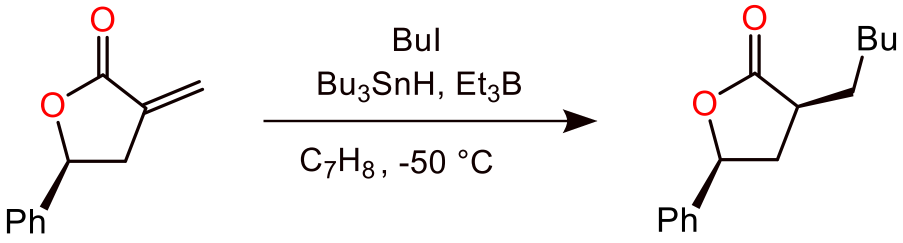


Lewis Acid	Chelation/Felkin
---	**1 : 25**
$ZnCl_2 \cdot OEt_2$	**1 : 1.4**
$Ti(OiPr)_3Cl$	**1 : 3**
$MgI_2 \cdot OEt_2$	**17 : 1**

Renaud, *JACS*, 1995, 6607

Stereo-selective Addition to α-Methylenebutyrolactones

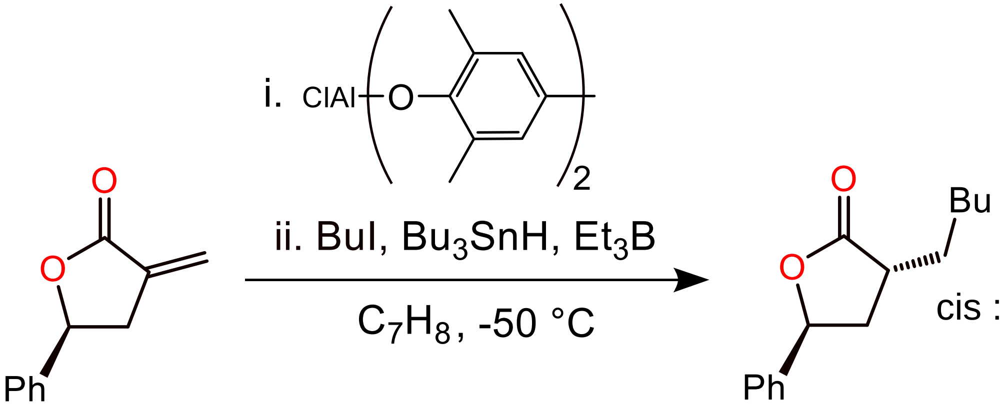
- Reactions in the absence of Lewis Acid are highly diastereoselective.



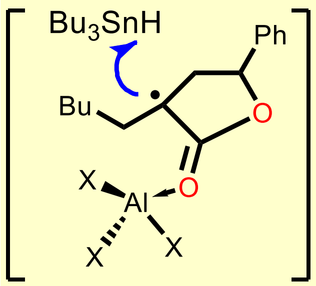
cis : trans = 90 : 10

  - π Radical is generated by addition of alkyl radical to α,β-unsaturated ester.
  - Major product formed by H• delivery from face opposite phenyl group.

- Reversal of diastereoselectivity using bulky Lewis Acids



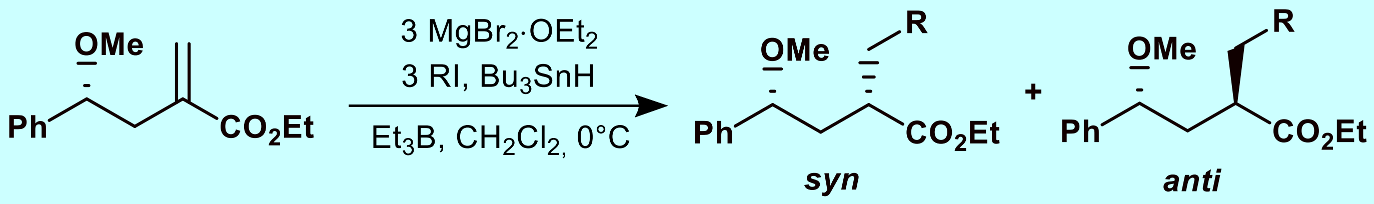
cis : trans = 40 : 60



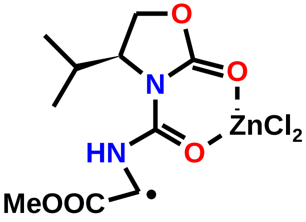
Sato, *Chem. Commun.*, 1995, 1043

Chelation Controlled 1,3-Asymmetric Induction

- Reduction Reactions



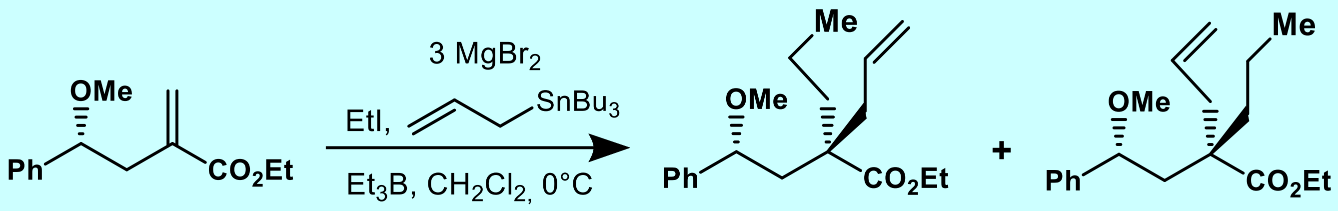
via



R	Yield (%)	*syn* : *anti*
i-Pr	86	1 :1.4
i-Pr	96	4.3 : 1
c-Hex	70	3.7 : 1
t-Bu	91	1 : 3.8

← no $MgBr_2$

- Allylation Reactions



The allylation reaction did not proceed without Lewis Acid.

R'	Yield (%)	*syn* : *anti*
Ph	48	5.5 : 1
i-Pr	63	>50 : 1
t-Bu	56	>50 : 1

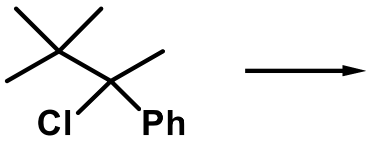
Nagano, *Synlett*, 1999, 53. Nagano, *Synlett*, 2000, 1073

Ways To Introduce Chirality

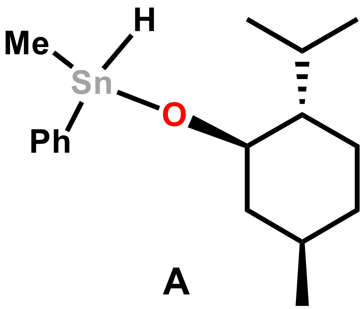
- ✓ Chiral Reagent
- ✓ Chiral Auxiliary
- ✓ Chiral Lewis Acid

N.B. Most radicals are extremely reactive intermediates and present early transition states in their reactions.

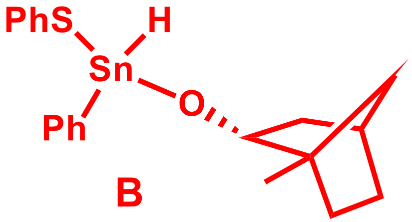
The First Example (Reductive Dehalogenation)



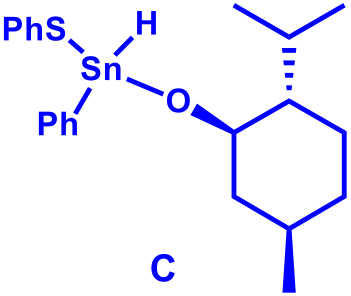
Hydride	Yield	$[\alpha]^{D}_{20}$
A	53%	+ 2.42
B	21%	- 2.99
C	75%	- 3.47
D	42%	- 3.51



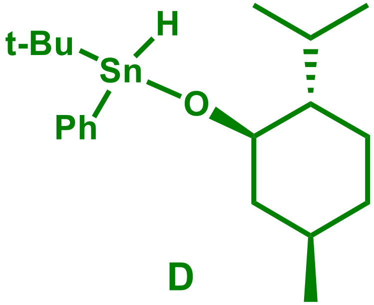
A



B



C

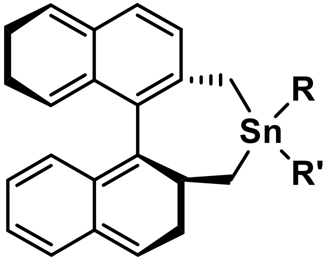


D

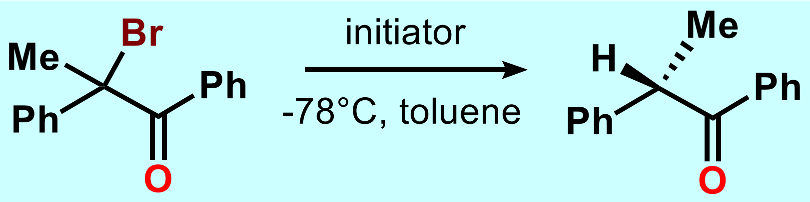
Chirality at Tin is transferred in reductive dehalogenation!

Schumann, H; Pachaly, B.; Schutze, B.C. *J. of Organometallic Chemistry*. **1984**, *265*, 145.

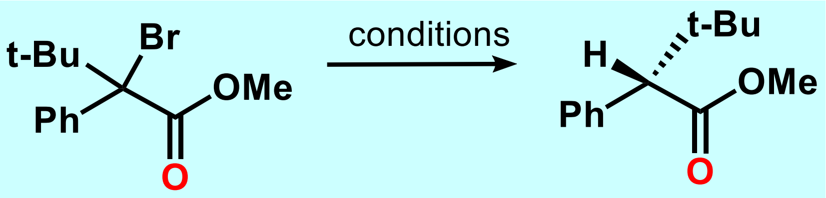
Dinaphthostannepins



R' = Me; R = H



R' = t-Bu, R = H



Initiator	Yield (%)	ee (%)
AIBN	54	20
0.3eq. Et_3B every 2h for 16h	12	30
10eq. Et_3B	35	11
0.3eq. Et_3B every 10min for 30min	30	41

Initiator	Yield (%)	ee (%)
R = H, I eq. Et_3B, -78	93	52
1 mol% Sn; R=Br *	98	26

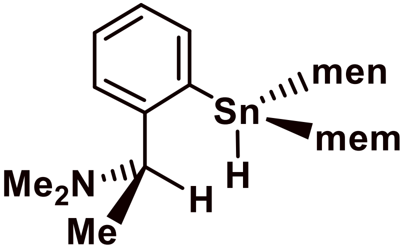
---

*3eq. $NaB(CN)H_3$ Catalytic conditions

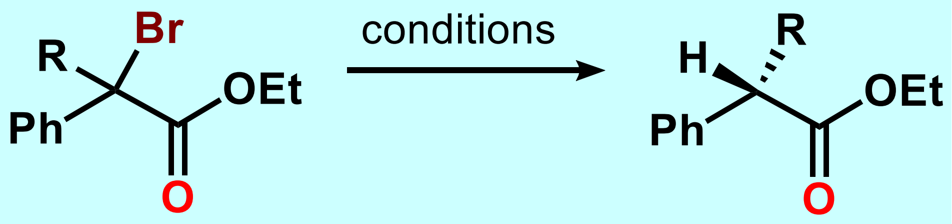
Nanni, D; Curran, D.P. *Tetrahedron: Asymmetry* **1996**, *7*,2417.

Blumenstein, M.; Schwalzkopf, K.; Metzger, J.O. *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 235.

DAAP Ligands



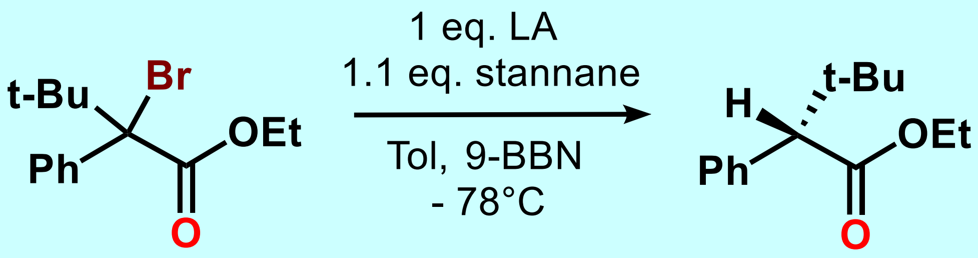
dr 58:42 at Sn



R	Conditions	Yield (%)	ee (%)
Me	20°C, 1h, 1.5 eq. Sn	98	6
Et	20°C, 3h, 1.5 eq. Sn	99	4
i-Pr	20°C, 3h, 1.5eq. Sn	99	1
t-Bu	20°C, 2h, 2.0eq. Sn	98	-6
t-Bu	20°C, 1h, 0.13eq. Sn	11	-23

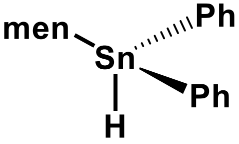
Schwalzkopf, K; Blumenstein, M.; Hayen, A.; Metzger, J.O. *Eur. J. Org. Chem*. **1998**, 177.

L.A. Enhanced Enantioselectivity

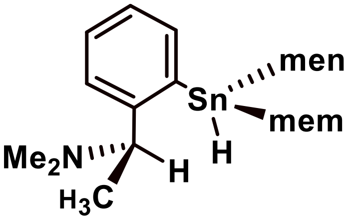


Bu_3SnH

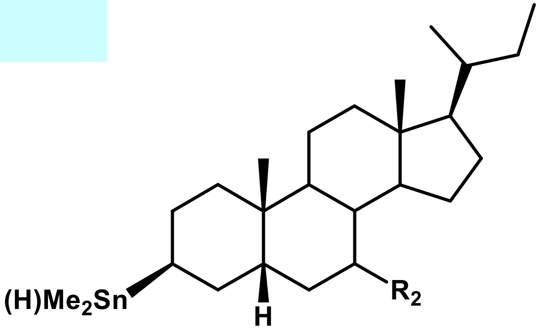
--%, 8% ***ee***



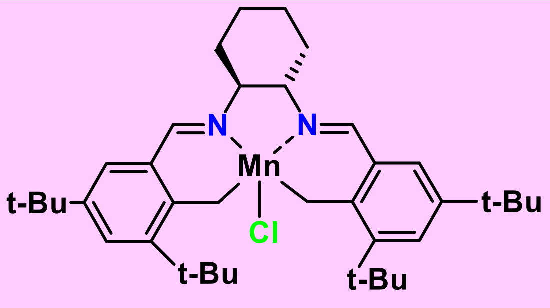
74%, 72% ***ee***



76%, 80% ***ee***

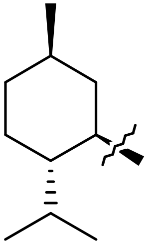


72%, 82% ***ee***



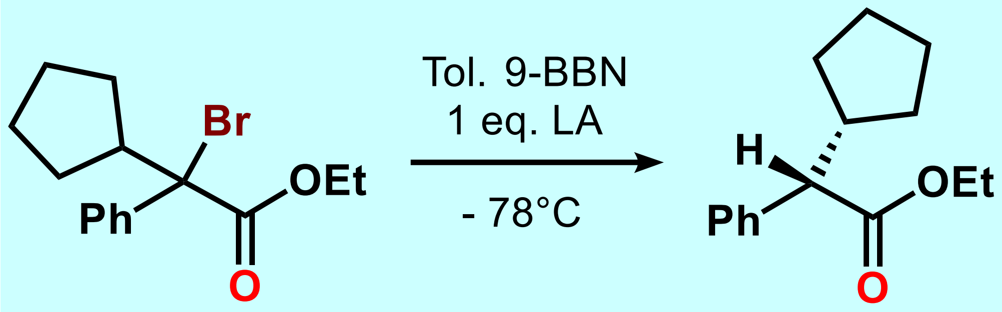
LA

men =

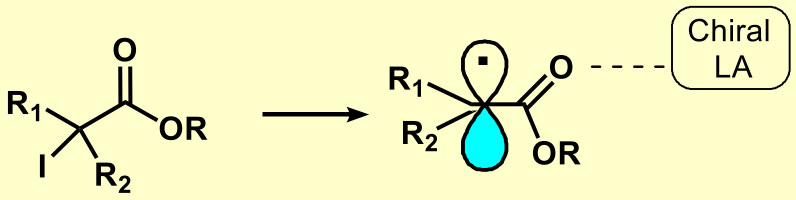


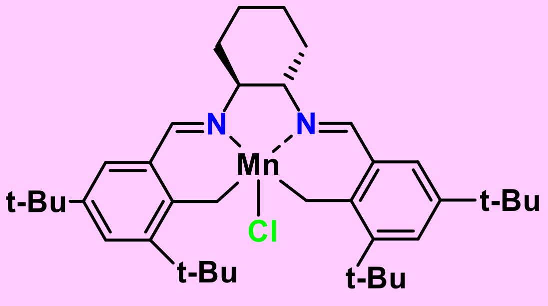
Dakternieks, D.; Dunn, K.; Perchyonok, V.T.; Schiesser, C.H. *Chem. Common*. **1999,** 1665.

Steroidal Ligands

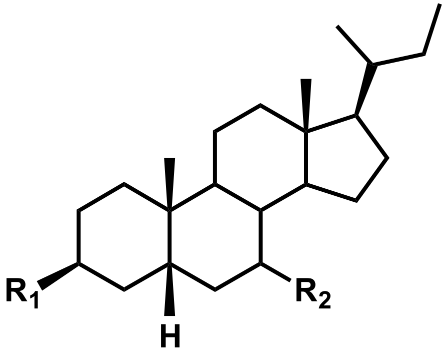


A 90%, 62% ***ee***
B 90%, 90% ***ee***





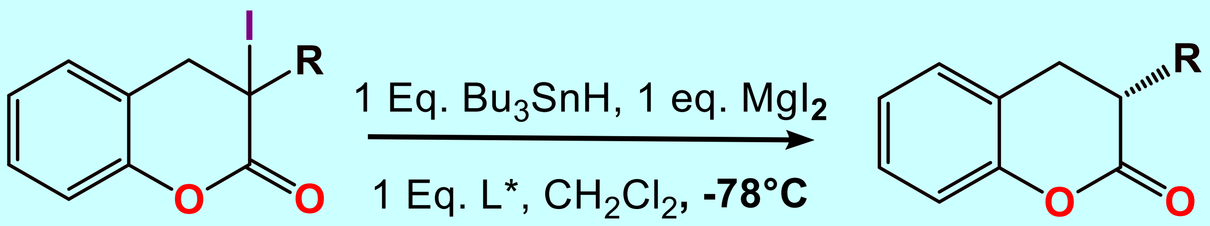
LA



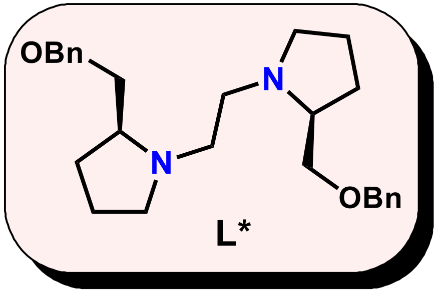
A R^1 = Sn(H)Me_2, R^2 = H
B R^1 = H, R^2 = Sn(H)Me_2

Schiesser, C.H.; Skidmore, M.A.; White, J.M. *Aust. J. Chem*. **2001**, *54*, 199.

A Different Approach



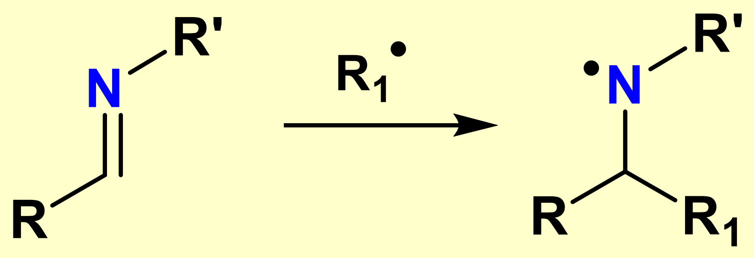
R	Yield(%)	*ee*(%)
CH_2OMe	88	62
CH_2OEt	84	65
CH_2OBn	89	58
Me	78	30



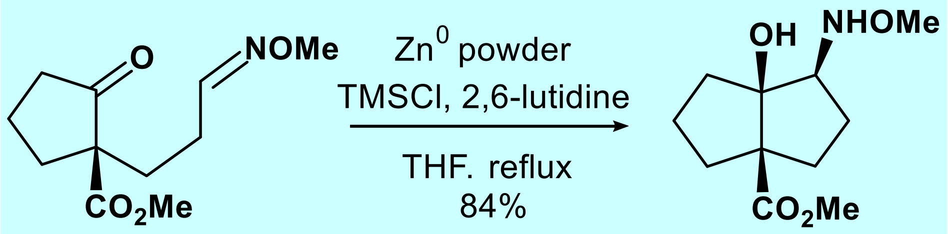
- α-Halo-esters can be reduced with moderate to good ee's.
- Size is very important, large ligands on tin and large Lewis acids coordinating substrate lead to best ee's.
- Not practical for large scale due to toxicity of tin and use of stoichiometric amount of Lewis acid.

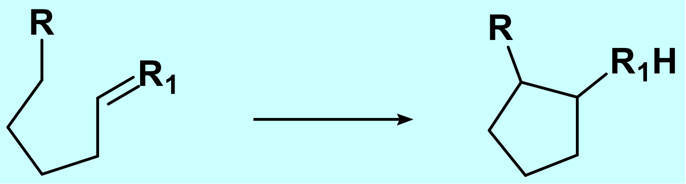
Murakata, M.; Tsutsui, H.; Takeuchi, N.; Hoshino, O. *Tetrahedron* **1999**, 10295., *J. Am. Chem. Soc*. **1997**, *119*, 11713.

C=N Acceptors



R’ = NR_2. OR, R



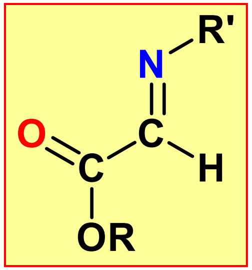


R’	k_{obs} (s^{-1})
CH_2	5.5×10^5
NBn	6×10^6
$NHMe_2$	2.4×10^7
NOBn	3.3×10^7

Corey, E.J.; Pyne, S.G. *Tet. Lett.*, **1983**, *24*, 2821.

Fallis, A.G.; Brinza, I.M. *Tetrahedron* **1997**, *53*, 17543.

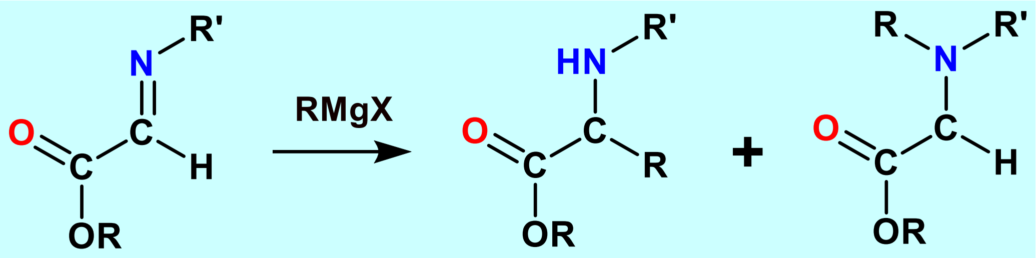
Glyoxylate Imines

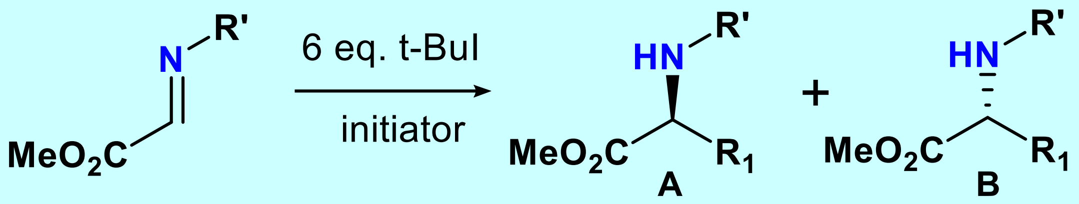


Provide access to alpha amino acids through ene, cycloaddition, and Mannich reactions. Addition of organometallics suffers from regioselectivity.

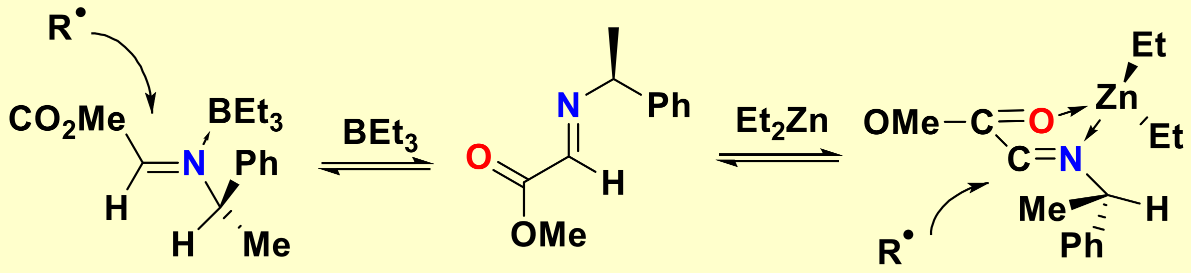
R1	A:B
Et	5:95
n-Pr	4:96
i-Pr	40:60
t-Bu	100:0

Fiaud, J.C.; Kagan, H.B. *Tet. Lett*. **1971**, *15*, 1019.



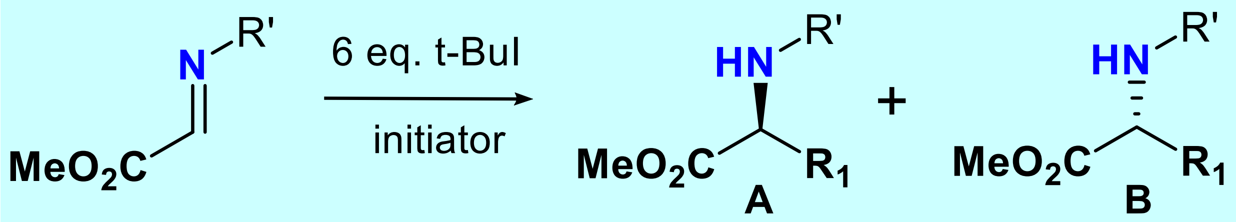


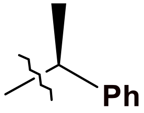
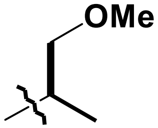
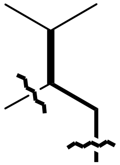
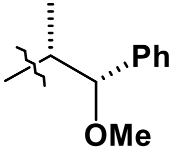
Radical addition can be an alternative owing the complete regioselectivity to carbon atom.



Chiral auxiliary mediated addition to iminines

Radical Addition to Glyoxylate Imines



	Initiator	Temp.	Yield(%)	Ratio **(A:B)**
 Ph	BEt_3	20°C	41	69:31
	Et_2Zn	20°C	41	40:60
 OMe	BEt_3	20°C	48	58:42
	Et_2Zn	20°C	43	30:70
	BEt_3	20°C	42	55:45
	Et_2Zn	20°C	41	87:13
 Ph OMe	BEt_3	20°C	42	65:35
	Et_2Zn	20°C	39	22:78

Bertrand, M.P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951.

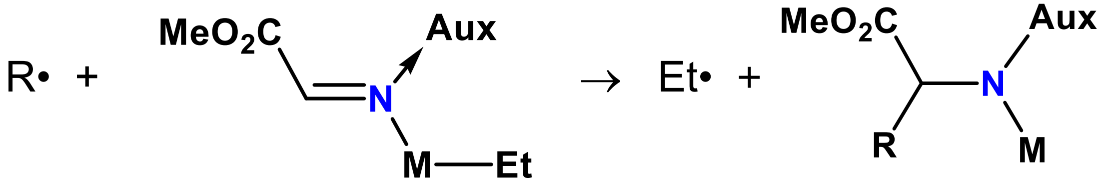
Radical Addition to Glyoxylate Imines

Sn-Free Radical Reactions

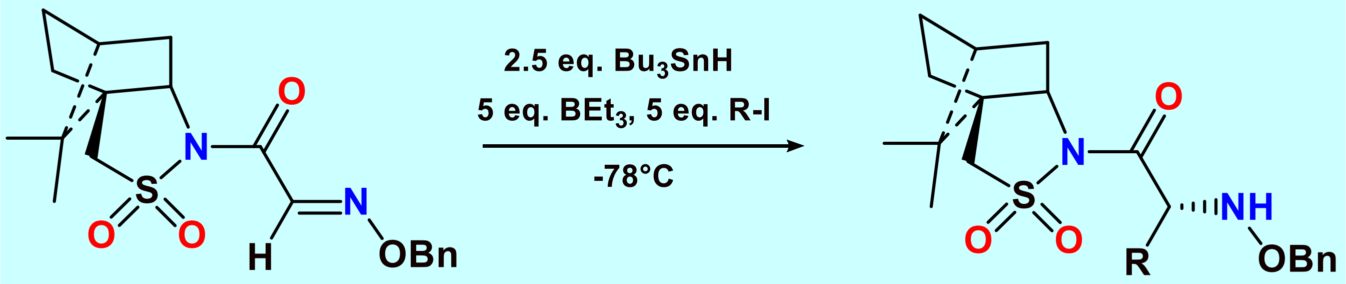
- MEt_x acts as initiator, chain transfer agent, and activating Lewis acid.
- No Sn is required, however a large excess of MEt_x and alkyl iodide (RI) is used in these reactions
- Autoxidation of organometallics provides the initiation step.

$$Et_xM + O_2 \rightarrow \bullet O\text{–}O\text{–}Met_{x-1} + Et\bullet$$

$$Et\bullet + RI \rightarrow Et\text{-}I + R\bullet$$



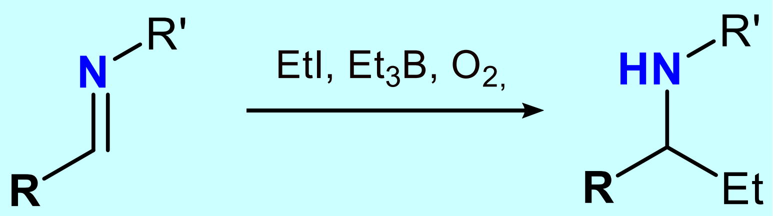
Glyoxylate Oximes to Chiral Amides



R	Lewis Acid	Solvent	Yield (%)	Selectivity
i-Pr	none	Et_2O	71	96:4
i-Pr	BF_3*OEt_2	CH_2Cl_2	80	96:4
Et	none	Et_2O	54	96:4
Et	BF_3*OEt_2	CH_2Cl_2	80	95:5
T-Bu	none	Et_2O	25	98:2
T-Bu	BF_3*OEt_2	CH_2Cl_2	83	98:2
C-Hexyl	none	Et_2O	74	96:4
C-Hexyl	BF_3*OEt_2	CH_2Cl_2	86	96:4

Miyabe, H.; Ushiro, C.; Naito, T. *Chem. Commun*. **1997**, 1789.

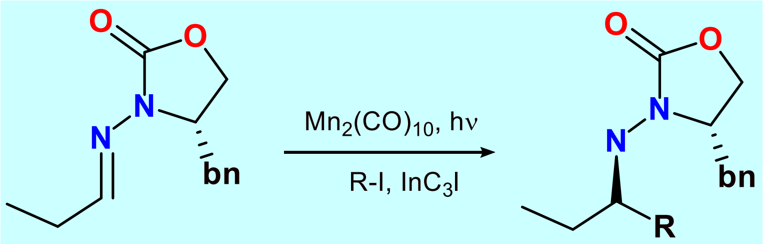
A Possible Limitation?



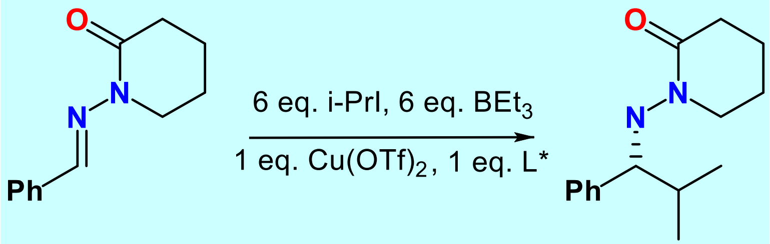
R	R'	Lewis Acid	Yield (%)
CO_2Me	OBn	none	97
Et	OBn	none	n.r.
Et	OBn	$BF_3{*}OEt_2$	95
CO_2Me	NPh_2	none	41
Et	NPh_2	none	n.r.
Et	NPh_2	$BF_3{*}OEt_2$	n.r.

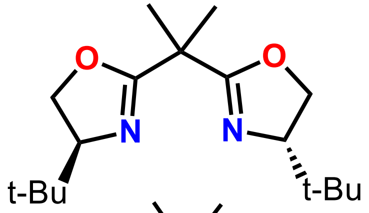
Miyabe, H.; Ushiro, C.; Shibata, R.; Sangawa, M.; Naito, T. *Tetrahedron* **1998**, *54*, 11431.

Non-Glyoxylate Derived Hydrazones
Chiral Auxiliary and Chiral Lewis Acids

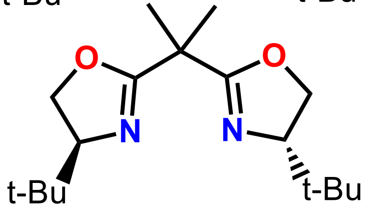


R	Yield%	dr
Pr	66	94:6
Bu	78	95:5
i-Bu	54	95:6
i-Pr	75	95:5

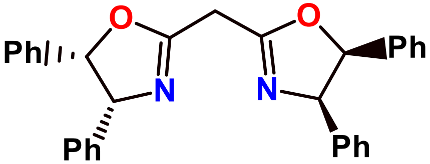




94% Yield -86% ee



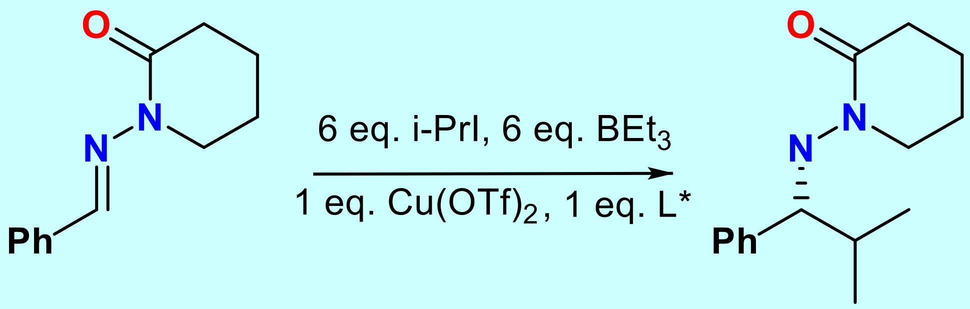
74% Yield 72% ee

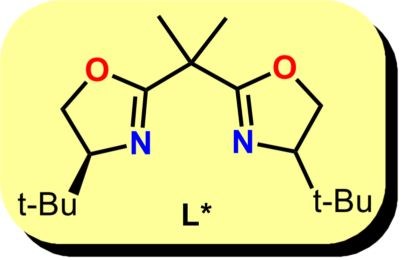


73% Yield 94% ee

Friestad, G.K.; Qin, J. *J. Am. Chem. Soc*. **2001**, *123*, 9922.
Friestad, G.K.; Shen, Y.; Ruggles, E.L. *Angew. Chem. Int Ed*. **2003**, *42*, 5061.

Non-Glyoxylate Derived Hydrazones Catalytic Chiral Lewis Acids





Eq. Cu(OTf)$_2$	Yield%	ee
1.0	66	96
0.5	71	81
0.2	83	58
0.1	74	46

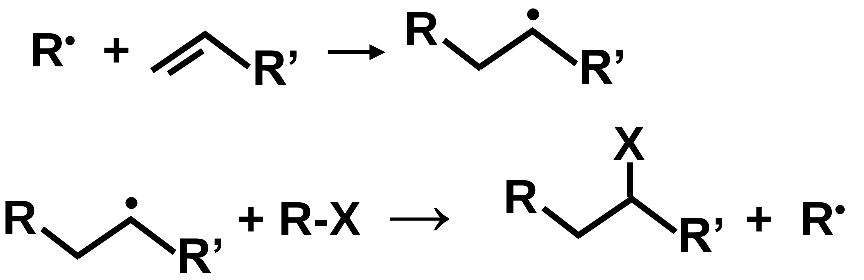
Summary of C=N addition:

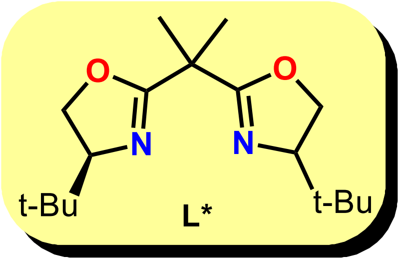
- Radicals add to C=N bonds faster than they do to C=C bonds.
- Intermolecular radical additions have been shown for imines, oximes, and hydrazones.
- Additions to hydrazones have been carried out enantioselectively with catalytic amounts of chiral Lewis acid.

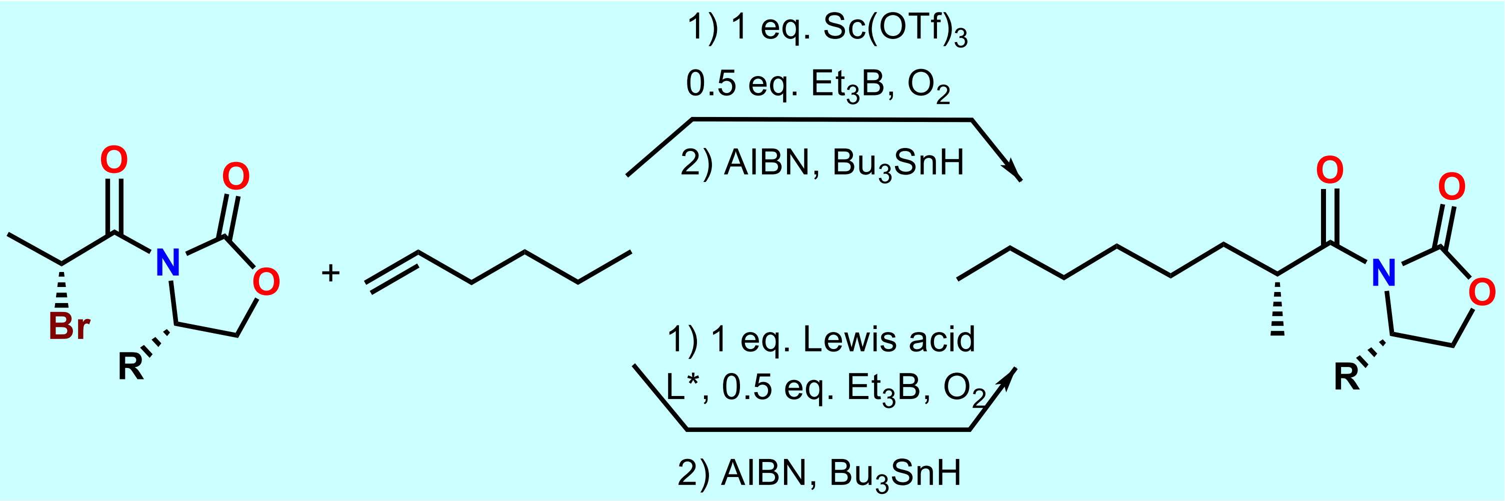
Friestad, G.K.; Shen, Y.; Ruggles, E.L. *Angew. Chem. Int. Ed.* **2003**, *42,* 5061.

Radical Addition to Unactivated Alkenes
Atom Transfer Reactions

$\text{R-X} + \text{Initiator} \rightarrow \text{R}^{\bullet} + \text{Initiator-X}$







1) 1 eq. $Sc(OTf)_3$

0.5 eq. Et_3B, O_2

2) AIBN, Bu_3SnH

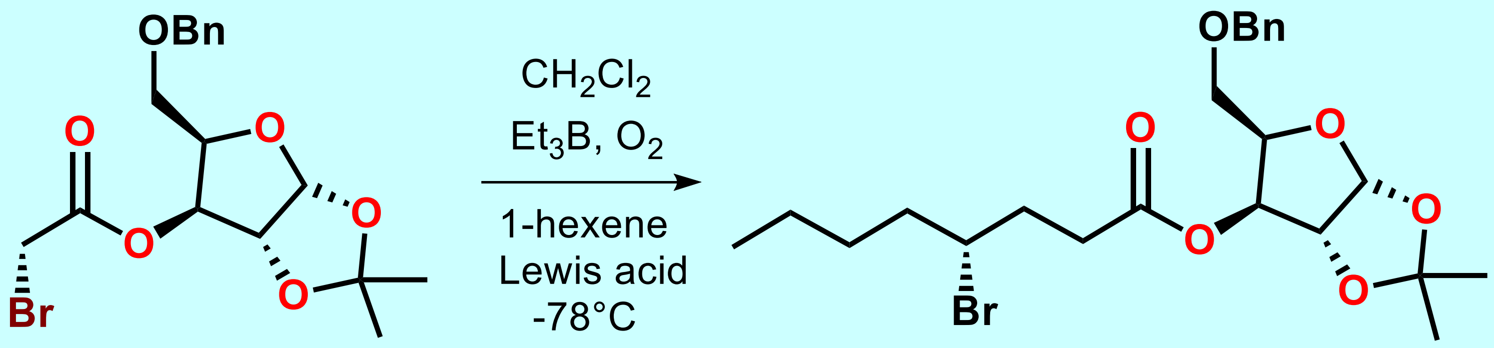
1) 1 eq. Lewis acid

L*, 0.5 eq. Et_3B, O_2

2) AIBN, Bu_3SnH

Mero, C.L.; Porter, N.A. *J. Am. Chem. Soc*. **1999**, *121*, 5155.

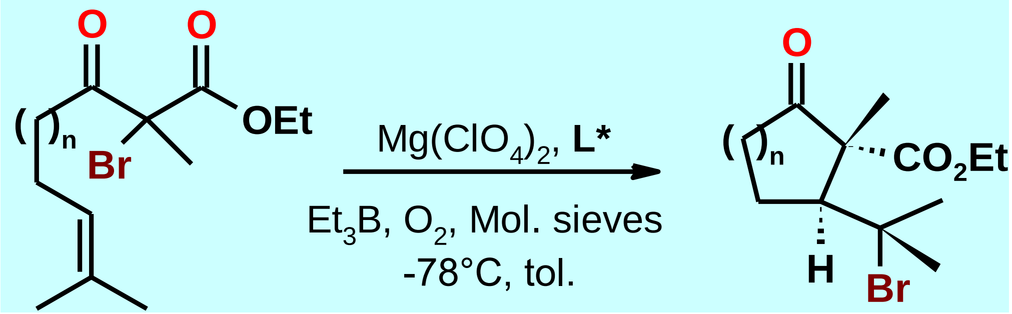
D-Xylose as a Chiral Auxiliary



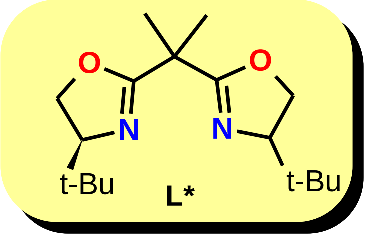
LA	Temp. (°C)	Yield(%)	dr
$Eu(OTf)_3$	25	56	1.7:1
$Yb(OTf)_3$	25	63	1.7:1
$Eu(OTf)_3$	30	65	2.8:1
$Yb(OTf)_3$	30	62	2.2:1
$Eu(OTf)_3$	**-78**	**71**	**12.5:1**
$Yb(OTf)_3$	-78	65	1:1

Enholm, E.J.; Bhardawaj, A. *Tetrahedron Lett*. **2003**, *44*, 3763.

Intramolecular Enantioselective Atom Transfer

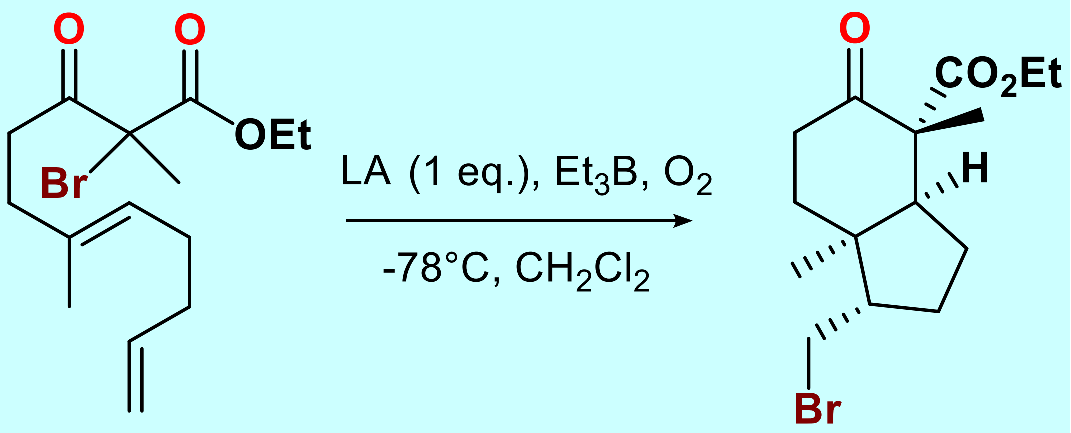


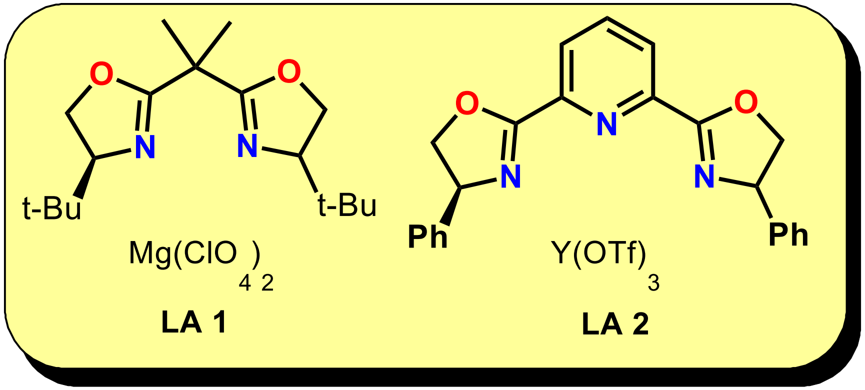
n	R	R_2	**$Mg(ClO_4)_2$eq.**	**Yield** (%)	**ee(%)**
1	Me	Me	0.3	68	92
2	Me	Me	0.5	53	94
2	H	Et	0.3	81 (1/1.4)	74/95
2	Et	H	0.3	58 (1/1)	74/87



Yang, D.; Gu, S.; Yan, Y.; Zhu, N.; Cheung, K. J. *Am. Chem. Soc.* **2001**, *123*, 8612.

Construction of Polycyclic Rings





$Mg(ClO_4)_2$

LA 1

$Y(OTf)_3$

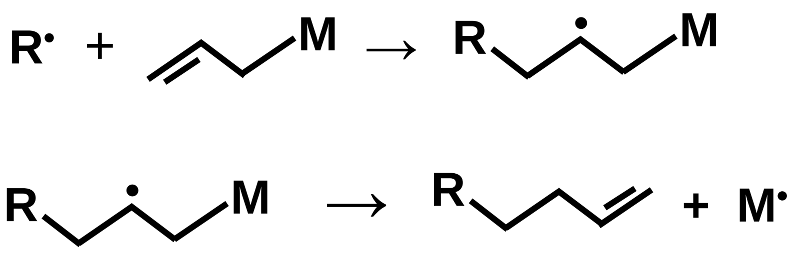
LA 2

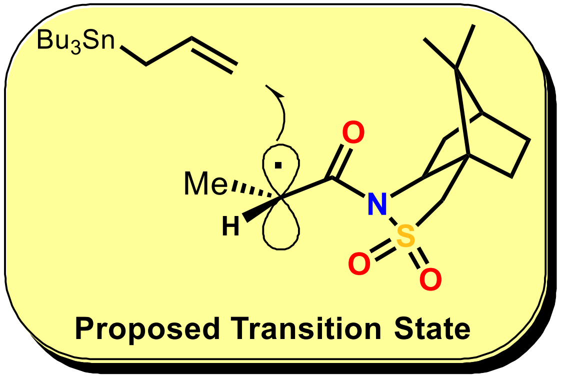
LA	Additive	*ee*(%)	*ee*(%)
1	none	41	13
1	mol. sieve	24	33
2	none	60	66
2	mol. sieve	11	-56

Yang, D.; Gu, S.; Yan, Y.; Zhao, H.; Zhu, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3014.

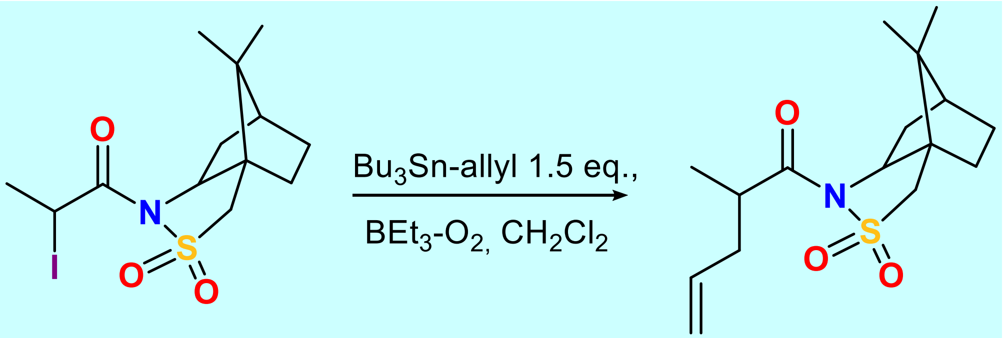
Radical Addition to Allylic Species

R-X + Initiator → R• + Initiator-X





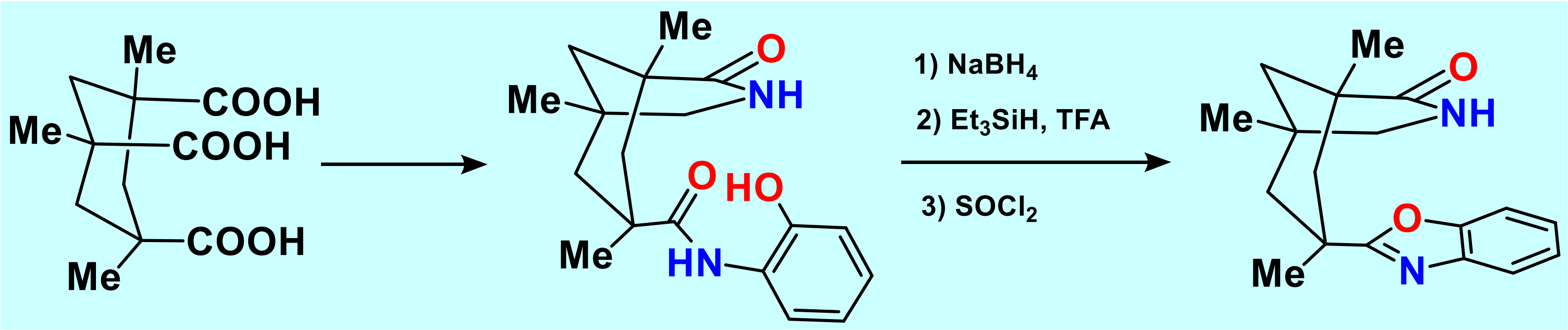
Proposed Transition State

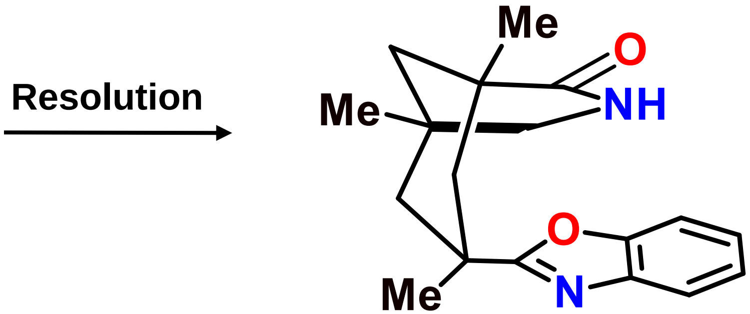


Temp.(°C)	Yield%	dr
80	>90	12:1
25	>90	14:1
0	>90	22:1
-20	>90	25:1
-78	>90	>30:1

Curran, D.P.; Shen, W.; Zhang, J.; Heffner, T.A. *J.* Am. *Chem. Soc.* **1990,** *112,* 6738.

A Further Attempt

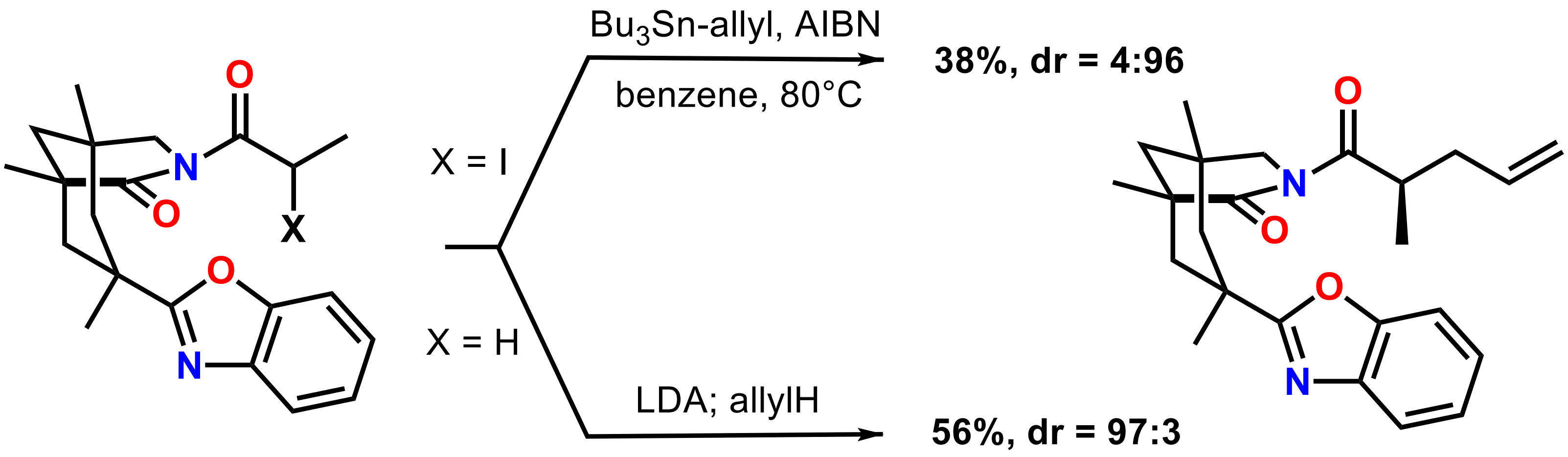




(R) Isomer shown
approx. 25% overall yield

Stack, J.G.; Curran, D.P.; Geib, S.V.; Rebek Jr., J.; Ballester, P *J. Am. Chem. Soc.* **1992**, *114*, 7007.

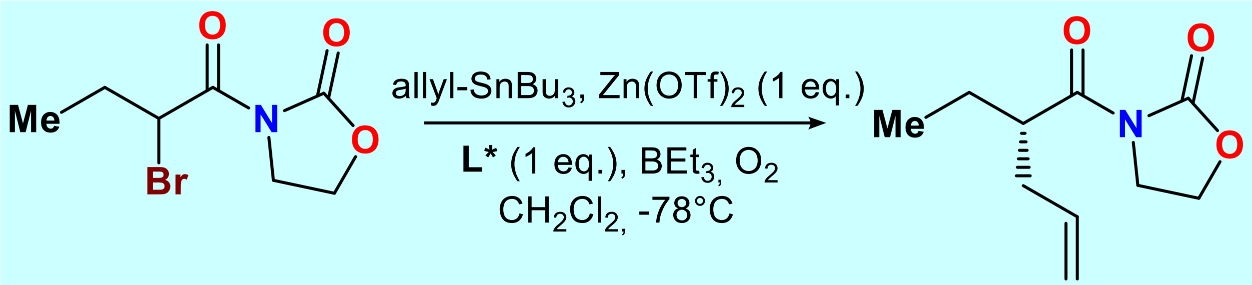
Allylation with Curran's Auxiliary



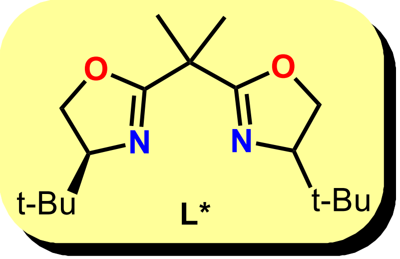
Ionic and radical pathways give complementary selectivity.

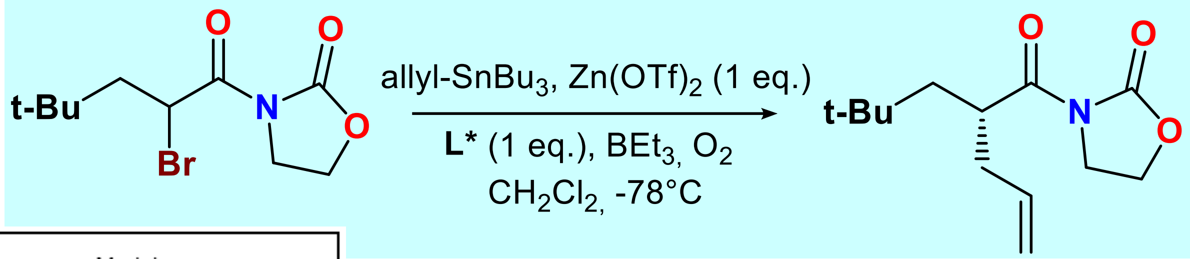
Stack, J.G.; Curran, D.P.; Geib, S.V.; Rebek Jr., J.; Ballester, P *J. Am. Chem. Soc*. **1992**, *114*, 7007

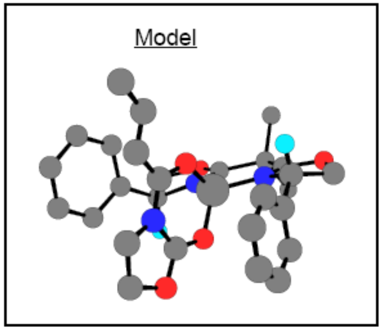
Oxazolidinone Template in Allyl Transfer



84% Yield; 42% ee







allyl$SnBu_3$ 63% Yield 74% ee
allylSiMes 88% Yield 90% ee

Porter, N.A.; Wu, J.H.; Zhang, G.; Reed, A.D. *J. Org. Chem.* **1997**, *62*, 6702.

Fragmentation and Enantioselective Trapping

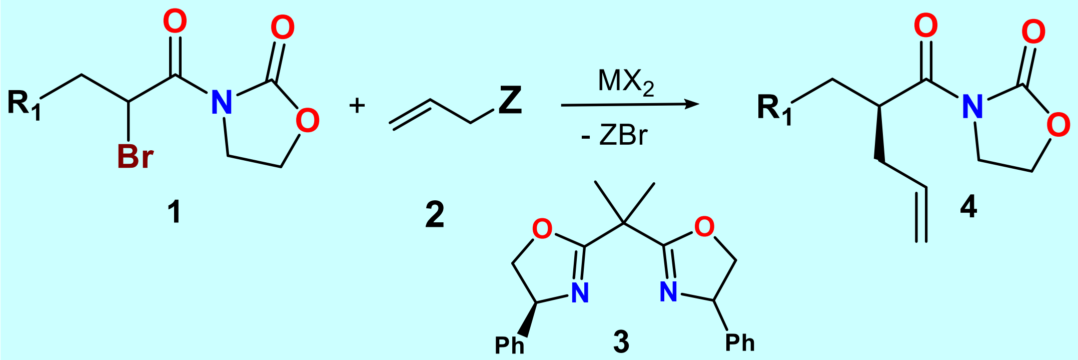


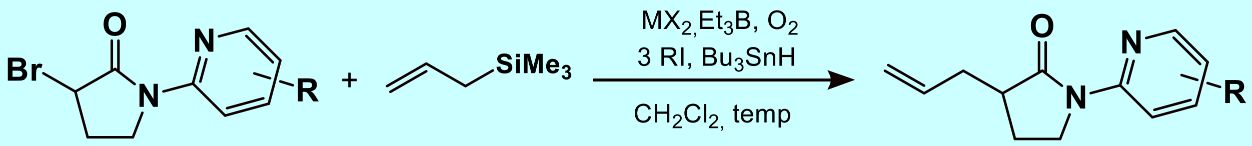
Table. Lewis Acid Promoted Reactions of Alkylsilanes and allylstannane[a]

entry	**R_1**	**R_2**	**R_3**	**3** config	MX_2	Z	**Yield** (%)	**4*R*:4*S***
1	Me	Me	Ph	(*R*,*R*)	$Zn(OTf)_2$	$Sn(Bu)_3$	84[b]	29:71
2	Me	Me	Ph	(*R*,*R*)	$Zn(OTf)_2$	$Si(OEt)_3$	65[b]	20:80
3	^{t}Bu	Me	Ph	(*R*,*R*)	$Zn(OTf)_2$	$Sn(Bu)_3$	63[b]	87:13
4	^{t}Bu	Me	Ph	(*R*,*R*)	$Zn(OTf)_2$	$Si(Me)_3$	88[c]	95:5
5	^{t}Bu	Me	Ph	(*R*,*R*)	MgI_2	$Si(Me)_3$	86[b]	16:84
6	^{t}Bu	Me	^{t}Bu	(*S*,*S*)	MgI_2	$Si(Me)_3$	61[c]	89:11
7	^{t}Bu	$-(CH_2)-$	^{t}Bu	(*S*,*S*)	MgI_2	$Si(Me)_3$	65[c]	94:6
8	^{t}Bu	Me	^{t}Bu	(*S*,*S*)	MgI_2	$Si(Me)_3$	83[c]	91:9

[a] Reaction as described in eq 3. [b] Isolated yield. [C] Yield based on GC internal standard.

Porter, N. A. *J. Org. Chem*. **1997**, *62*, 6702.

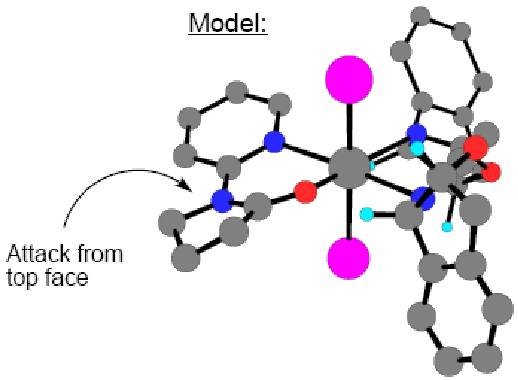
Fragmentation and Enantioselective Trapping: Manipulation of the Template

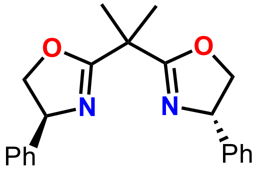


164a-d **165** **166**

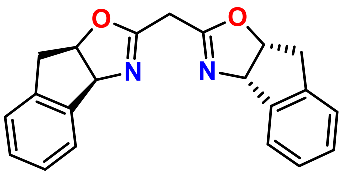
	R
a	H
b	4-Me
c	5-Cl
d	5-CO$_2$Me

Entry	**Substrate**	**Ligand**	**MX$_2$(eq.)**	**T (°C)**	**Yield (%)**	**ee** (%)
1	**164a**	**120**	Zn(OTf)$_2$ (1.0)	-78	70	59 (*S*)
2	**164a**	**167**	Zn(OTf)$_2$ (1.0)	-78	75	96 (*S*)
3	**164a**	**168**	Zn(OTf)$_2$ (1.0)	-78	42	75 (*R*)
4	**164a**	**167**	MgBr$_2$ (1.0)	-78	54	84 (*R*)
5	**164a**	**167**	Zn(OTf)$_2$ (2.0)	-78	83	>99 (*S*)
6	**164a**	**167**	Zn(OTf)$_2$ (2.0)	-20	94	95 (*R*)
7	**164b**	**167**	Zn(OTf)$_2$ (1.0)	-20	93	91 (*R*)
8	**164a**	**167**	Zn(OTf)$_2$ (1.0)	-20	85	70 (*R*)
9	**164c**	**167**	Zn(OTf)$_2$ (1.0)	-20	88	67 (*S*)
10	**164d**	**167**	Zn(OTf)$_2$ (1.0)	-20	91	80 (*S*)
11	**164a**	**167**	Zn(OTf)$_2$ (0.2)	-20	69	81 (*S*)





120



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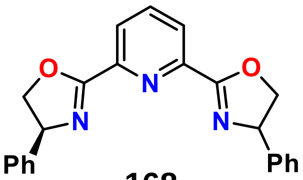
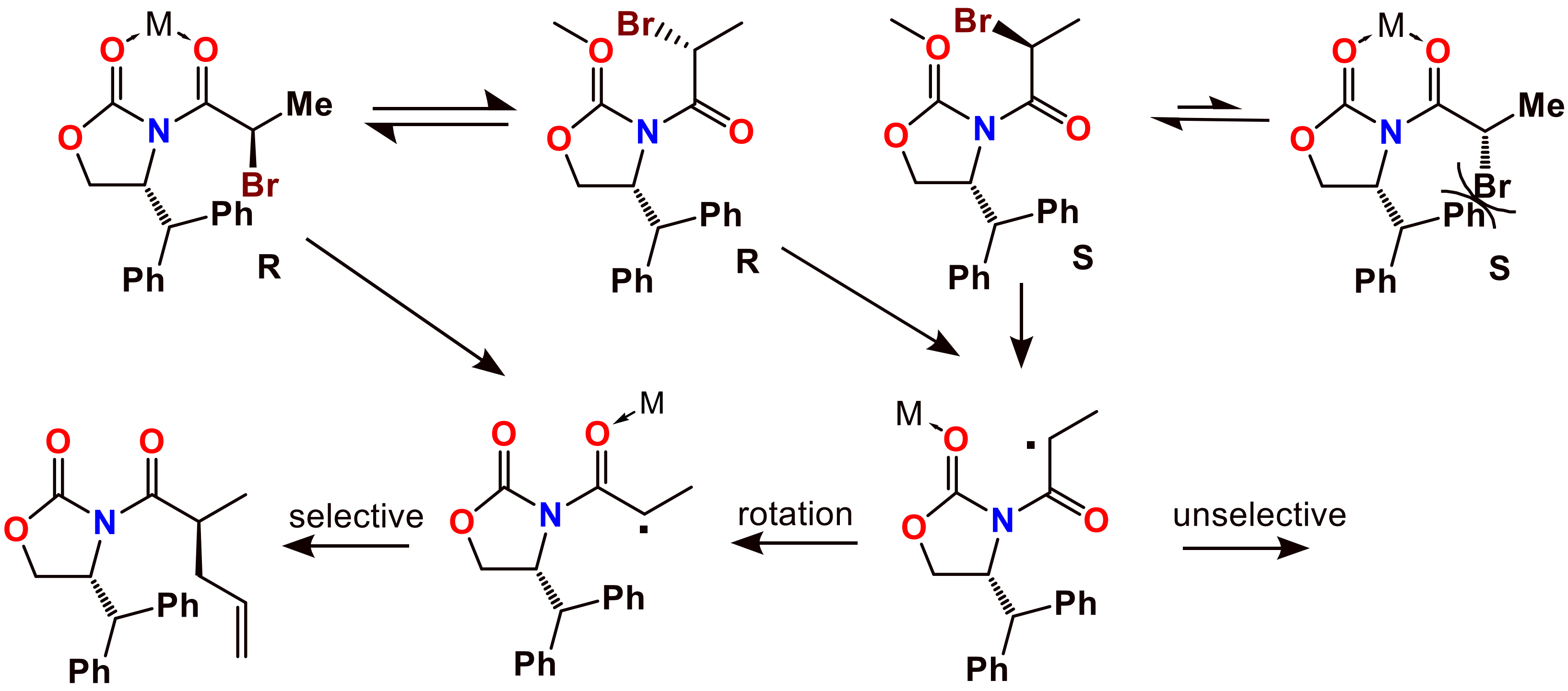


168

Porter, N. A. et al *Tetrahedron Lett*. **1999**, *40*, 671

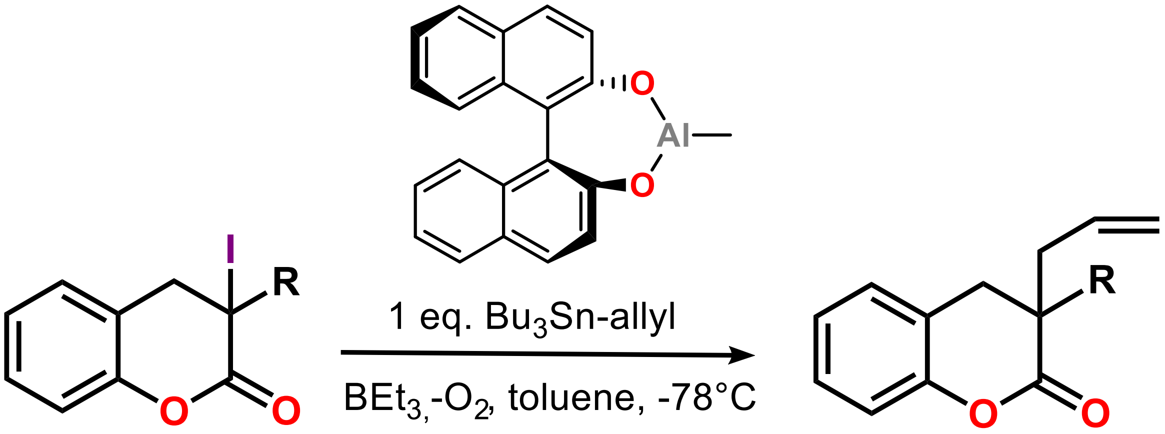
Explanation for the Reaction Selectivity



- Rate of rotation must increase with temperature faster than the rate of trapping with allyl stannane.
- The relative rates of rotation vs. allyl trapping explain why slower reacting allyl reagents show higher selectivity.

Sibi, *JACS*, **2000**, 122, 8873

Synthesis of Quaternary Centers



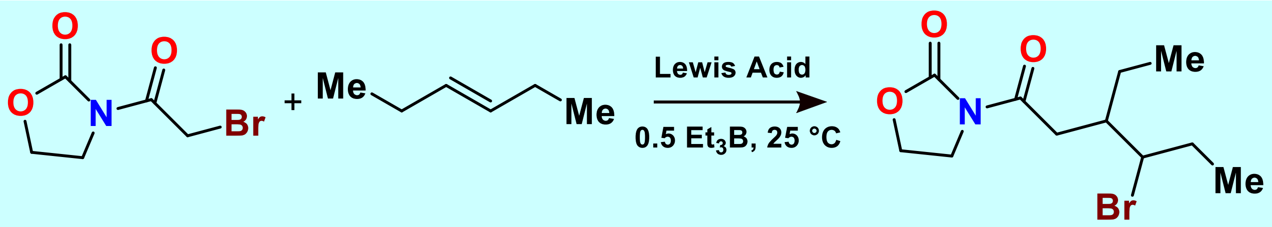
1 eq. Bu_3Sn-allyl

BEt_3-O_2, toluene, -78°C

R	**eq. LA**	**Additive**	**Yield** (%)	**ee(%)**	**Config.**
Me	1.0	none	72	27	R
Me	1.0	Et_2O	84	81	R
Me	0.1	Et_2O	83	72	R
CH_2OMe	0.1	Et_2O	76	74	R
CH_2OEt	0.1	Et_2O	74	70	R
CH_2OBn	0.1	Et_2O	78	71	R

Murakata, M.; Jono, T.; Mizuno, Y.; Hoshino, O. *J. Am. Chem. Soc.* **1997,** *119*, 11713.

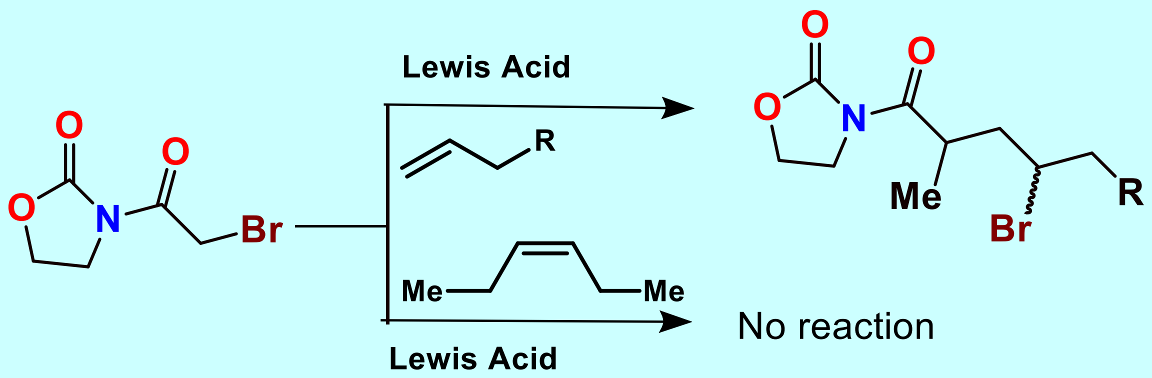
Lewis Acid Promoted Atom-Transfer Radical Additions



- With Lewis Acid activation, alkenes are nucleophilic enough to react with the radical intermediate.
- Atom transfer products can be isolated if alkenes, rather than allyl-metal reagents, are used as nucleophiles

Lewis Acid (1 equiv)	**Conv. %**
None	< 10
$Mg(OTf)_2$	16
$Sc(OTf)_3$	47
$Yb(OTf)_3$	100

Secondary Bromides

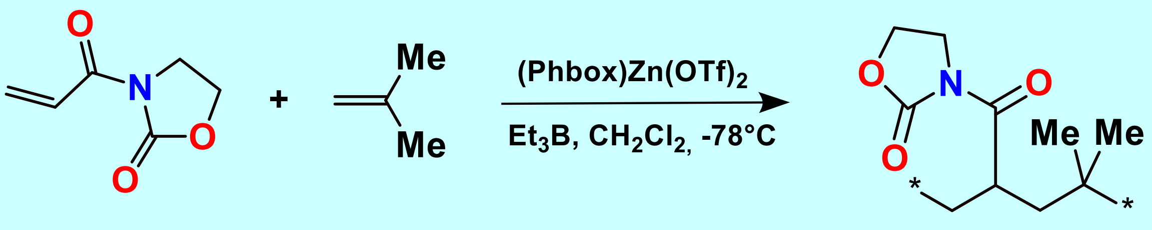


No reaction

Porter, *JACS*, **1999**, *121*, 5155

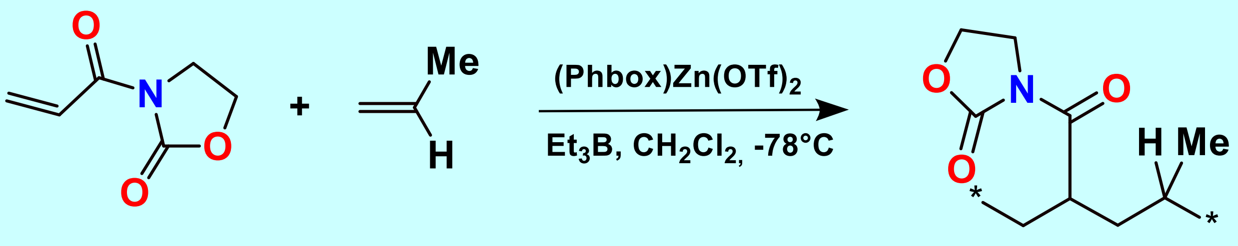
Free-Radical Polymerization of Acrylimides

- Diastereoselective Copolymerization



  - Degree of copolymerization depended on Lewis Acid. Sc(OTf)$_3$ in Et$_2$O gave best results (1:1).
  - R = Bn provided > 95:5 diastereoselectivity.

- Enantioselective Copolymerization

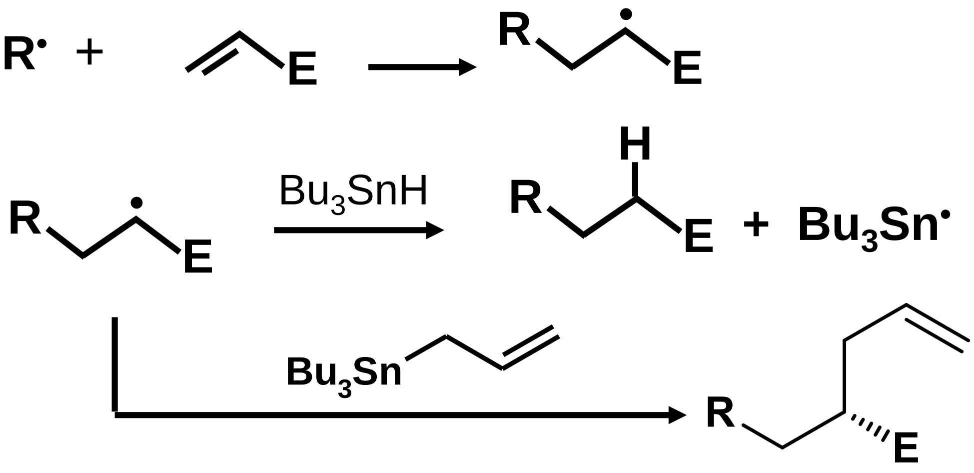


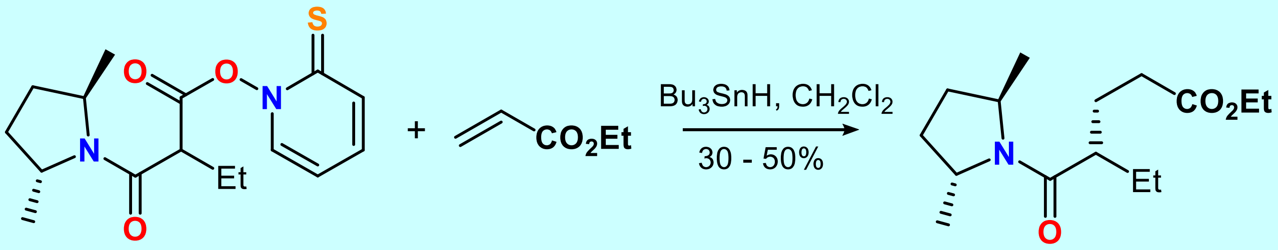
  - To get good copolymerization, 3.7 equiv. of Zn were required.
  - Polymer was formed in approximately 60% ee.

Porter, *JOC*, **2000**, 775.

Radical Conjugate Addition

R-X + Initiator → $R^{\bullet}$ + Initiator-X

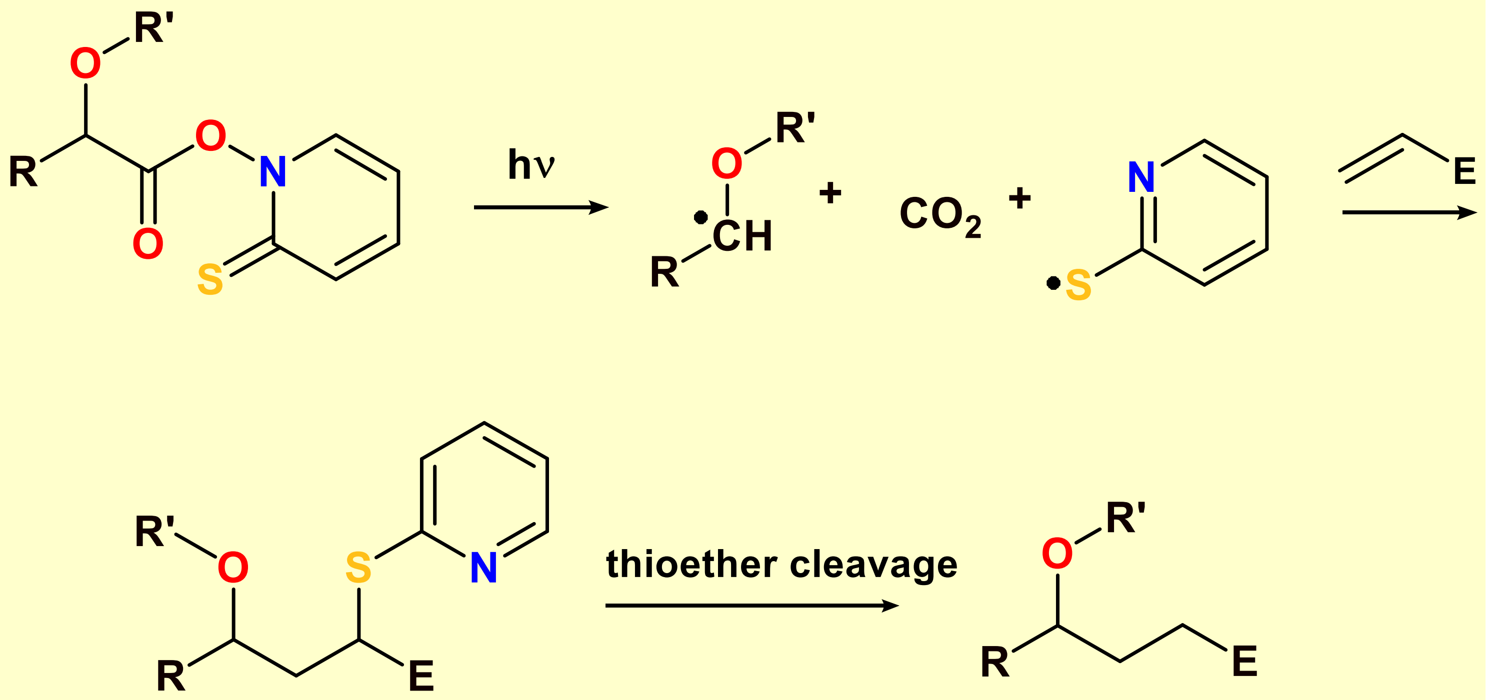




Temp.	dr
80 (benzene)	12:1
23	25:1
-24	36:1

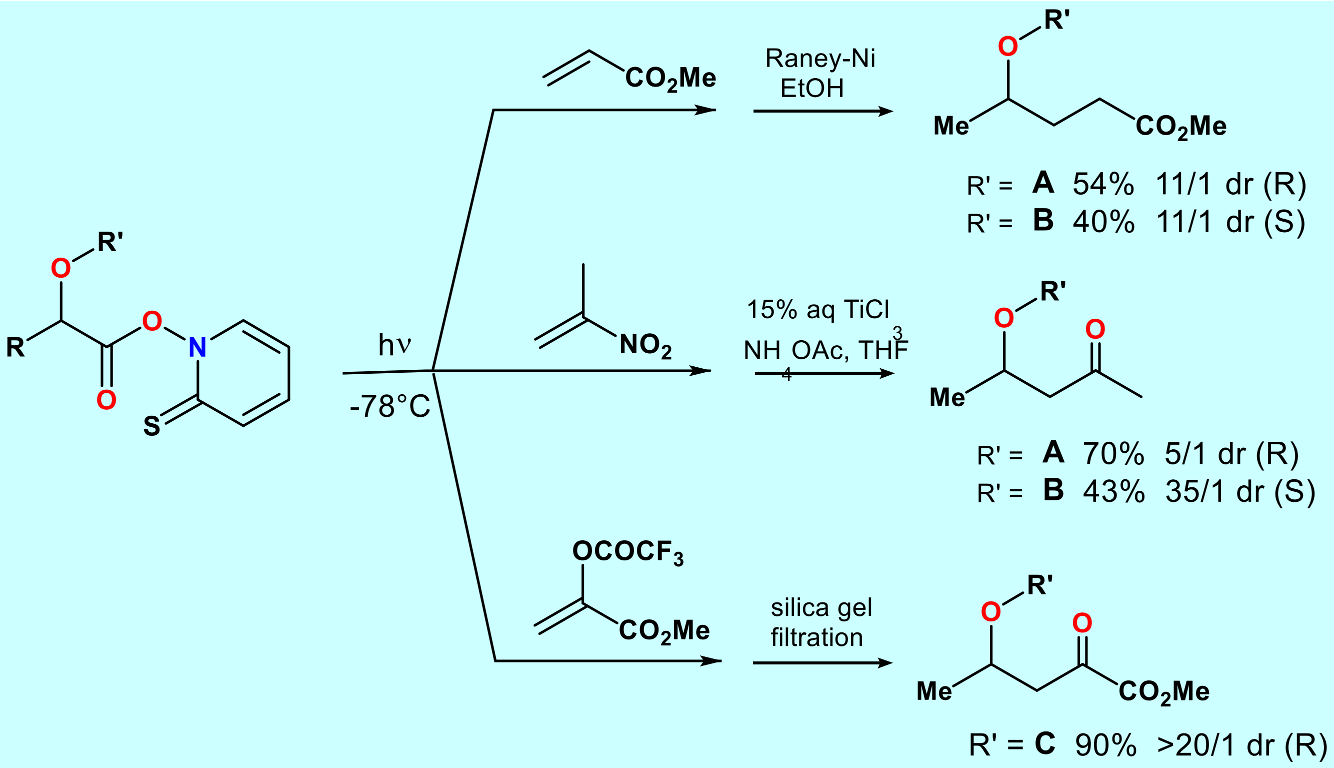
Porter, N.A.; Swann, E.; Nally, J.; McPhail, A.T. *J. Am. Chem. Soc.* **1990**, *112,* 6740.

Hydroxyalkyl Radicals – Chiral Auxiliaries



Garner, P.P.; Cox, P.B.; Klippenstein, S.J. *J. Am. Chem. Soc.* **1995**, *117*, 4183.

Hydroxyalkyl Radicals – Chiral Auxiliaries

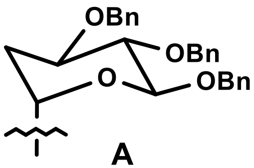


R' = **A** 54% 11/1 dr (R)
R' = **B** 40% 11/1 dr (S)

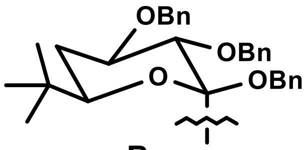
R' = **A** 70% 5/1 dr (R)
R' = **B** 43% 35/1 dr (S)

R' = **C** 90% >20/1 dr (R)

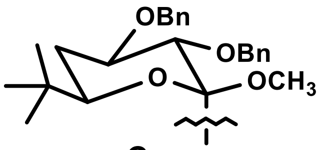
R' =



A



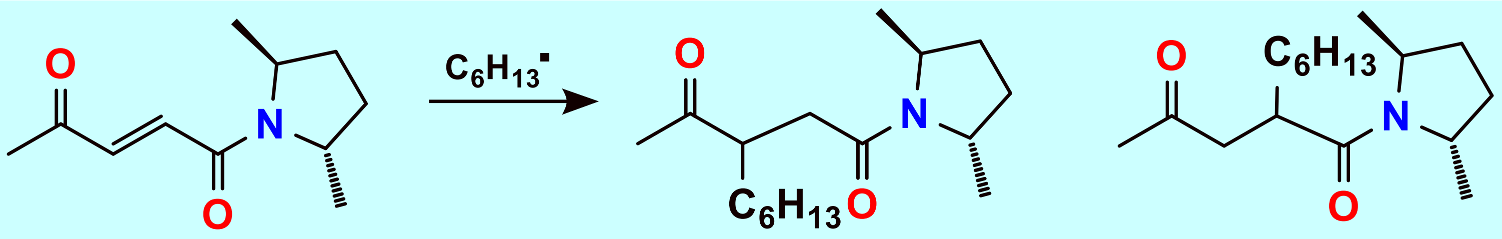
B



C

Garner, P.; Anderson, J.T.; Cox, P.B.; Klippenstein, S.J.; Leslie, R.; Scardovi, N. *J. Org. Chem*. **2002**, *67*, 61 95.

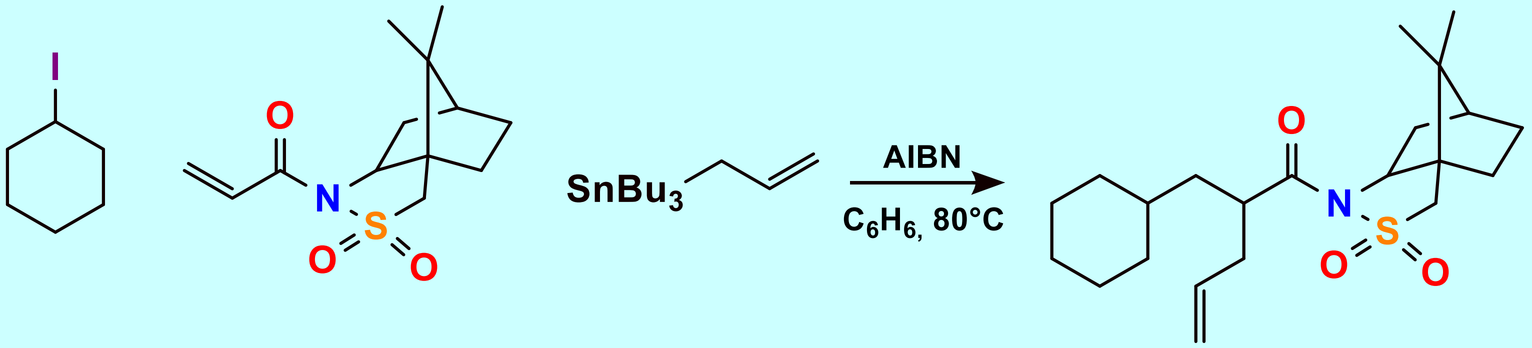
Chiral Michael Acceptors



A **B**

80°C AIB = 1.1 dr A = 1.5 dr B = 7.2

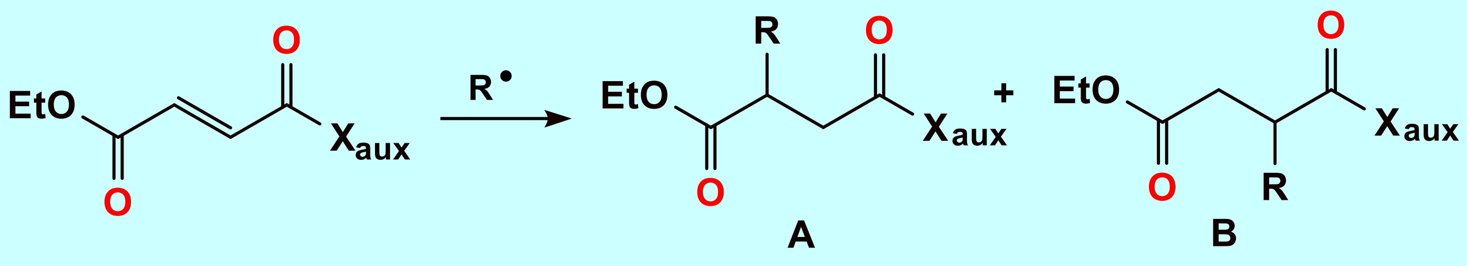
0°C A/B = .95 dr A = 1.5 dr B = 15.0

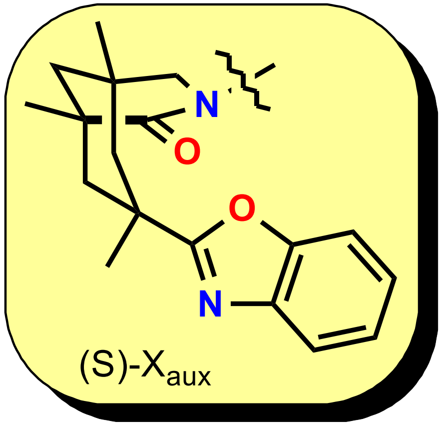


80% (11/1)

Porter, N.A.; Scott, D.M.; Lacher, B. *J. Am. Chem. Soc.* 1989, *111*, 831 1.
Curran, D.P.; Shen, W.; Zhang, J.; Heffner, T.A. *J. Am. Chem. Soc*. 1990**,** *112*, 6738.

Curran's Auxiliary in Conjugate Addition



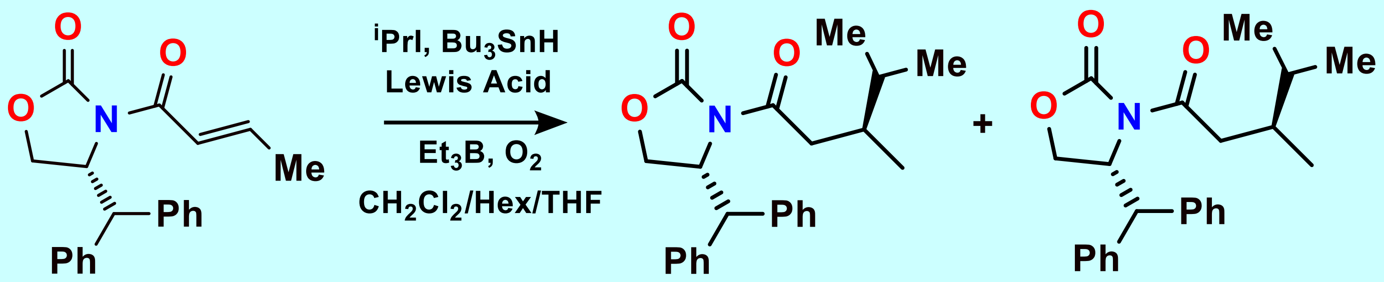


R	Temp.	Yield%	A:B	A dr
t-Bu	80	64	97:3	78:19
n-Bu	0	69	97:3	88:9
i-Bu	-20	68	>99:1	94:6
i-Pr	0	42	>99:1	82:18

Stack, J.G.; Curran, D.P.; Geib, S.V.; Rebek Jr., J.; Ballester, P *J. Am. Chem. Soc*. **1992**, *114*, 7007.

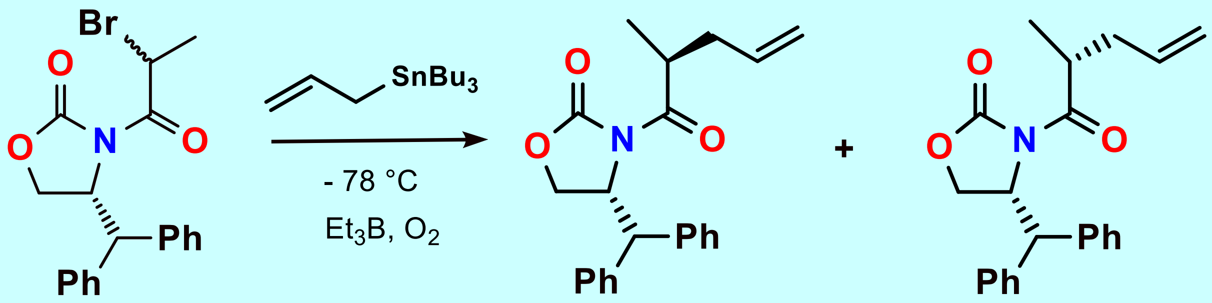
Complex Controlled Diastereoselective Conjugate Additions

Conjugate Addition



	1.3	1 (60%)
$Yb(OTf)_3$ (2 equiv.)	25	1 (90%)

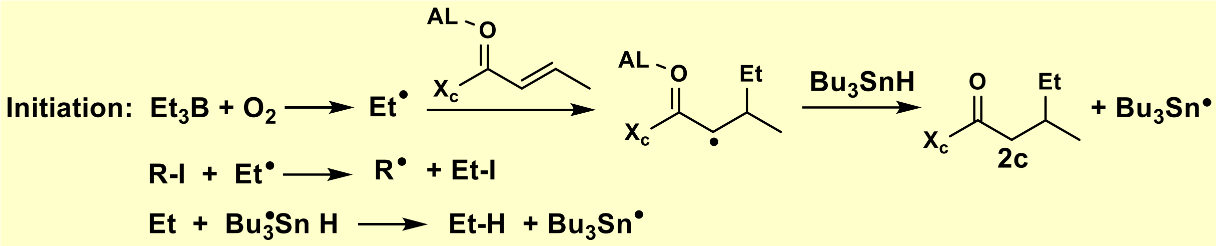
Fragmentation

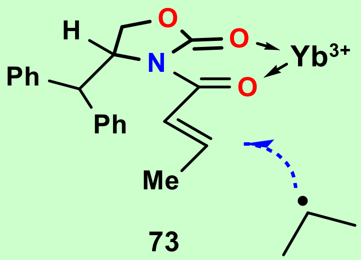


	1	1.8 (93%)
$MgBr_3$ (1 equiv.)	39	1 (94%)

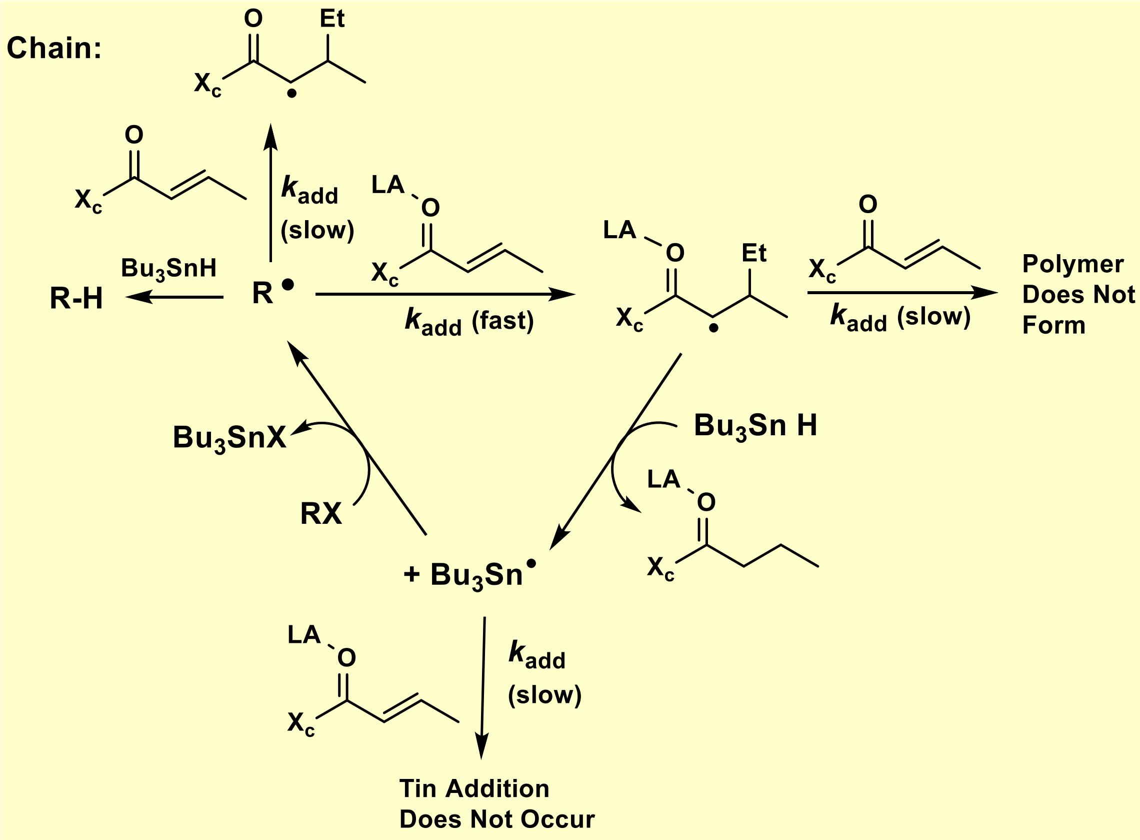
Sibi, M. P. et al *J. Am. Chem. Soc.* **1999**, *121*, 7517; **2000**, *122*, 887.

Complex Controlled Diastereoselective Conjugate Additions

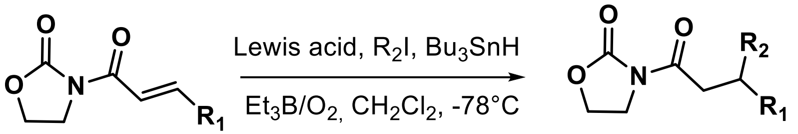




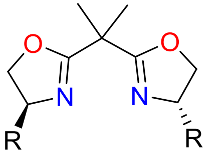
73



Enantioselective Conjugate Addition



5a R_1 = Ph
5b R_1 = CH_3
5c R_1 = H



6a R_1 = t-Bu (S,S)
6b R_1 = t-Bu (S,S)
6c R_1 = Ph (S,S)

7a R_1 = Ph, R_2 = i-Pr
7b R_1 = CH_3, R_2 = t-Bu
7c R_1 = CH_3, R_2 = c-C_6H_{11}

Wu, J.H.; Radinov, R.; Porter, N.A. *J. Am. Chem. Soc.* **1995**, *117*, 11029.
Sibi, M. P. et al *J. Am. Chem. Soc*. **1996**, *118*, 9200; **2001**, *123*, 9472.

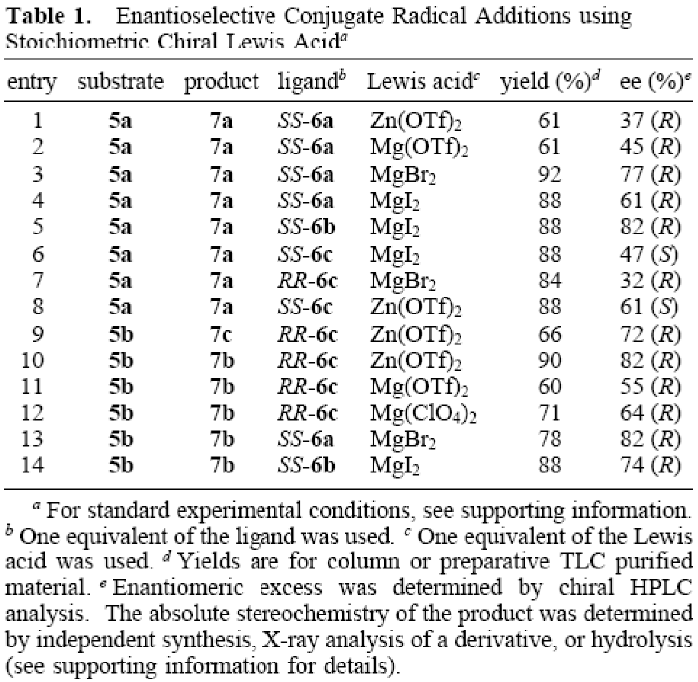


Table 1. Enantioselective Conjugate Radical Additions using Stoichiometric Chiral Lewis Acid[a]

entry	substrate	product	ligand[b]	Lewis acid[c]	yield (%)[d]	ee (%)[e]
1	**5a**	**7a**	*SS*-**6a**	$Zn(OTf)_2$	61	37 (*R*)
2	**5a**	**7a**	*SS*-**6a**	$Mg(OTf)_2$	61	45 (*R*)
3	**5a**	**7a**	*SS*-**6a**	$MgBr_2$	92	77 (*R*)
4	**5a**	**7a**	*SS*-**6a**	MgI_2	88	61 (*R*)
5	**5a**	**7a**	*SS*-**6b**	MgI_2	88	82 (*R*)
6	**5a**	**7a**	*SS*-**6c**	MgI_2	88	47 (*S*)
7	**5a**	**7a**	*RR*-**6c**	$MgBr_2$	84	32 (*R*)
8	**5a**	**7a**	*SS*-**6c**	$Zn(OTf)_2$	88	61 (*S*)
9	**5b**	**7c**	*RR*-**6c**	$Zn(OTf)_2$	66	72 (*R*)
10	**5b**	**7b**	*RR*-**6c**	$Zn(OTf)_2$	90	82 (*R*)
11	**5b**	**7b**	*RR*-**6c**	$Mg(OTf)_2$	60	55 (*R*)
12	**5b**	**7b**	*RR*-**6c**	$Mg(ClO_4)_2$	71	64 (*R*)
13	**5b**	**7b**	*SS*-**6a**	$MgBr_2$	78	82 (*R*)
14	**5b**	**7b**	*SS*-**6b**	MgI_2	88	74 (*R*)

[a] For standard experimental conditions, see supporting information. [b] One equivalent of the ligand was used. [c] One equivalent of the Lewis acid was used. [d] Yields are for column or preparative TLC purified material. [e] Enantiomeric excess was determined by chiral HPLC analysis. The absolute stereochemistry of the product was determined by independent synthesis, X-ray analysis of a derivative, or hydrolysis (see supporting information for details).

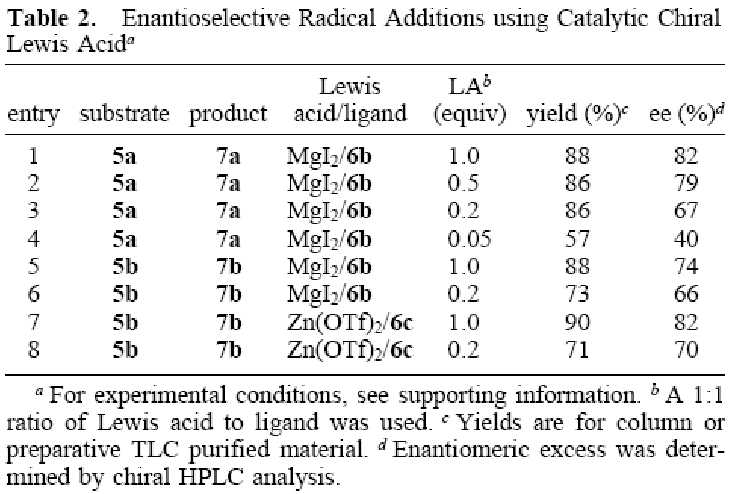
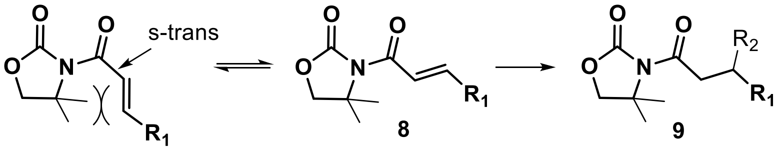


Table 2. Enantioselective Radical Additions using Catalytic Chiral Lewis Acid[a]

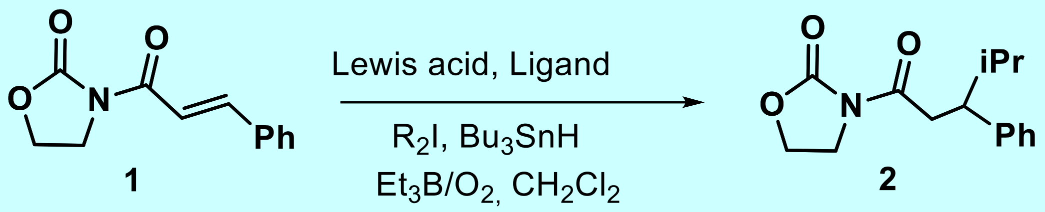
entry	substrate	product	Lewis acid/ligand	LA[b] (equiv)	yield (%)[c]	ee (%)[d]
1	**5a**	**7a**	MgI_2/**6b**	1.0	88	82
2	**5a**	**7a**	MgI_2/**6b**	0.5	86	79
3	**5a**	**7a**	MgI_2/**6b**	0.2	86	67
4	**5a**	**7a**	MgI_2/**6b**	0.05	57	40
5	**5b**	**7b**	MgI_2/**6b**	1.0	88	74
6	**5b**	**7b**	MgI_2/**6b**	0.2	73	66
7	**5b**	**7b**	$Zn(OTf)_2$/**6c**	1.0	90	82
8	**5b**	**7b**	$Zn(OTf)_2$/**6c**	0.2	71	70

[a] For experimental conditions, see supporting information. [b] A 1:1 ratio of Lewis acid to ligand was used. [c] Yields are for column or preparative TLC purified material. [d] Enantiomeric excess was determined by chiral HPLC analysis.



$MgBr_2$ 52%ee
$Zn(OTf_2)$ 72%ee

Enantioselective Conjugate Addition



1

Lewis acid, Ligand

R_2I, Bu_3SnH

Et_3B/O_2, CH_2Cl_2

2

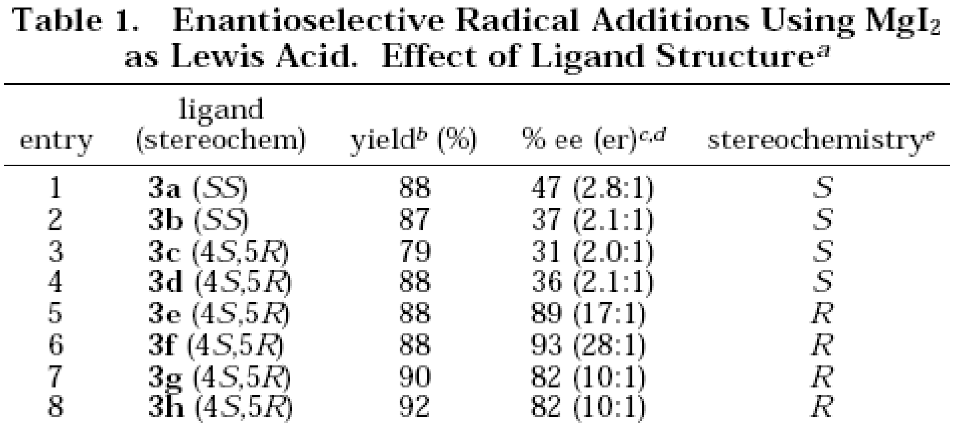
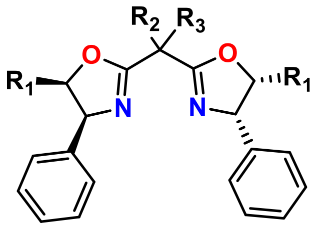
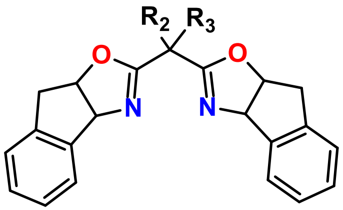


Table 1. Enantioselective Radical Additions Using MgI_2 as Lewis Acid. Effect of Ligand Structure[a]

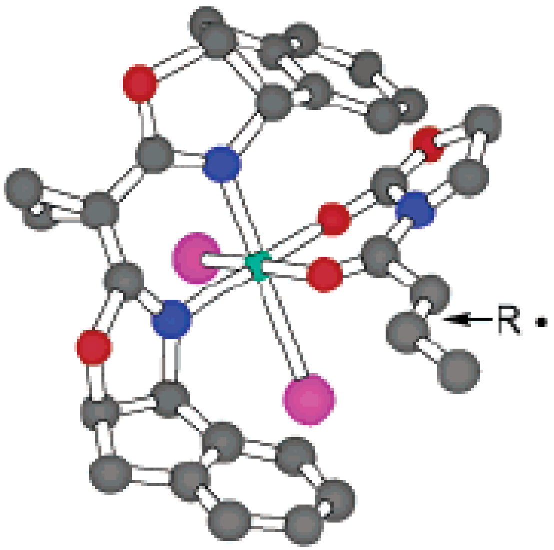
entry	ligand (stereochem)	yield[b] (%)	% ee (er)[c,d]	stereochemistry[e]
1	**3a** (*SS*)	88	47 (2.8:1)	*S*
2	**3b** (*SS*)	87	37 (2.1:1)	*S*
3	**3c** (4*S*,5*R*)	79	31 (2.0:1)	*S*
4	**3d** (4*S*,5*R*)	88	36 (2.1:1)	*S*
5	**3e** (4*S*,5*R*)	88	89 (17:1)	*R*
6	**3f** (4*S*,5*R*)	88	93 (28:1)	*R*
7	**3g** (4*S*,5*R*)	90	82 (10:1)	*R*
8	**3h** (4*S*,5*R*)	92	82 (10:1)	*R*



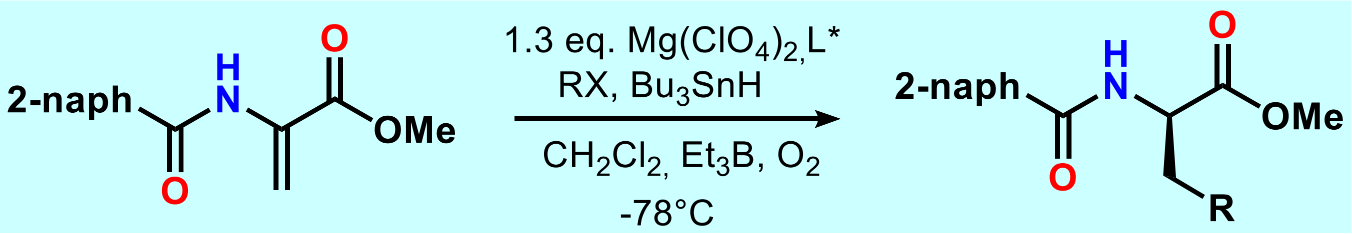


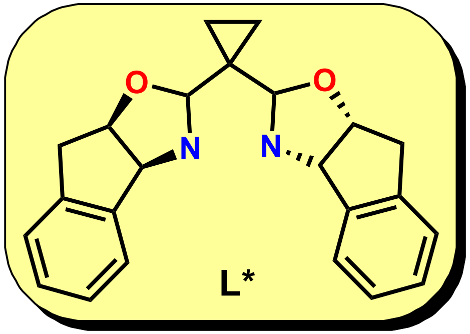
3a R_1 = H, R_2 = R_3 = CH_3
3b R_1 = H, R_2, R_3 = (CH_2CH_2)
3c R_1 = CH_3, R_2, R_3 = CH_3
3d R_1 = CH_3, R_2, R_3 = (CH_2CH_2))

3e R_1 = R_2 = CH_3
3f R_1, R_2 = (CH_2CH_2)
3g R_1, R_2 = ($CH_2CH_2CH_2$)
3h R_1, R_2= ($CH_2CH_2CH_2Ch_2$))



Amino Acid Synthesis

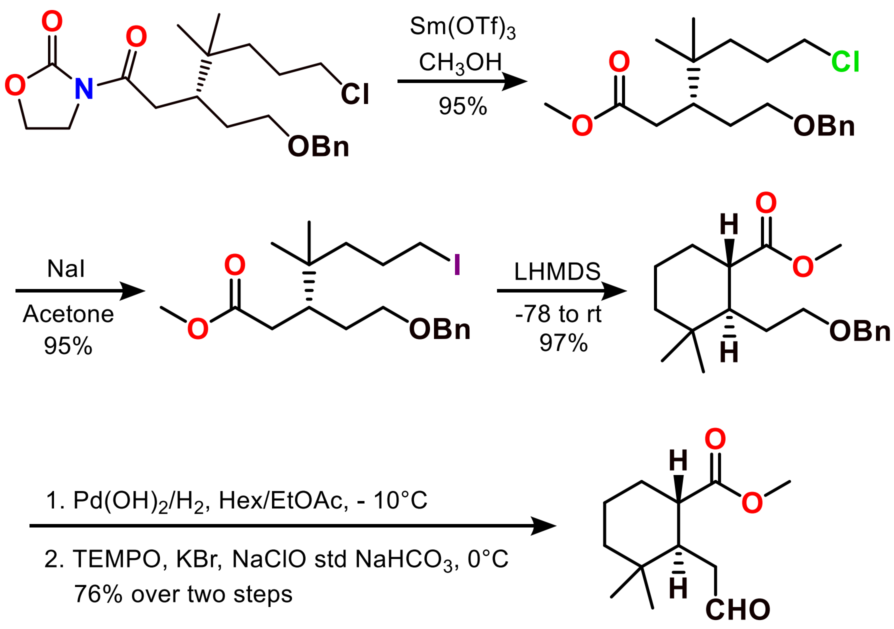


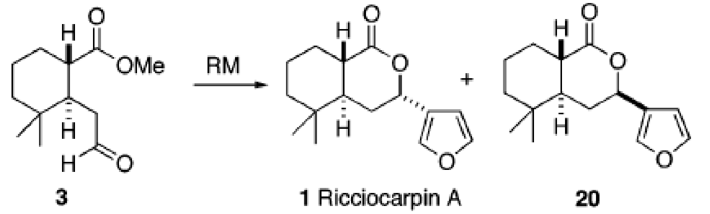


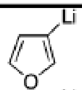
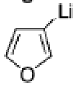
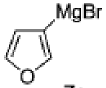
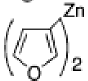
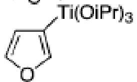
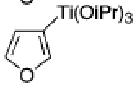
RX	Yield%	ee
$MeOCH_2Br$	71	65
EtI	72	85
C-HexI	62	55
i-PrI	62	83
T-BuI	54	27

Sibi, M.P.; Asano, Y.; Sausker, J.B. *Angew. Chem. Int Ed*. **2001**, *40*, 1293.

Enantioselective Conjugate Addition : Application to Synthesis



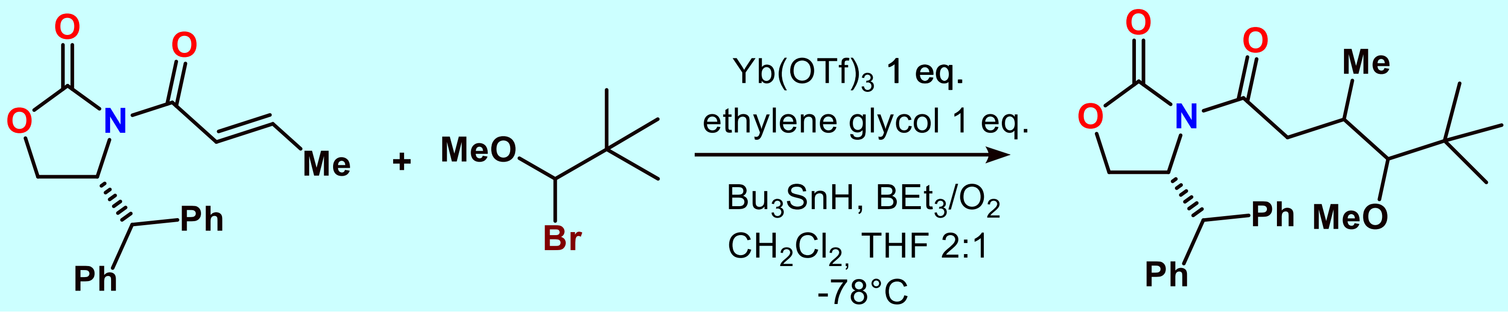


entry	RM	temp °C	solv.	time, h	yield, (%)[b]	ratio[c] 1:20
1	 Li	-78	THF	6	33	1:3
2	 Li	-78	Ether	5	26	1:7.8
3	 MgBr	-78	Ether	3	21	1:6
4[d]	 Zn, 2	0	Ether	10	8	1:3
5	 Ti(OiPr)$_3$	-78	THF	4	28	1:1
6	 Ti(OiPr)$_3$	-78	Ether	4	85	5.7:1

[a] For reaction conditions, see Supporting Information. [b] Isolated yield after column purification. [c] Determined by NMR. [d] Pseudo-ephedrine was used as a ligand.

Sibi, M. P. et al *Org. Lett.* **2004**, *6*, 1749.

Conjugate Addition of Prochiral Radicals



85% dr: 14:l

Alkene summary

- Chiral auxiliary and chiral Lewis acids have been used successfully in radical additions to alkenes.
- Oxazolidinones have proven to be the most versatile scaffold in these reactions.
- Aldol type products are accessible from appropriately substituted radicals or alkenes.

Sibi, M.P.; Rheault, T.R.; Chandrarnouli, S.V.; Jasperse, C.P. *J. Am. Chem. Soc***. 2002,** ***124,*** **2924.**