

Wolfgang Oppolzer

1937 - 1996



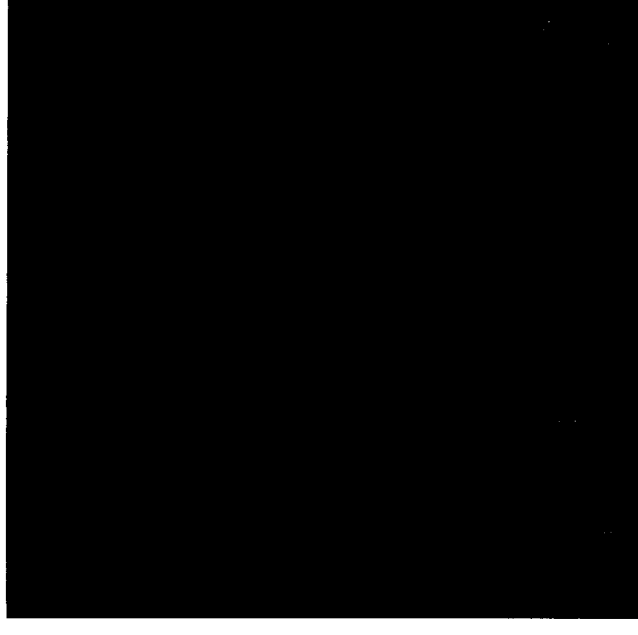
Chris Regens

SED Group Meeting

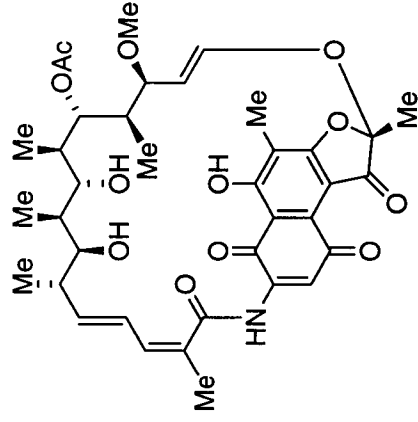
18.10.2005

Wolfgang Oppolzer: *Biographical Sketch*

- Professional Positions
 - Sandoz (now Novartis), 1967 - 1974
 - University of Geneva, 1974 - 1996
- Awards
 - Cliff S. Hamilton Award, 1987
 - Ernest-Guenther Award, ACS, 1991
 - Otto-Wallach Plakette, Soc. German Chemists, 1991
 - Quilico Medal, ICS, 1994
 - President of Bürgenstock Conf., 1993
- Over 200 Publications



Career of W. Oppolzer: *Time Line*



1960

Undergraduate
University of Vienna



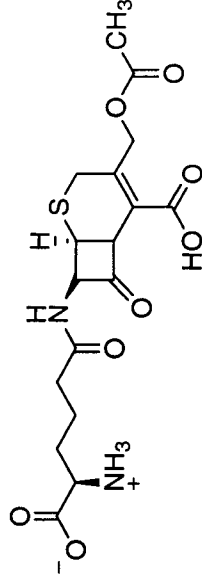
1960

Graduate study
with V. Prelog (ETH)
(structures of rifamycines)



1937

Born in Vienna,
Austria



1964

Postdoctoral study
with E.J.Corey
(sulfur ylides)

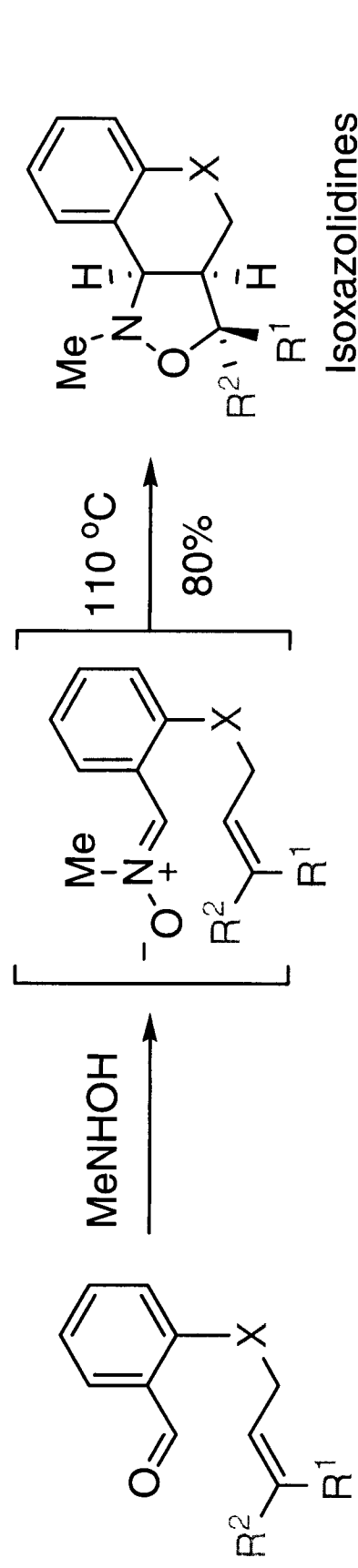


1966

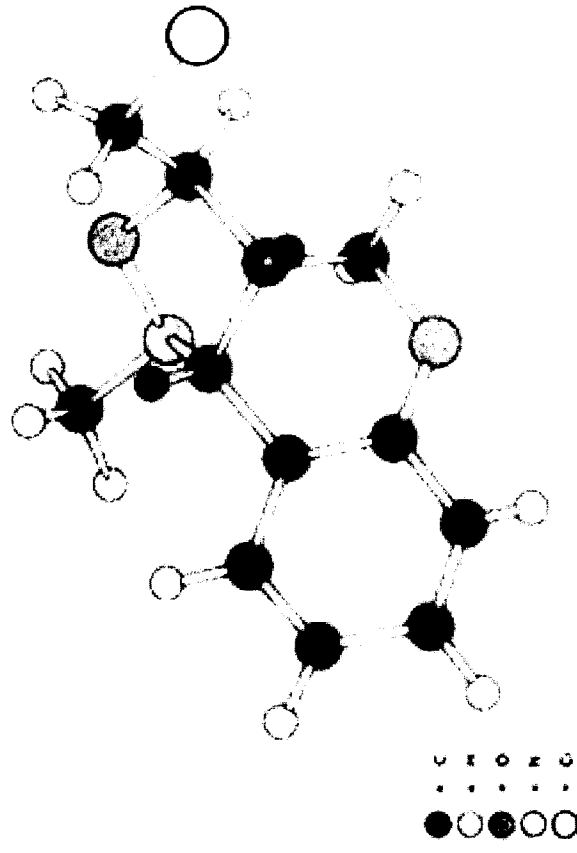
Woodward Research Inst.
R.B. Woodward
(Synthesis of cephalosporin C)



Intramolecular Cycloaddition: Nitrones



Isoxazolidines

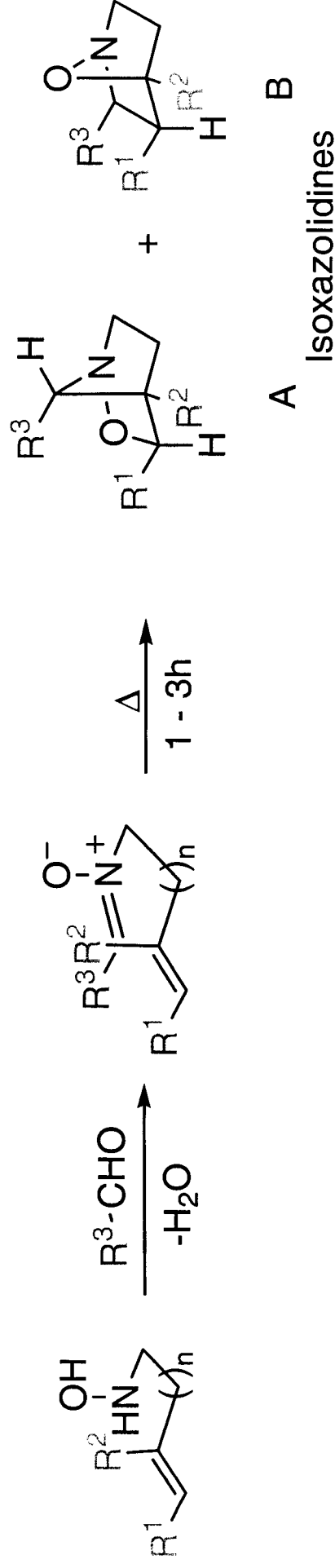


Entry	R ¹	R ²	X	yield (%)
1	H	H	O	80
2	H	H	N	80
3	CH ₃	CH ₃	O	75
4	CH ₃	H	O	46

Oppolzer, W.; Weber, H.P. *Tetrahedron Lett.* **1970**, *13*, 1117.

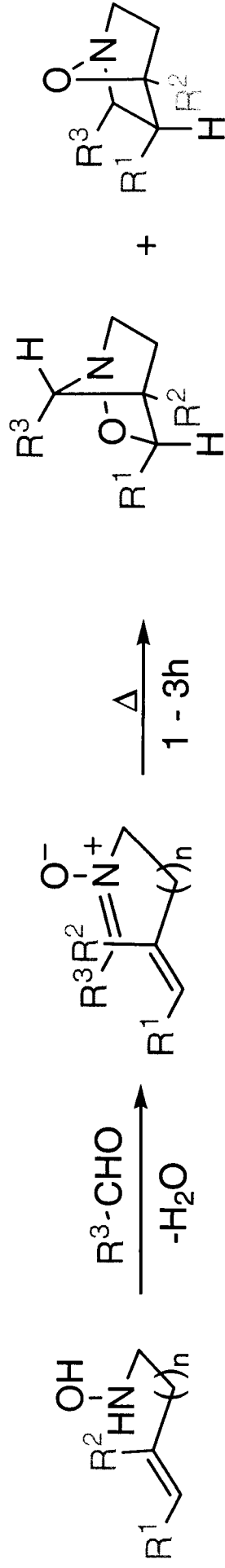
Oppolzer, W.; Weber, H.P. *Tetrahedron Lett.* **1970**, *13*, 1121.

Intramolecular Cycloaddition: Nitrones



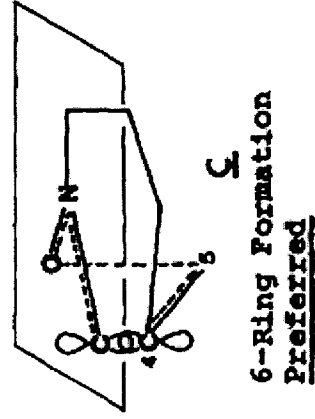
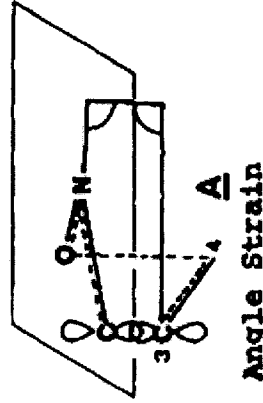
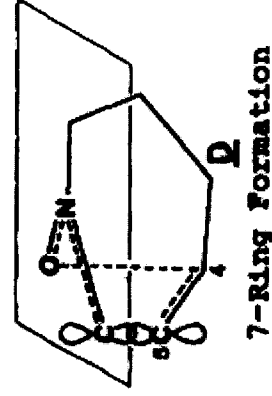
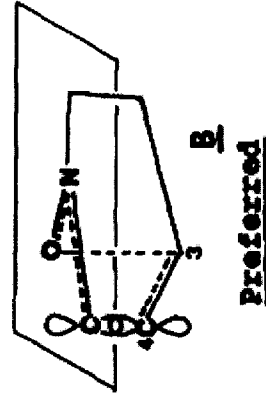
Entry	n	R ¹	R ²	R ³	A (%)	B (%)
1	1	CH ₃	H	H	0	76
2	2	CH ₃	H	H	95	0
3	3	CH ₃	H	H	68	23

Intramolecular Cycloaddition: Nitrones – Transition State



A B

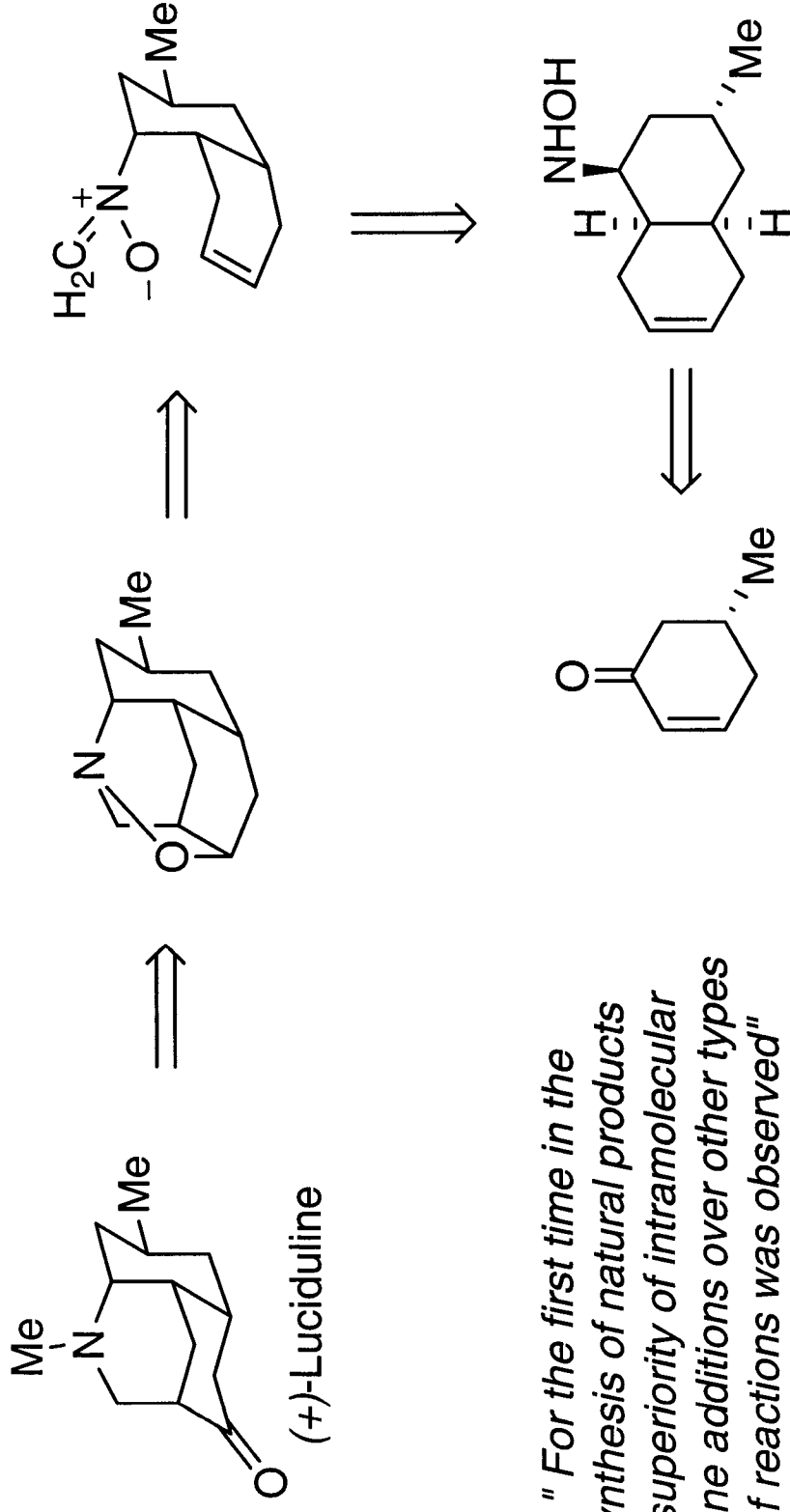
Isoxazolidines



• Assume the new C-C bond is more developed than C-O bond

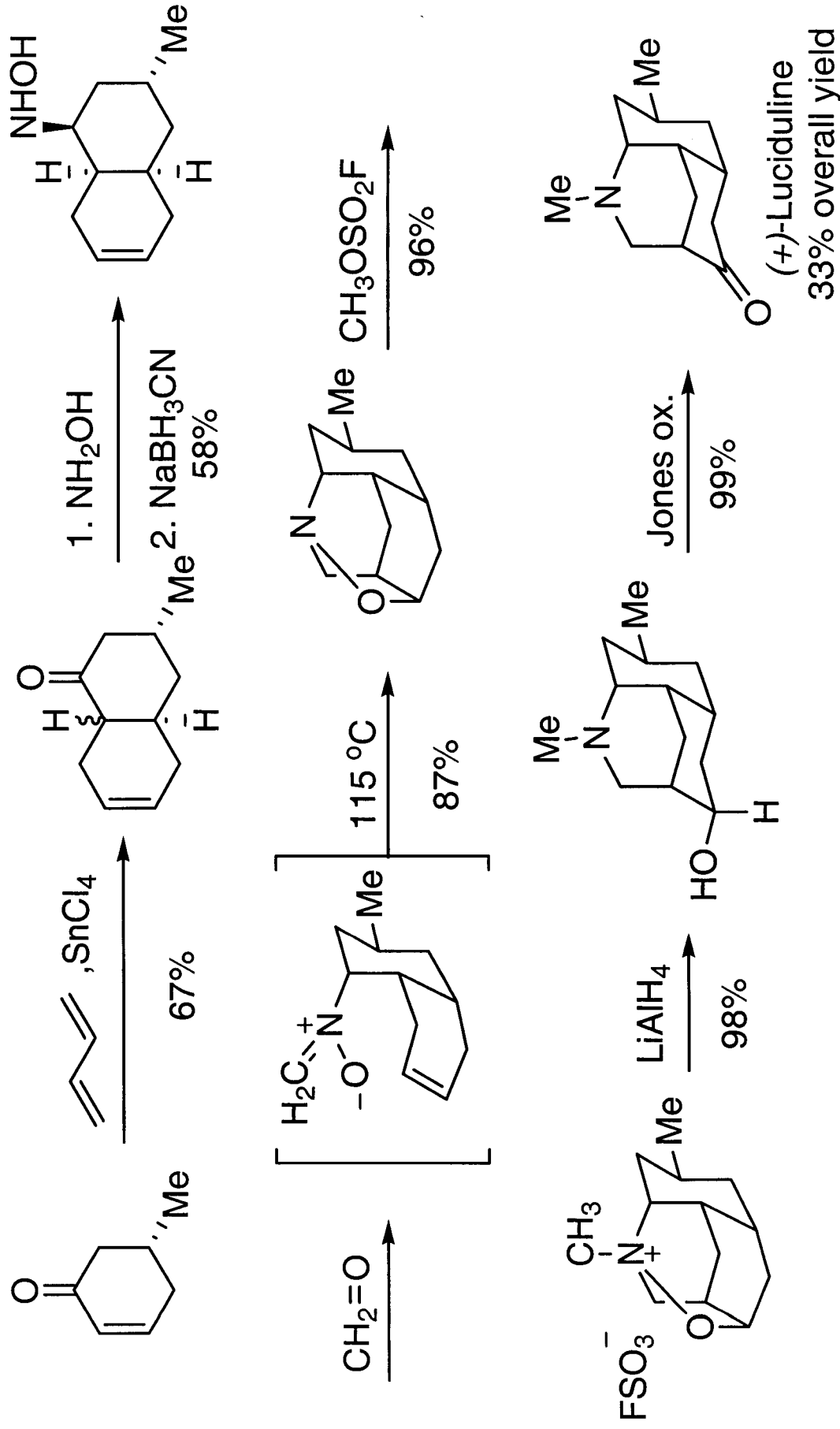
• C-C bond formation for 3-alkenyl nitrones to the “nearer” olefin implies strain A (exo) favoring B (endo)
 • Preference of C over D is ascribed to an entropically favored ring closure

Intramolecular Cycloaddition: Nitrones – Synthesis of (+)-Luciduline

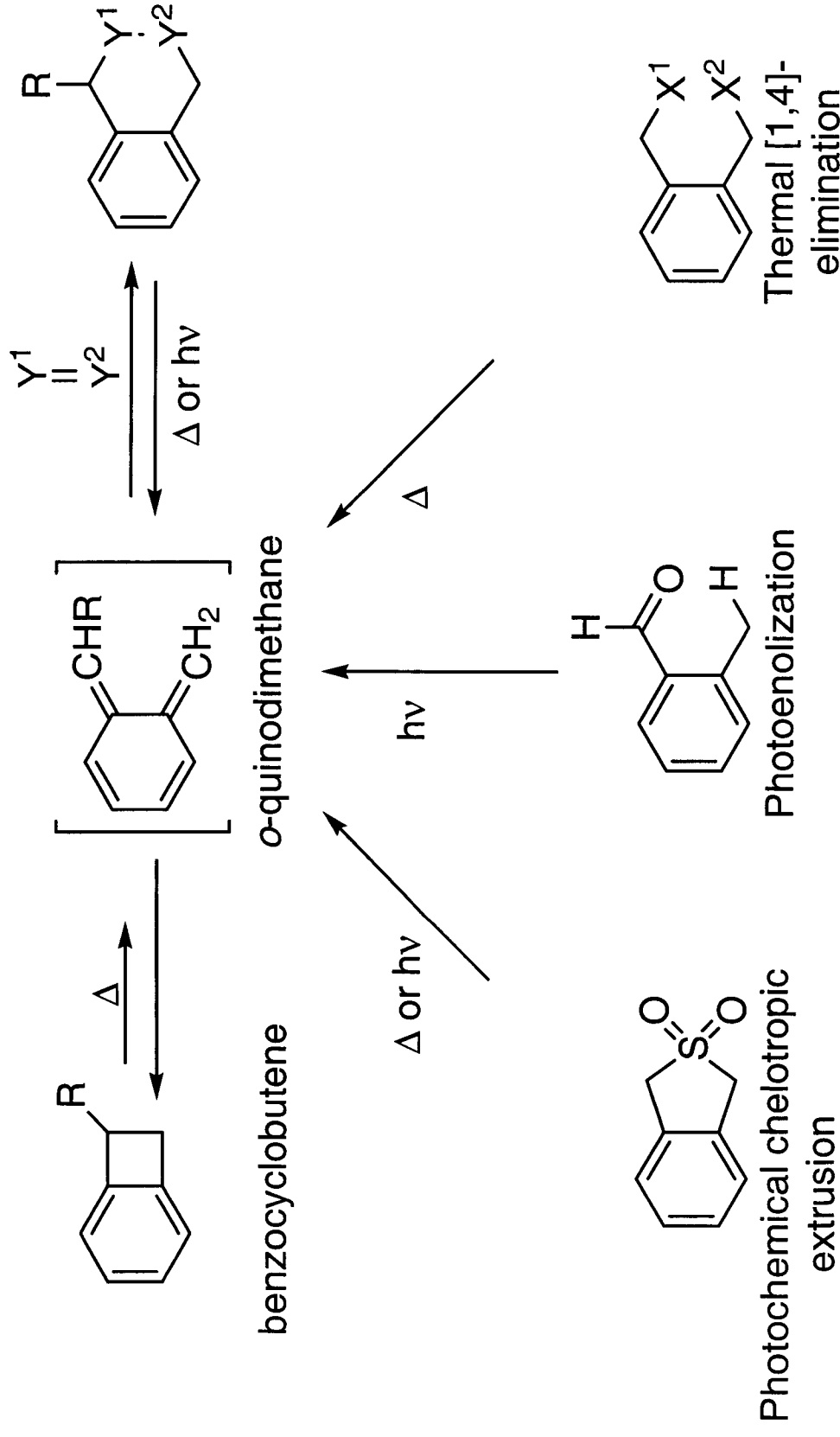


" For the first time in the synthesis of natural products a superiority of intramolecular nitronium additions over other types of reactions was observed"
-W. Oppolzer

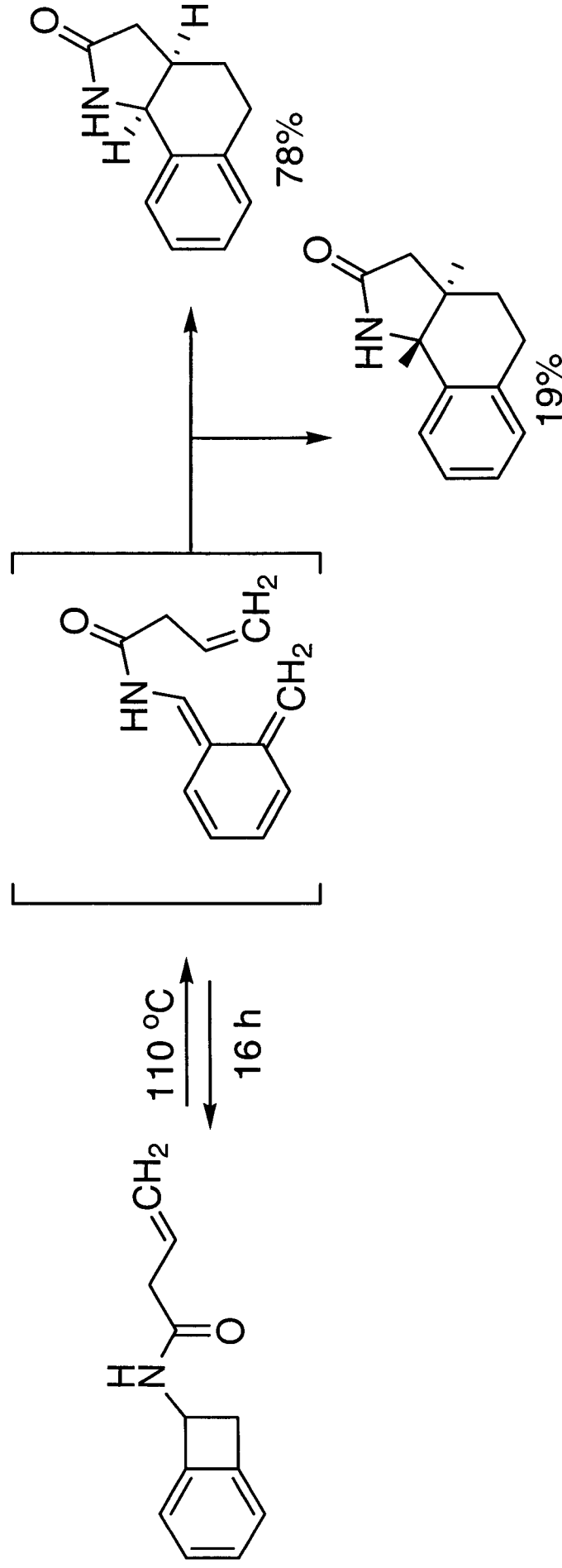
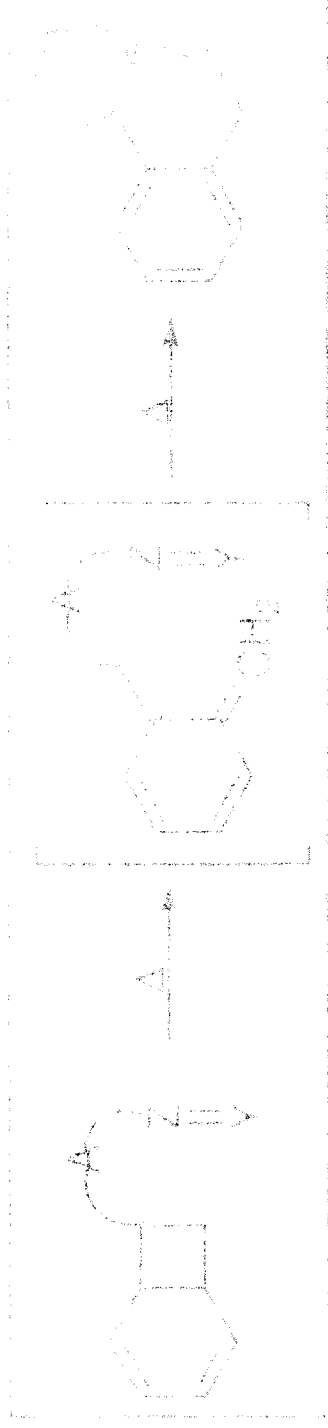
Intramolecular Cycloaddition: Nitrones – Synthesis of (+)-Luciduline



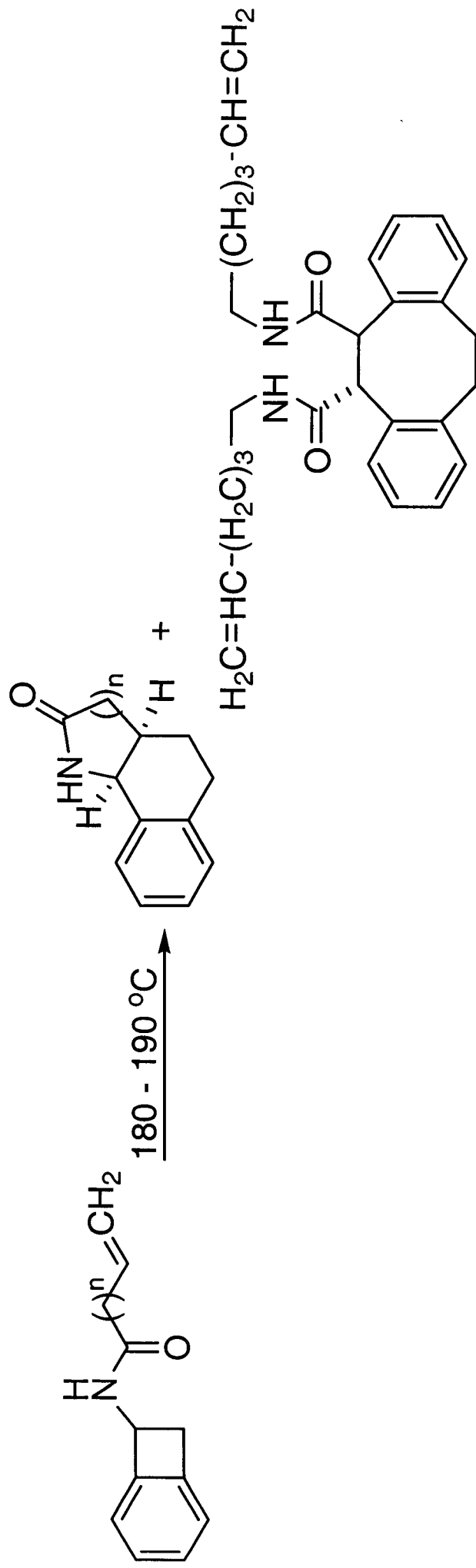
Intramolecular Cycloaddition: Generation of *o*-Quinodimethanes



Intramolecular Cycloaddition: Initial Results with *o*-Quinodimethanes

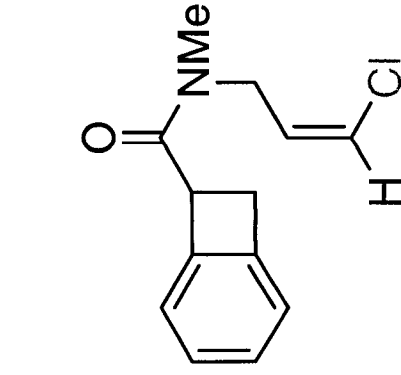


Intramolecular Cycloaddition: Initial Results with *o*-Quinodimethanes

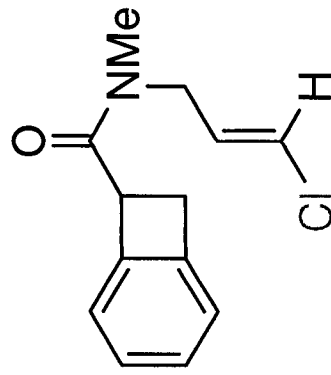


Entry	n	conc (%)	cis (%)	dimer (%)
1	1	8	80	-
2	2	8	80	-
3	3	0.5	20	6

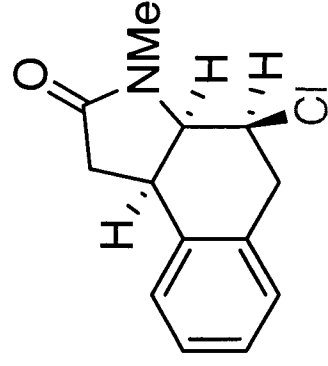
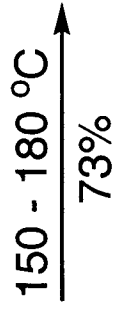
Intramolecular Cycloaddition: Concerted or Stepwise?



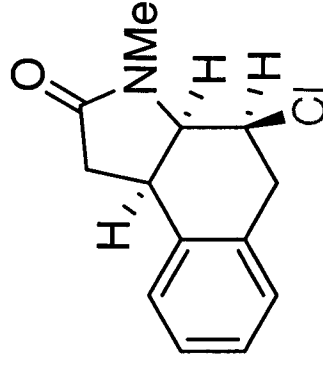
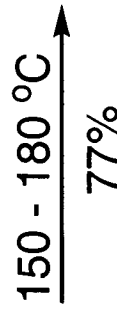
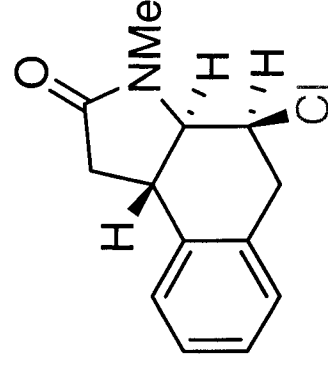
cis-chloroallylamide



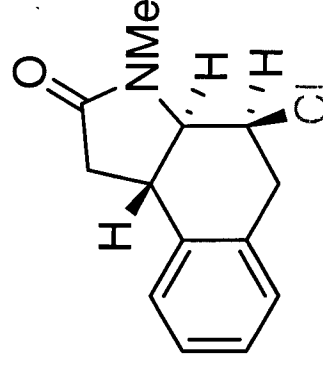
trans-chloroallylamide



+

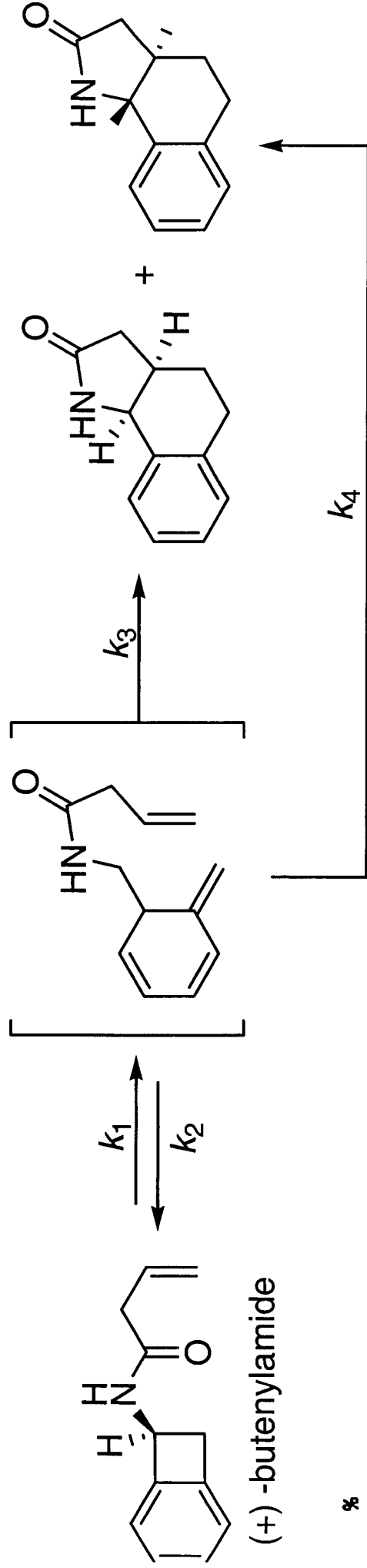


+



The observed stereochemical relationship suggests a concerted [4 + 2] process

Intramolecular Cycloaddition: Determination of Mechanism



- Reversible ring opening (k_1 and k_2)
- Irreversible intramolecular trapping (k_3 or k_4).
- 1st order disappearance of optically active butenylamide
- Both cycloadducts are racemic (suggesting achiral intermediate)
- Steady State ($k_1 \ll k_2$) \rightarrow TS for *cis* is 1.0 kcal/mol lower than *trans* (which is 0.2 kcal/mol higher than ring opening)

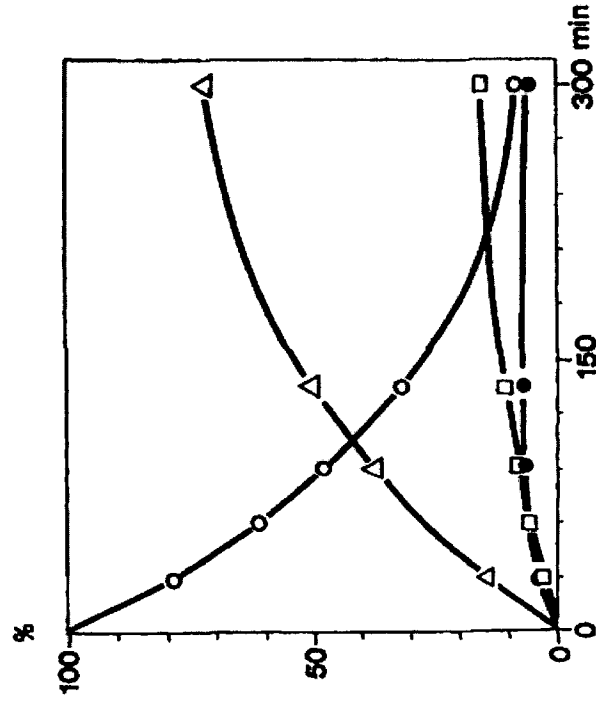
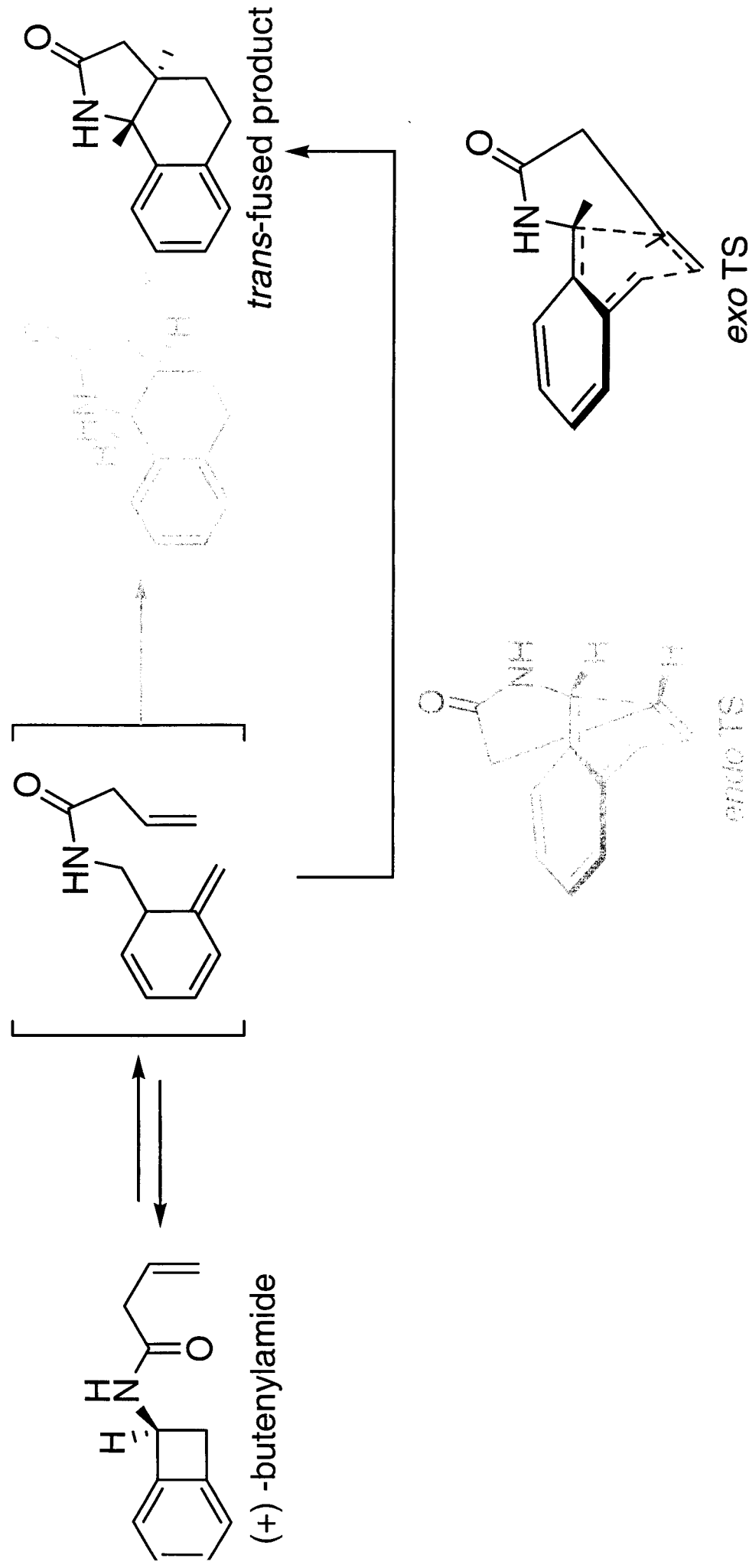
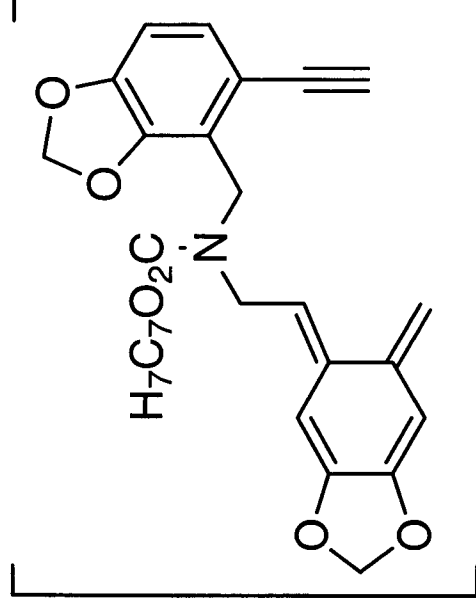
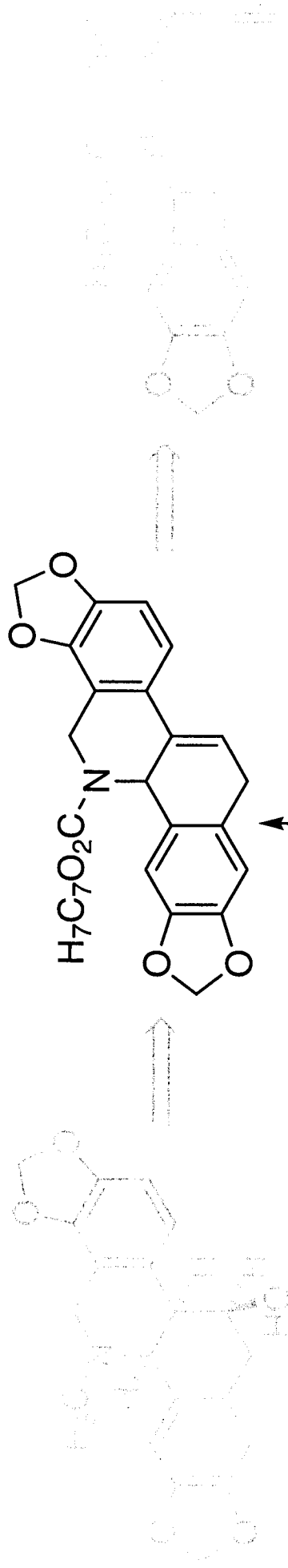


Figure 1. Kinetics of the rearrangement of optically active **1** in toluene (0.5% solution, 748 mm): \circ , concentration of optically active **1**; \bullet , concentration of racemic **1**; Δ , concentration of **3**; \square , concentration of **4**.

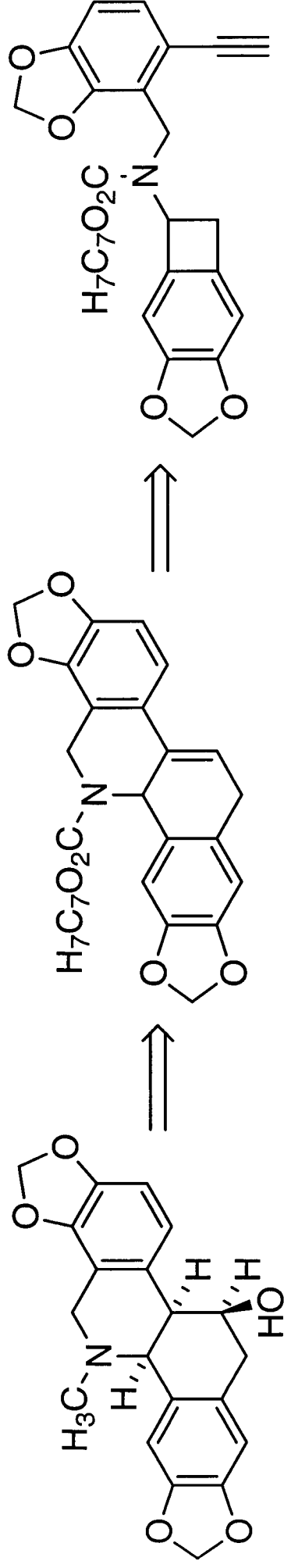
Intramolecular Cycloaddition: Transition States of Cis and Trans Fused



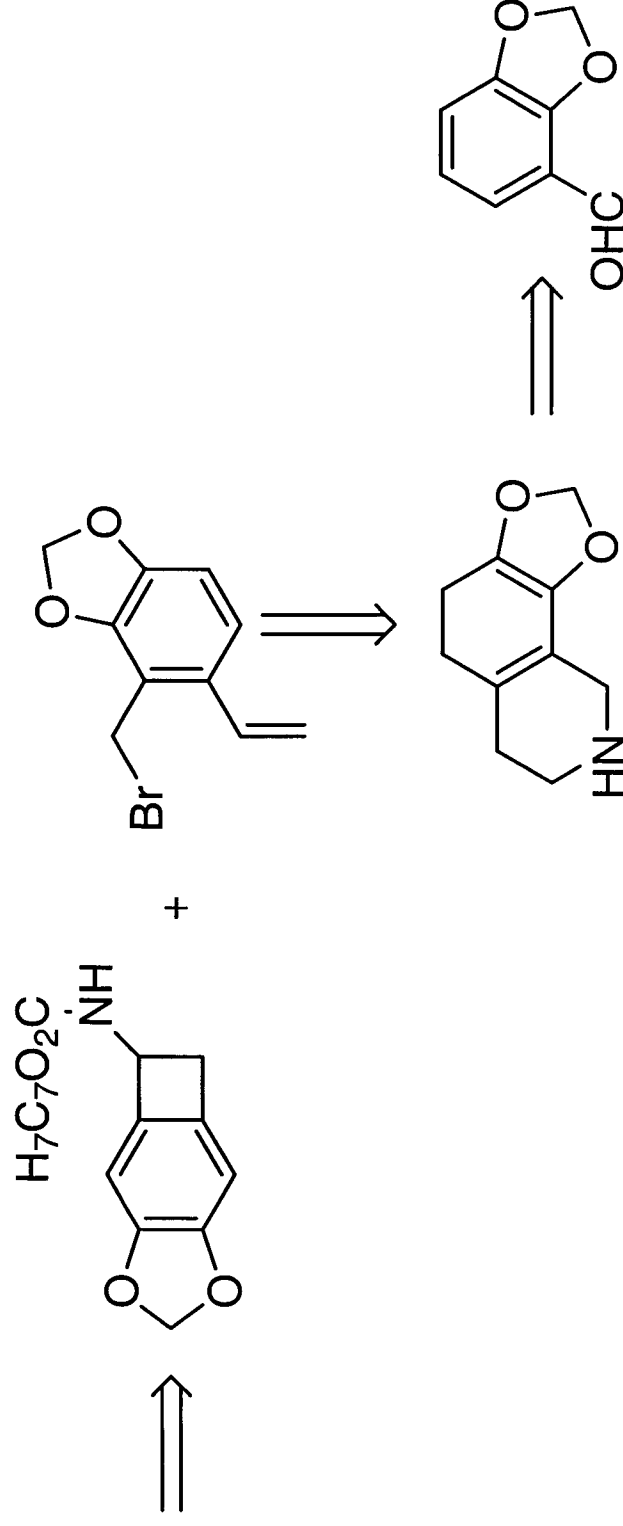
Intramolecular Cycloaddition: Total Synthesis of (\pm)-Chelidoniumine



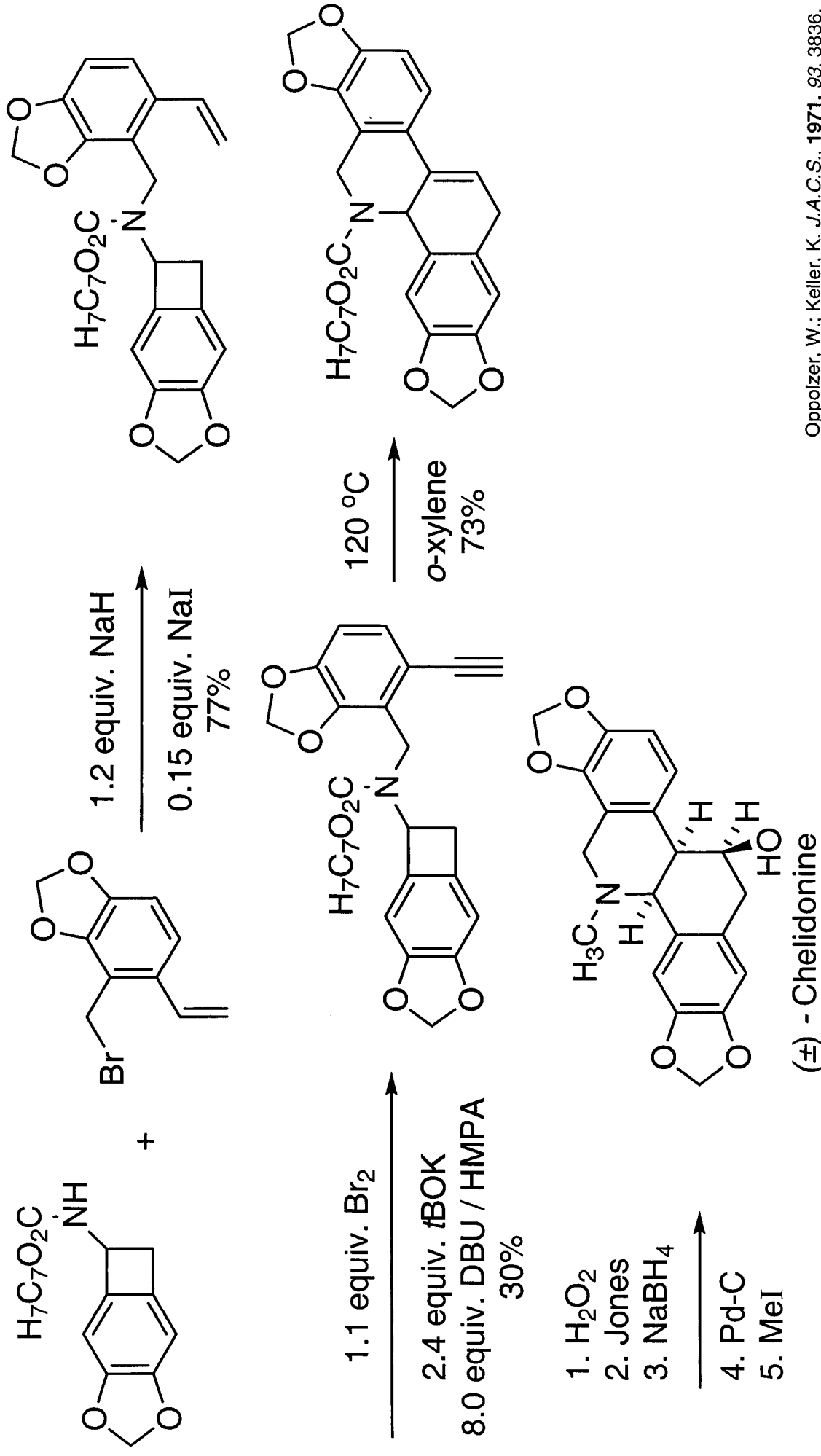
Intramolecular Cycloaddition: Total Synthesis of (\pm)-Chelidonine



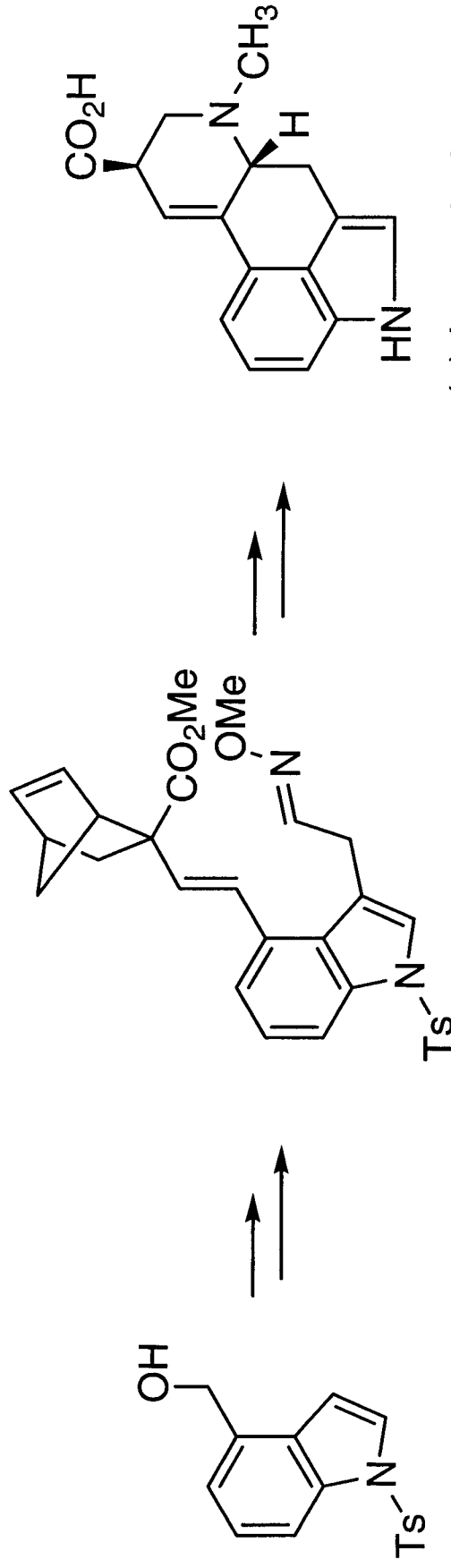
(\pm) - Chelidonine



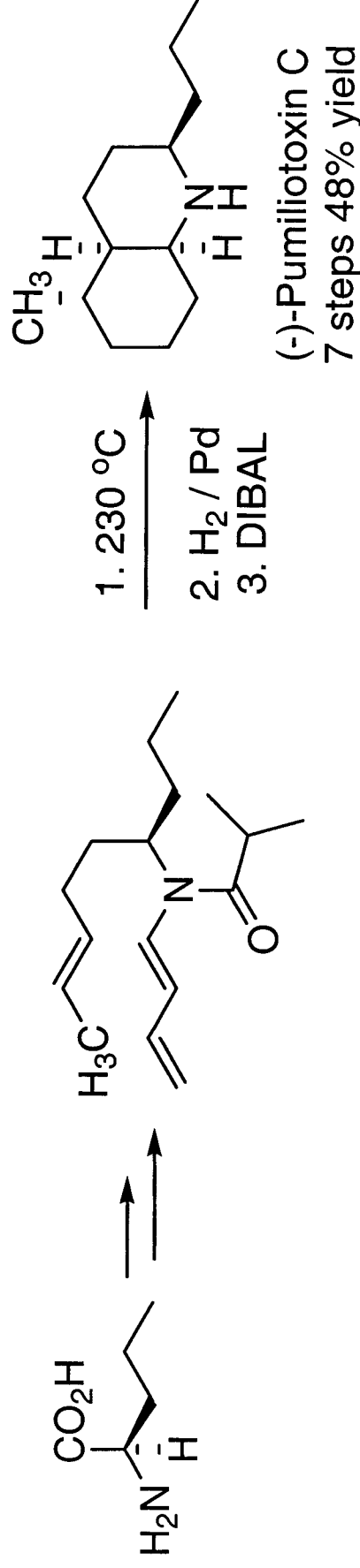
Intramolecular Cycloaddition: Total Synthesis of (±)-Chelidonine



Intramolecular Cycloaddition: Notable Syntheses



(±)-Lysergic Acid
9 steps 58% yield

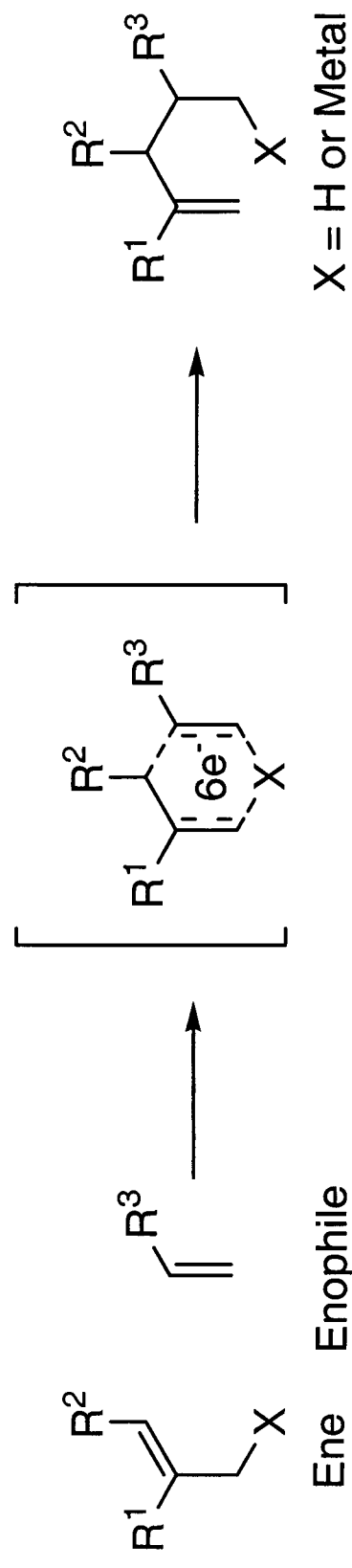


(-)-Pumiliotoxin C
7 steps 48% yield

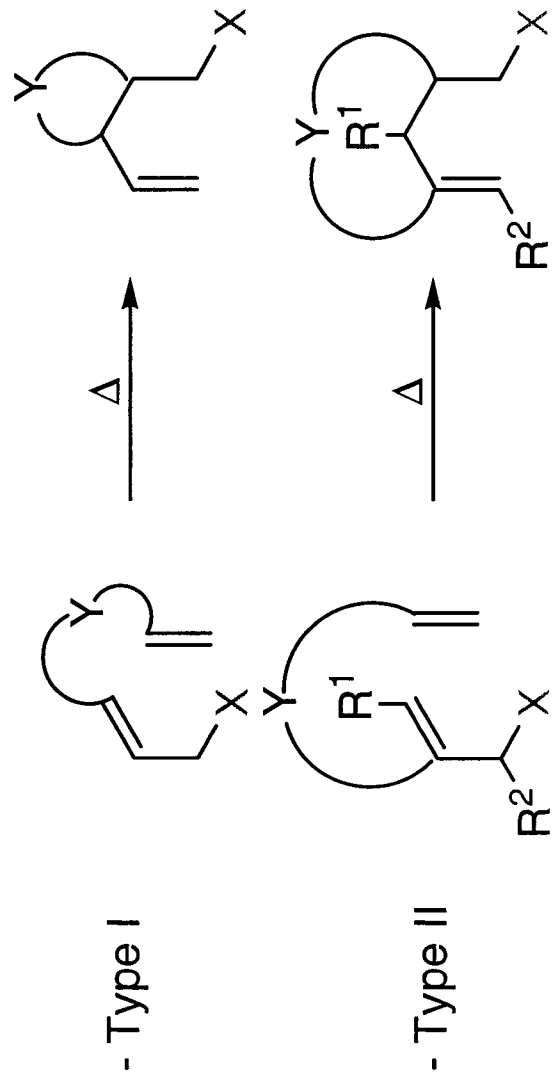
Oppolzer, W. et. al. *Helv.* 1981, 64, 478

Oppolzer, W. et. al. *Helv.* 1977, 60, 204.

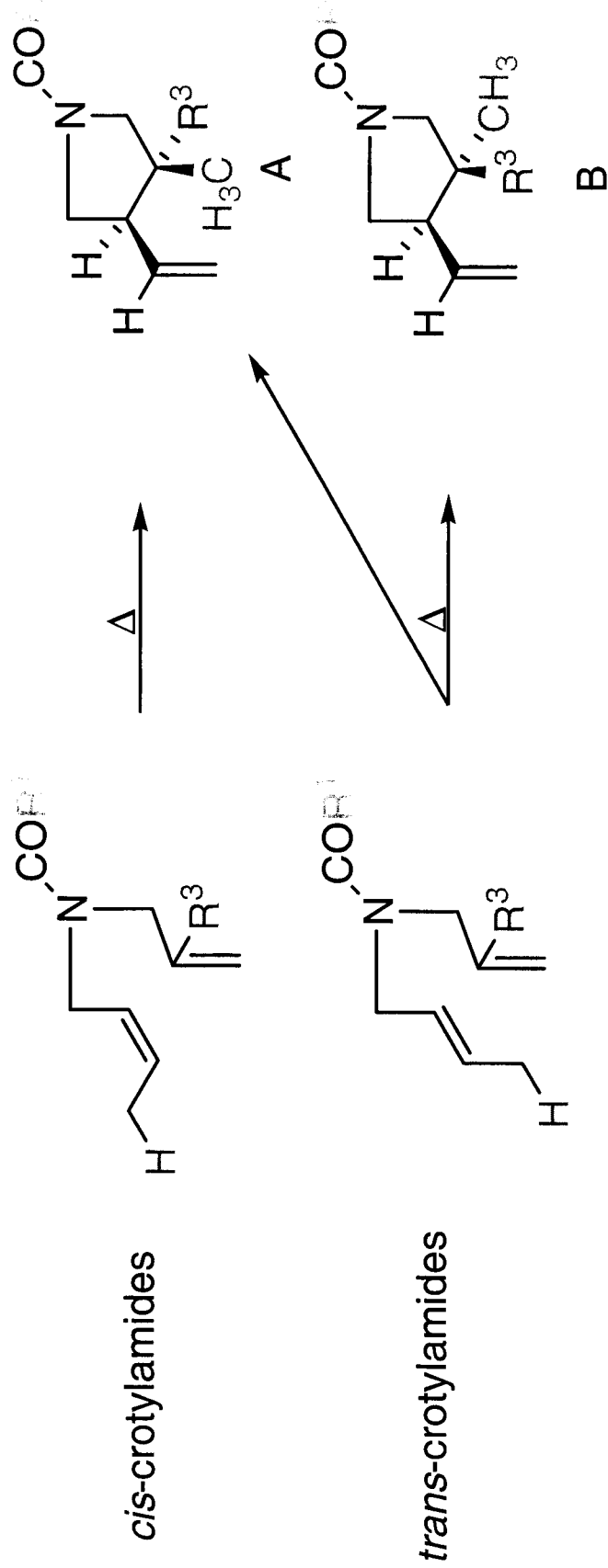
Intramolecular Ene: General Discussion



- Types of Intermolecular ene reactions

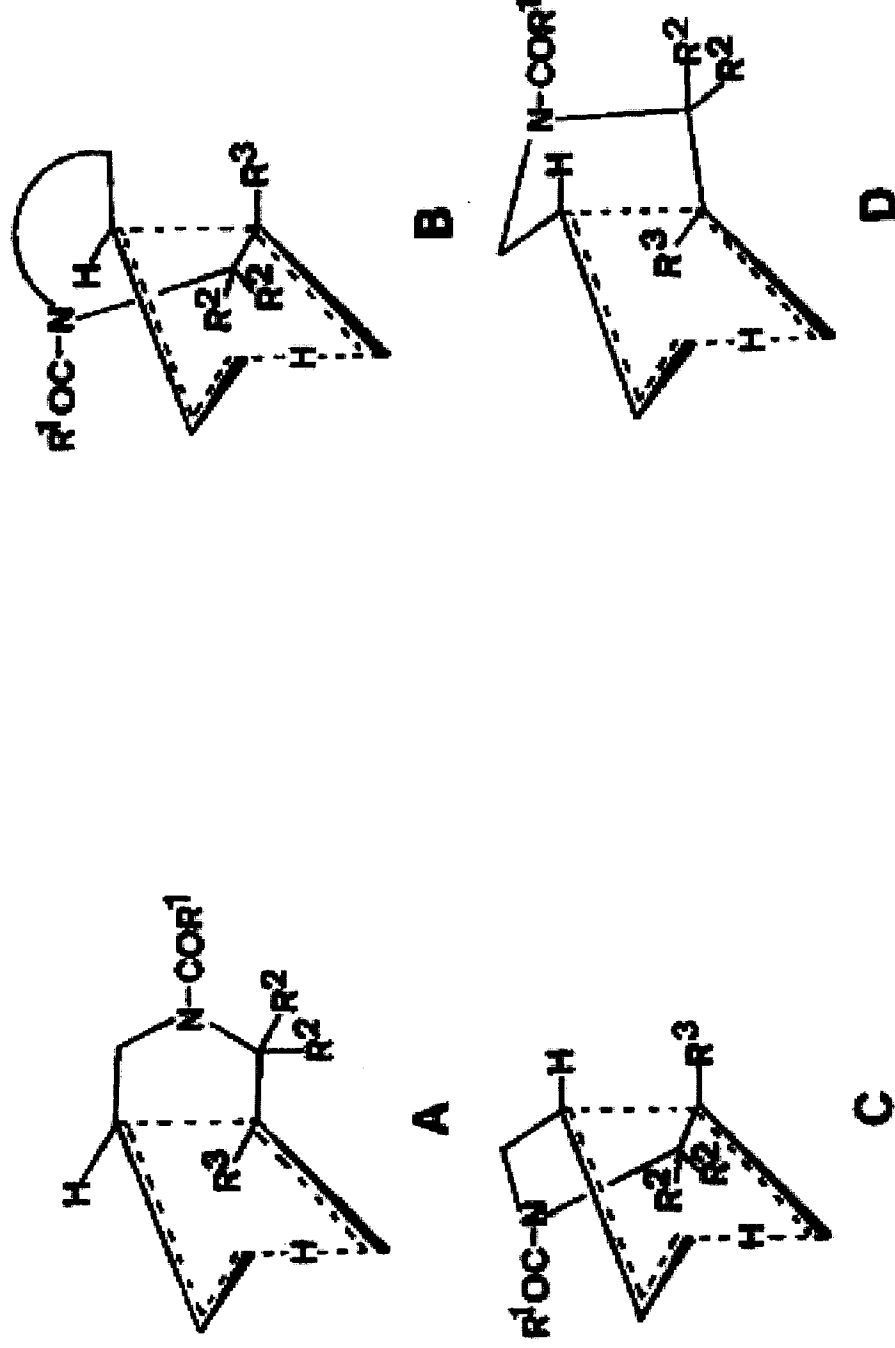


Intramolecular Ene: *Initial Results*



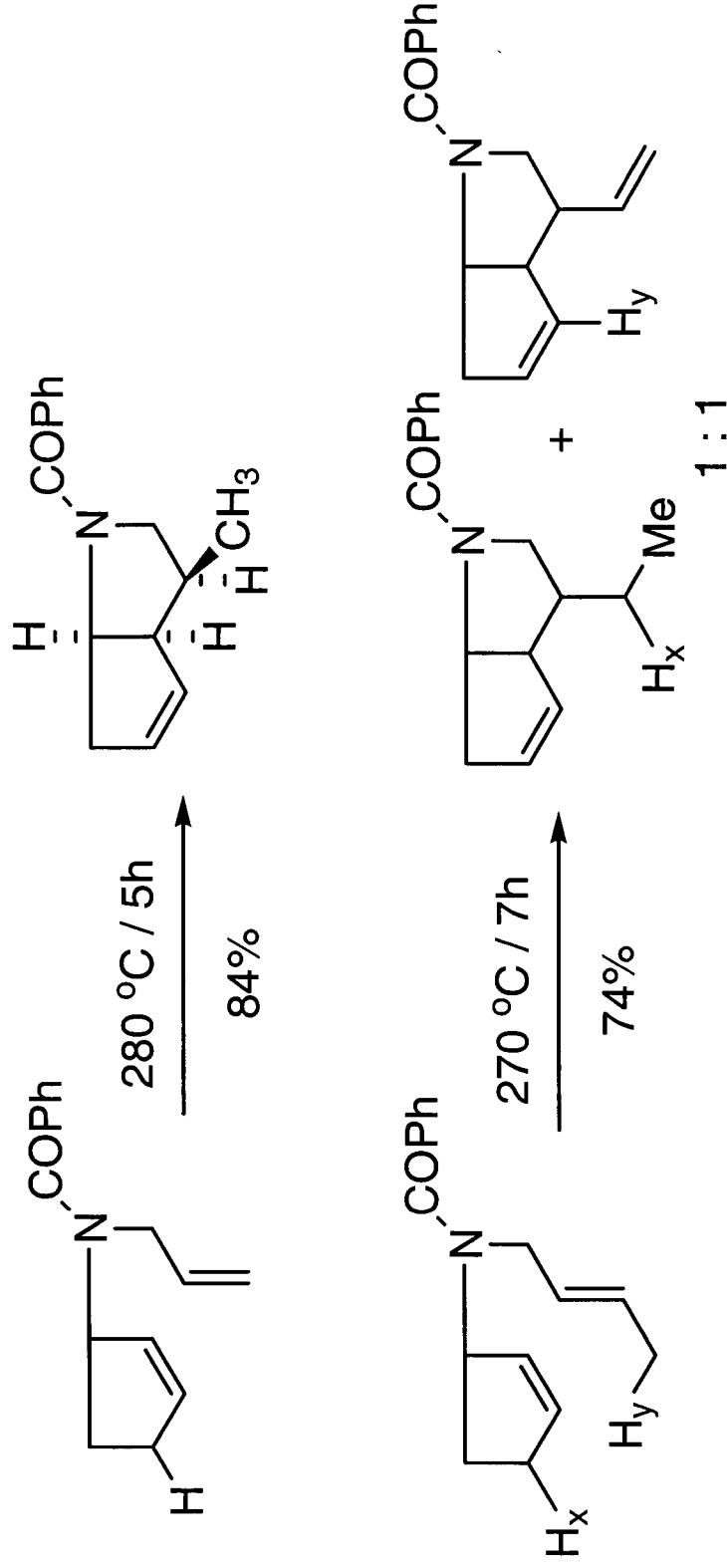
Entry	R ¹	R ³	geometry	A (%)	B (%)
1	CH ₃	H	<i>cis</i>	100	0
2	CH ₃	H	<i>trans</i>	89	11

Intramolecular Ene: *Transition State*



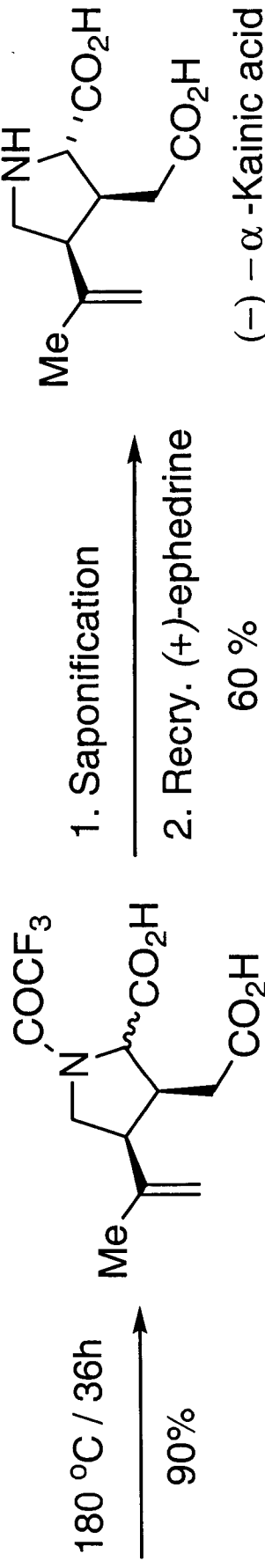
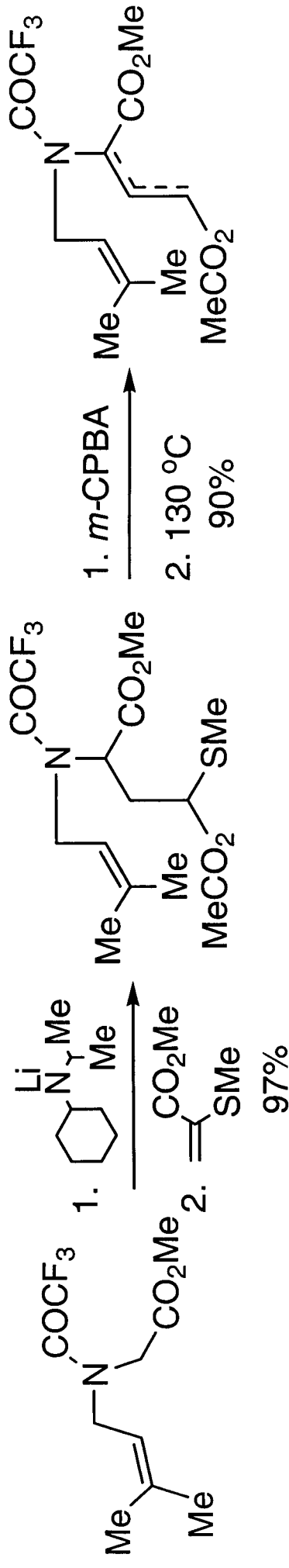
- Stereochemical relationship is consistent with supra-supra facial process
- *Cis*-crotylamides *exo*-transition state (A) leads to *cis*-pyrrolidines
- *Trans*-crotylamides both *endo* and *exo* are favored

Intramolecular Ene: Stereospecific Formation of Bicyclic Systems



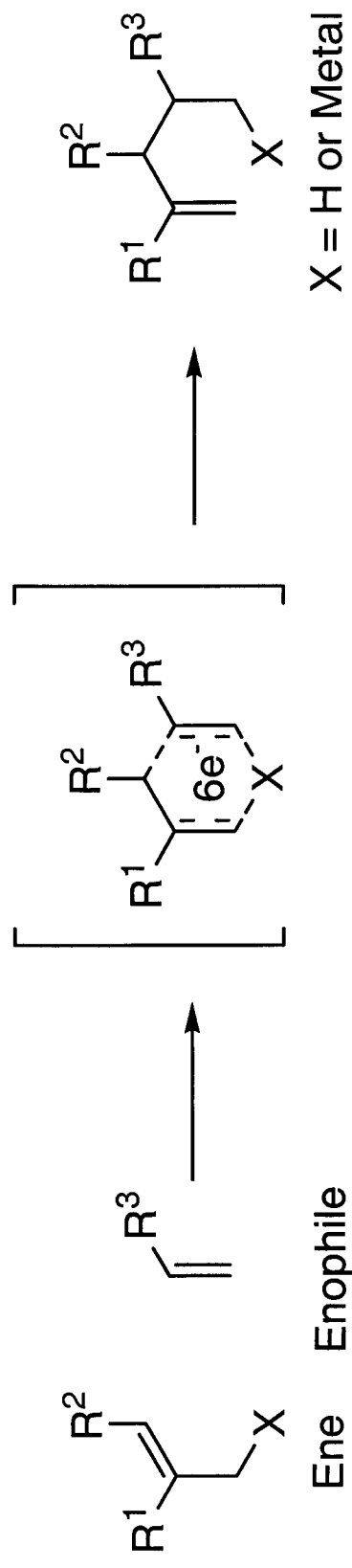
- Stereo-controlled formation of three centers of chirality in a single step
- 1 : 1 mixture suggests H_x must be transferred as fast as H_y,

Intramolecular Ene: Total Synthesis of (-) - α - Kainic Acid

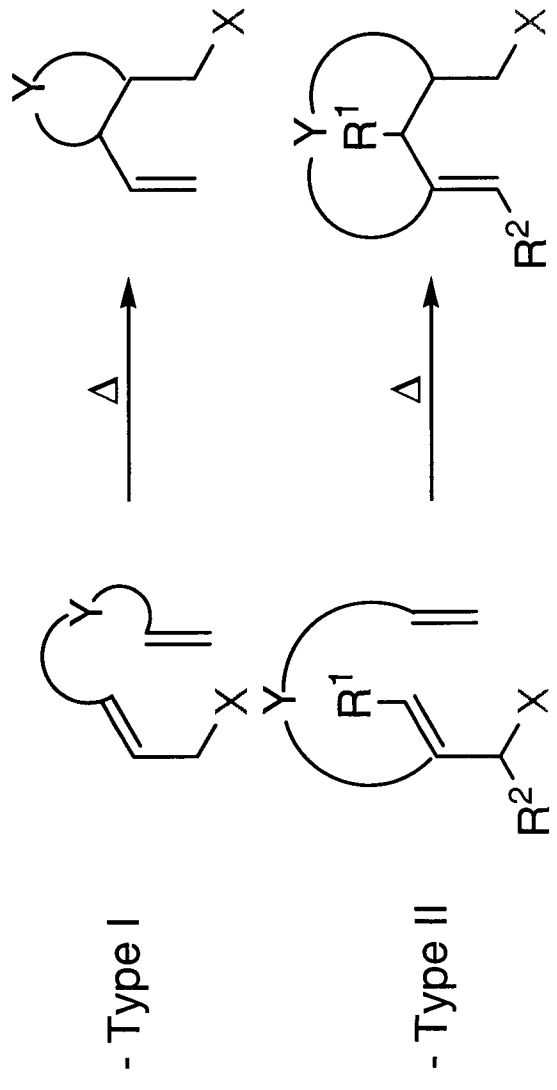


41% overall yield

Intramolecular Metalloene: *General Discussion*



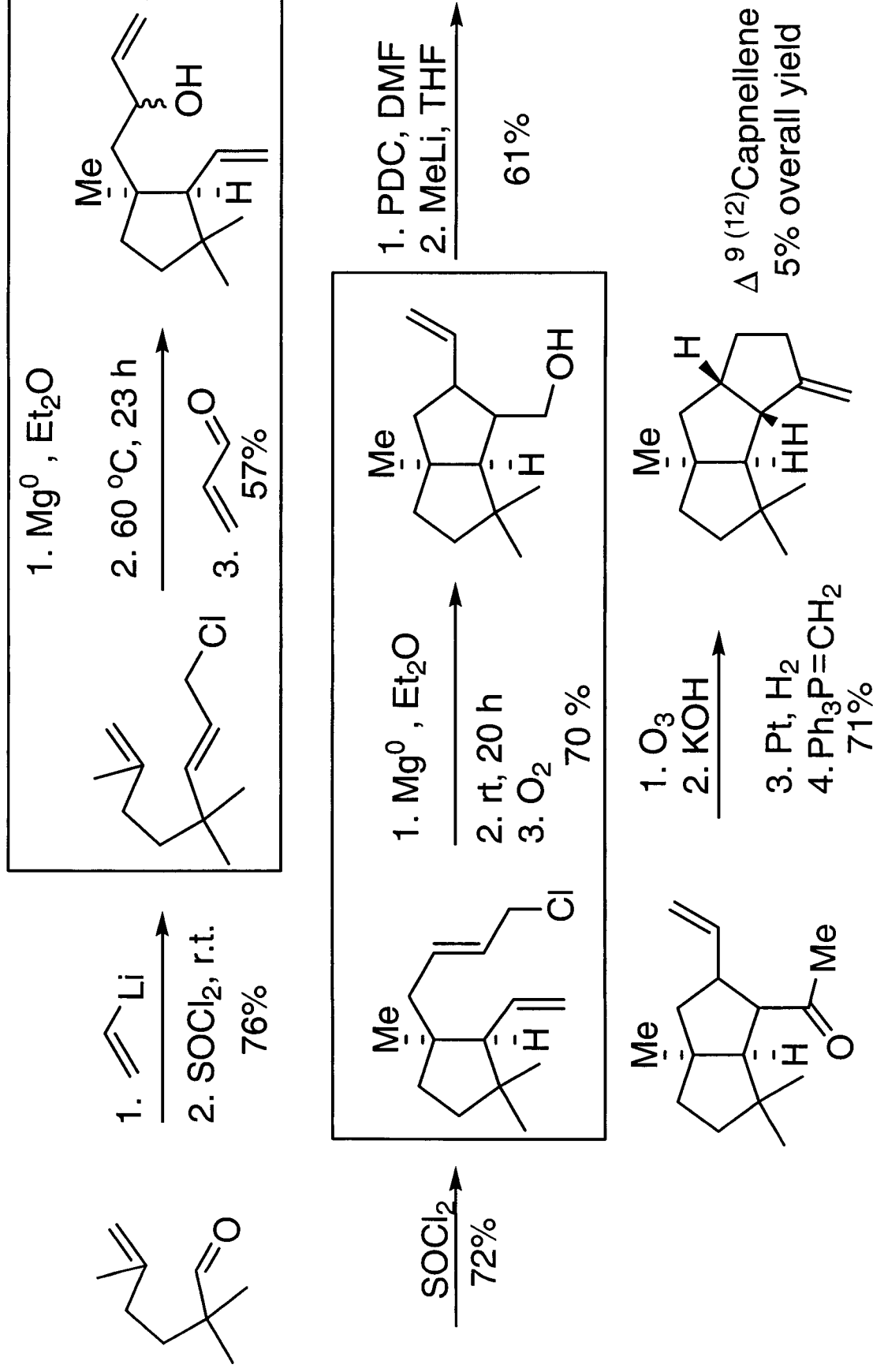
- Types of Intermolecular ene reactions



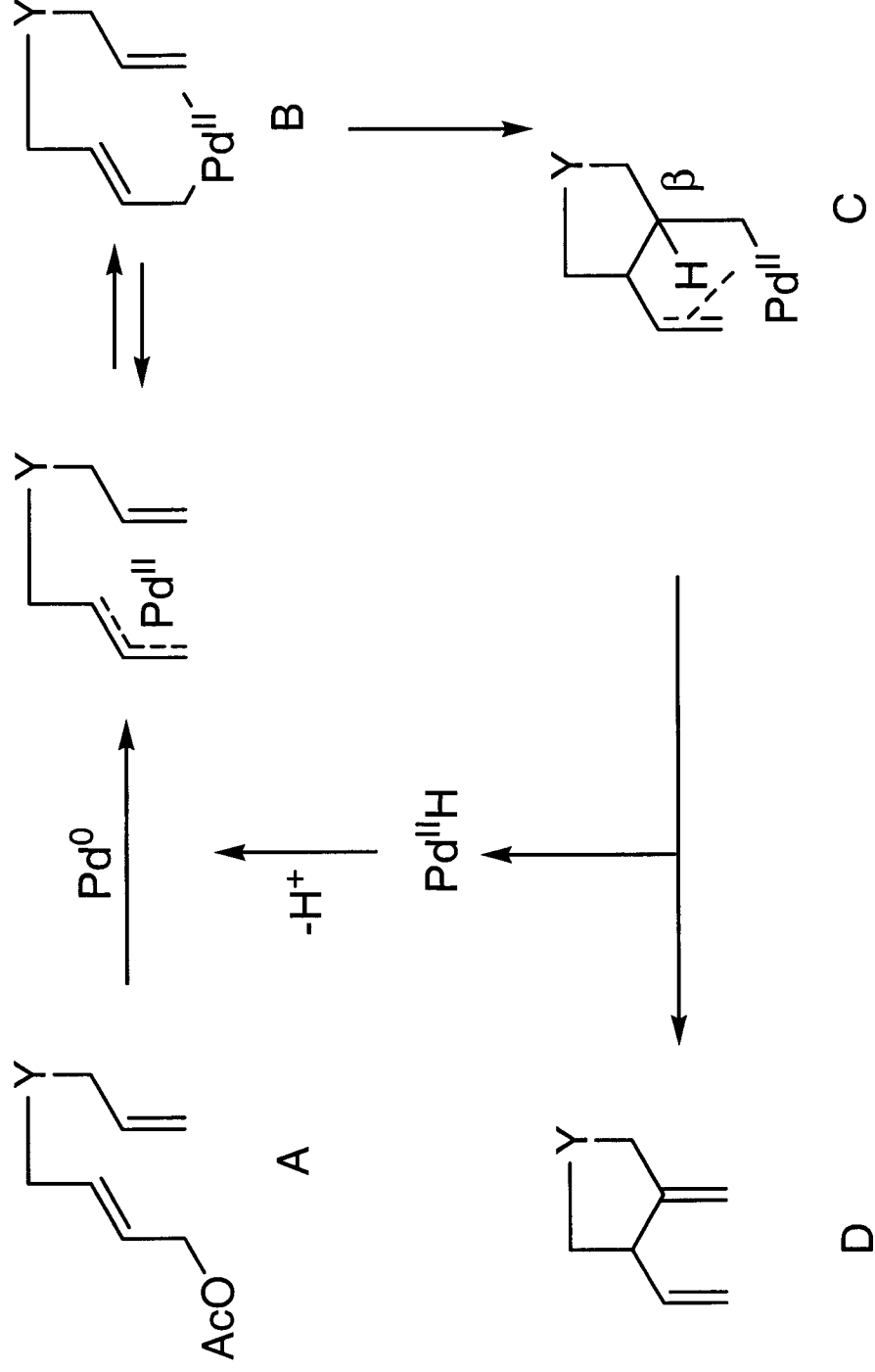
Enophile linked to terminal olefin

Enophile linked to internal olefin

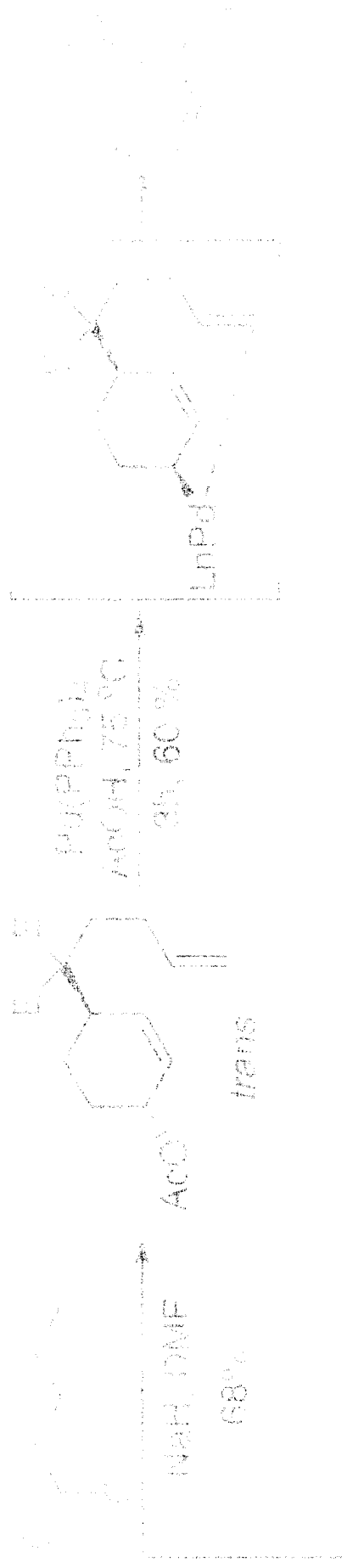
Intramolecular Metalloene: Total Synthesis of Δ^9 (12) Capnellene



Intramolecular Catalytic Metalloene: General Discussion

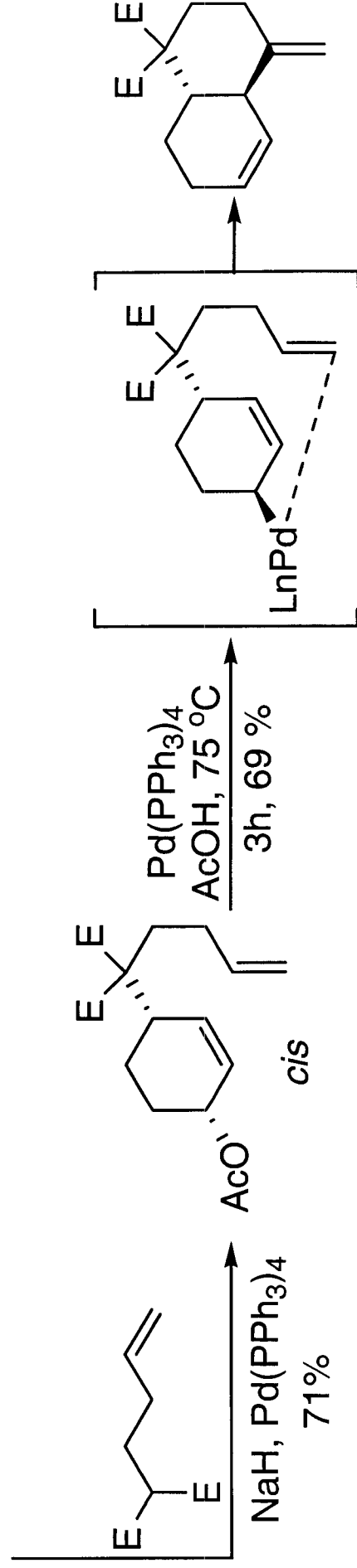
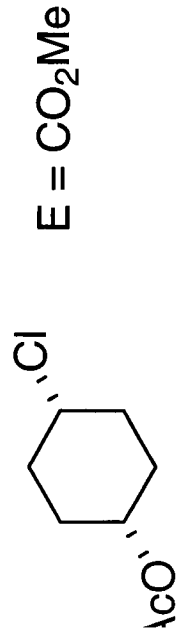


Intramolecular Catalytic Metalloene: *Initial Results*

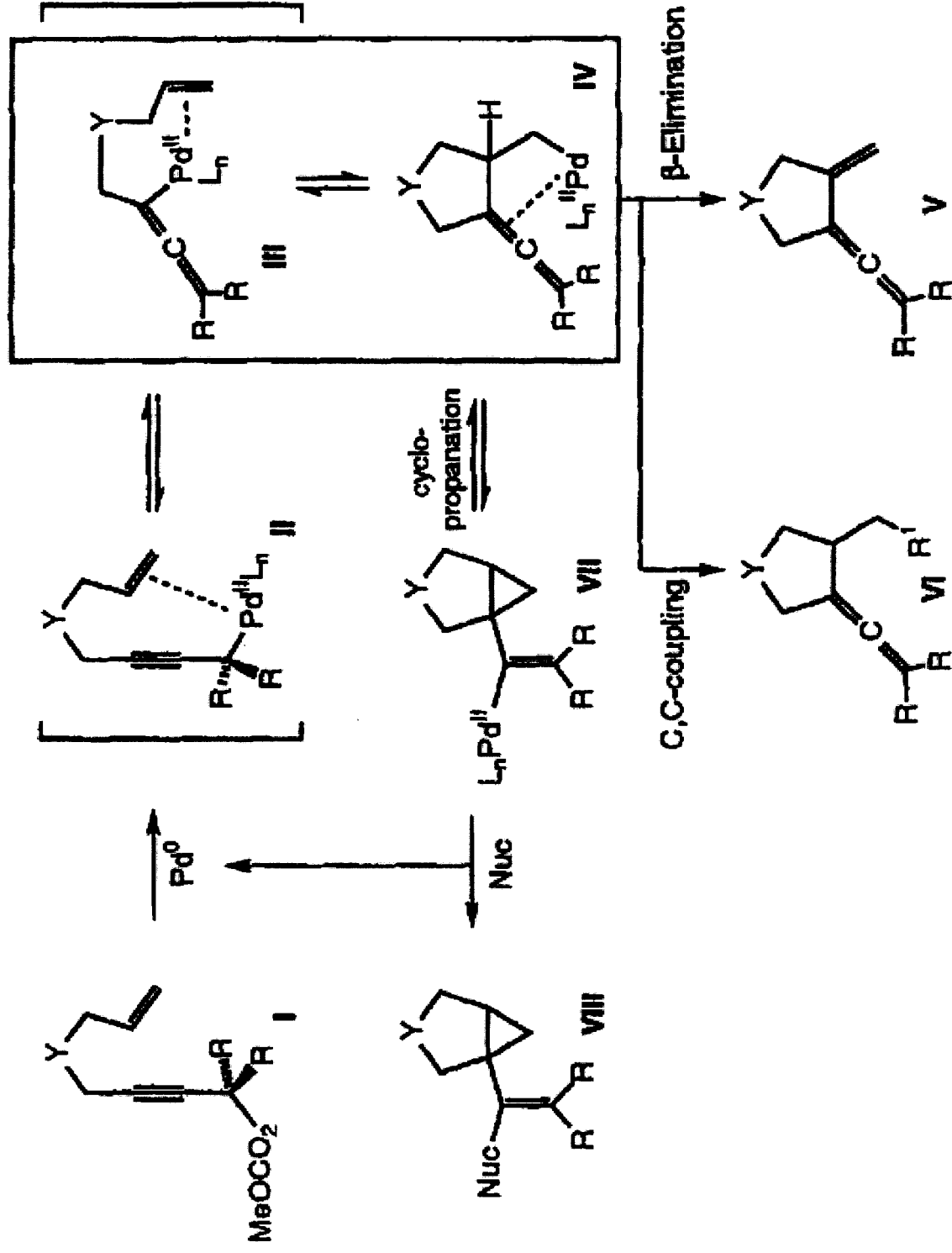


- Efficient C-O \rightarrow C-Pd \rightarrow C-C
 Chirality Transfer

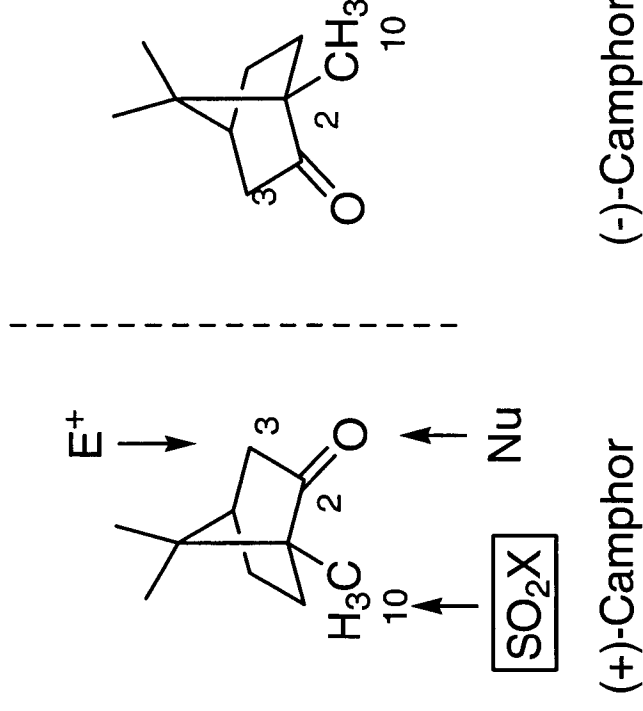
- Enophile - Insertion *cis* to Pd



Intramolecular Catalytic Metalloene: Summary of Reactions

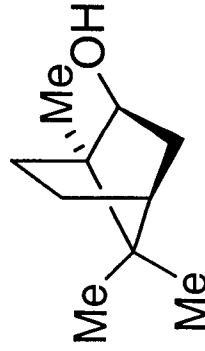


Chiral Auxiliaries: " Camphor a natural source of chirality in synthesis"

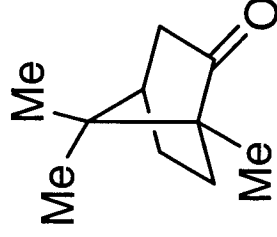


- Abundance and crystallinity and manifold for transformations make it desirable
- Rearrangements and manipulations of (C3), (C5), (C8), (C9) and (C10) allow versatility

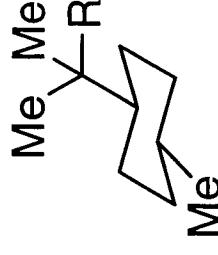
Chiral Auxiliaries: Camphor and other auxiliaries



Bornyl, Menthyl
(early 1900's)
(1946 - 1964)

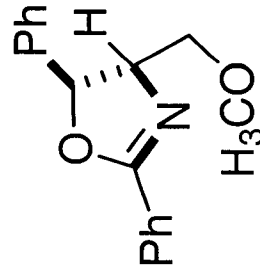


Camphor



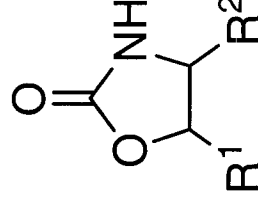
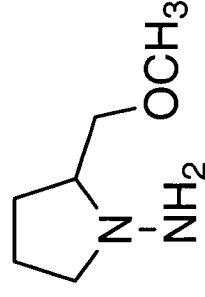
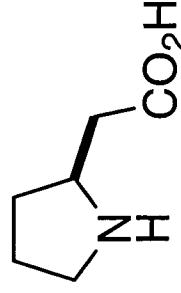
R = H Menthol
R = Ph (1965 - 1980)

" The topological bias of camphor allows the design of conformationally rigid derivatives..... that sterically shield one diastereotopic face of a reactive π -bond."



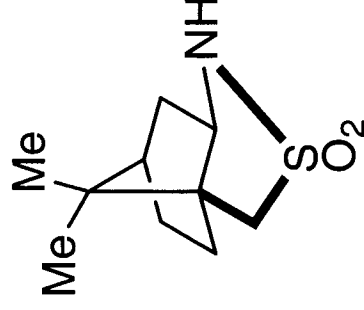
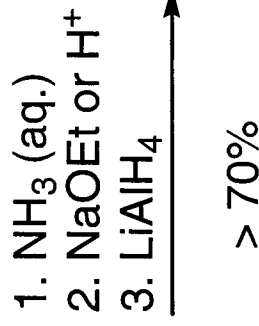
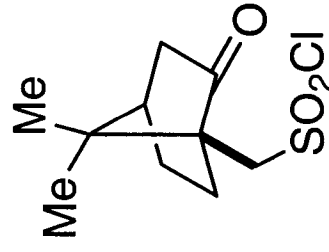
Oxazolines
(1965 - 1980)

-W. Oppolzer



Chiral templates from "natural" sources
(1980 -)

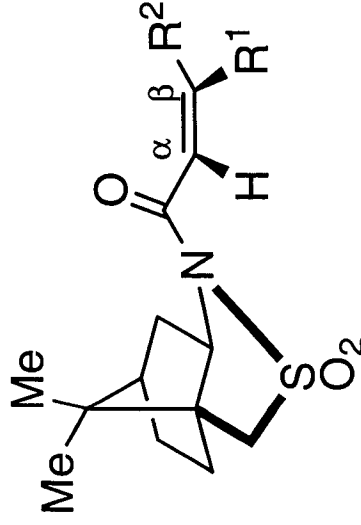
Chiral Auxiliaries: Bornane-10,2-Sultam



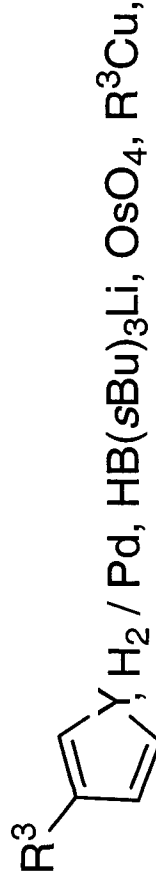
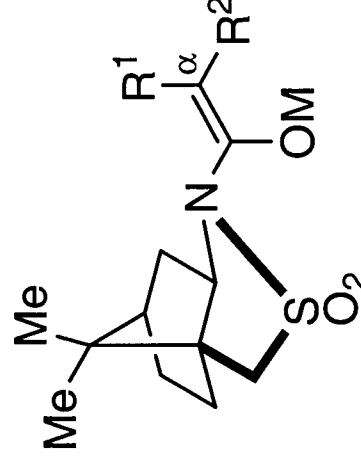
(+) - camphorsulfonic chloride

(-) - bornane -10,2-sultam

N- α , β ,-Enoyl Sultams



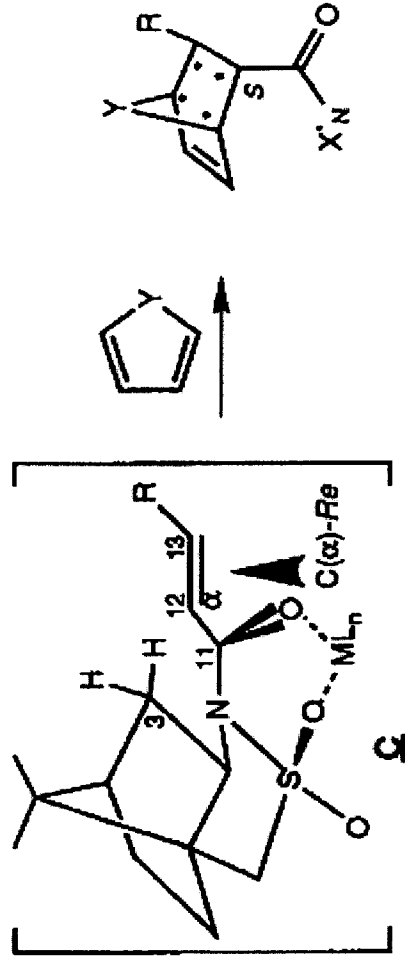
Sultam Enolates



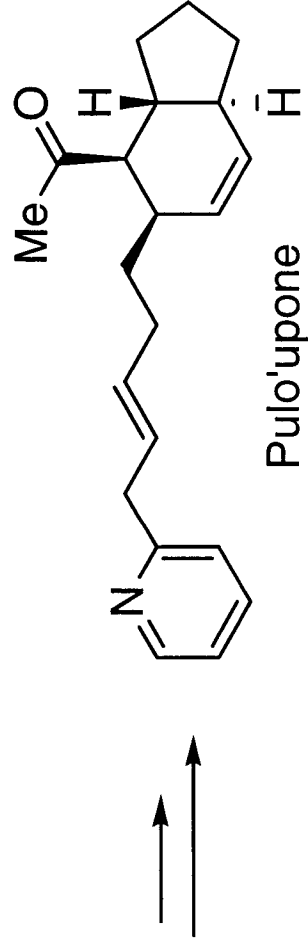
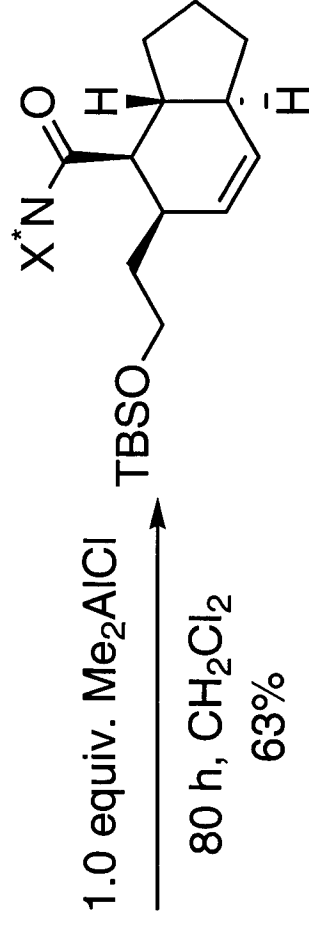
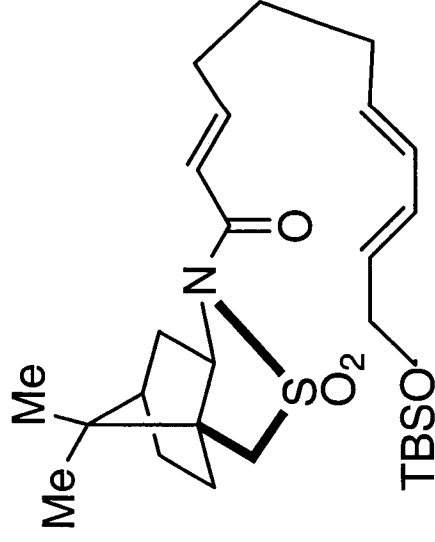
R^3MgCl , $\text{R}-\text{C}\equiv\text{N}-\text{O}$

H^+ , $\text{R}-\text{I}$, RCHO , RCOCl , NBS

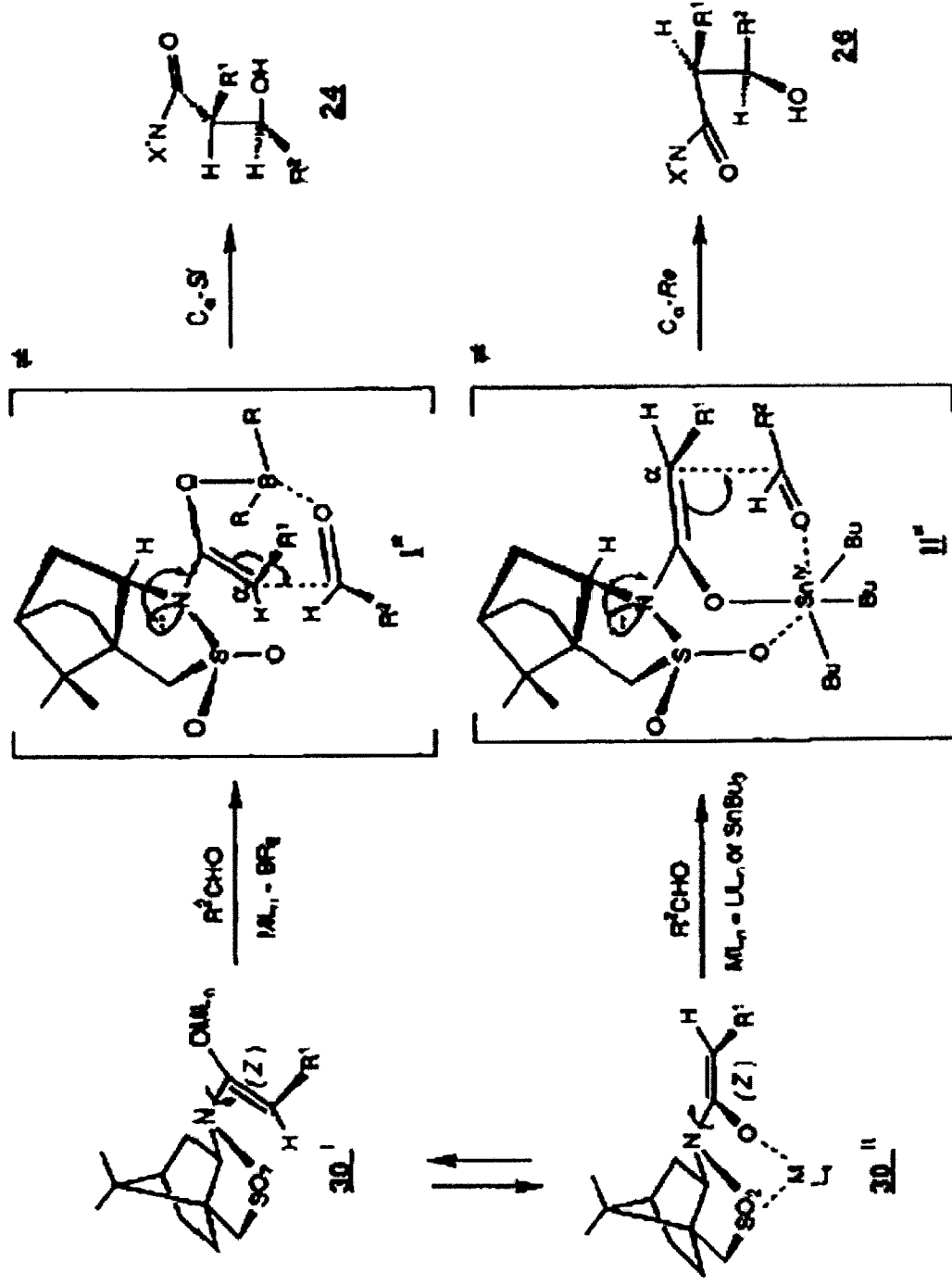
Chiral Auxiliaries: Dienophile auxiliaries



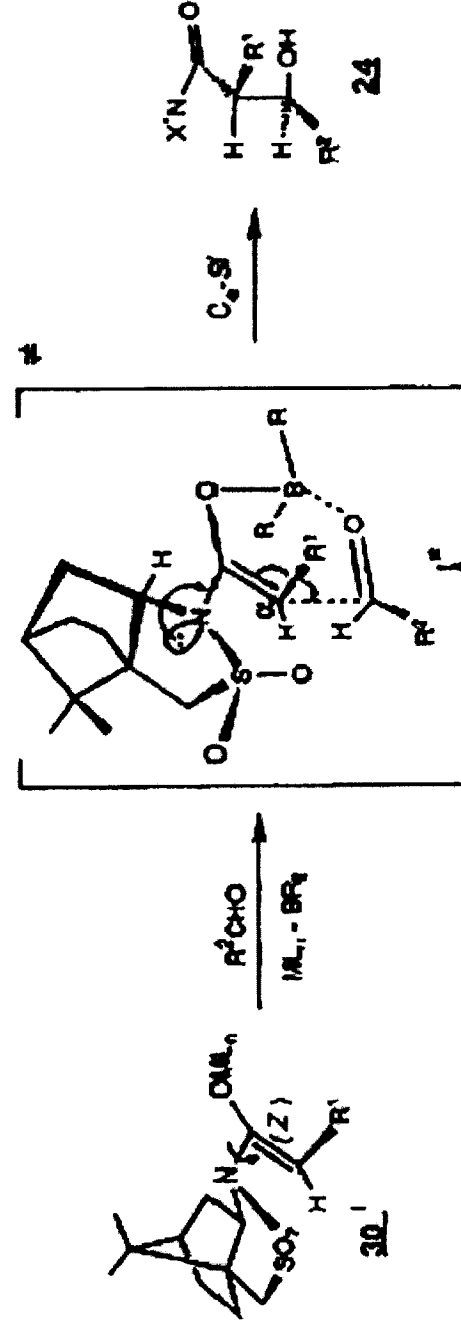
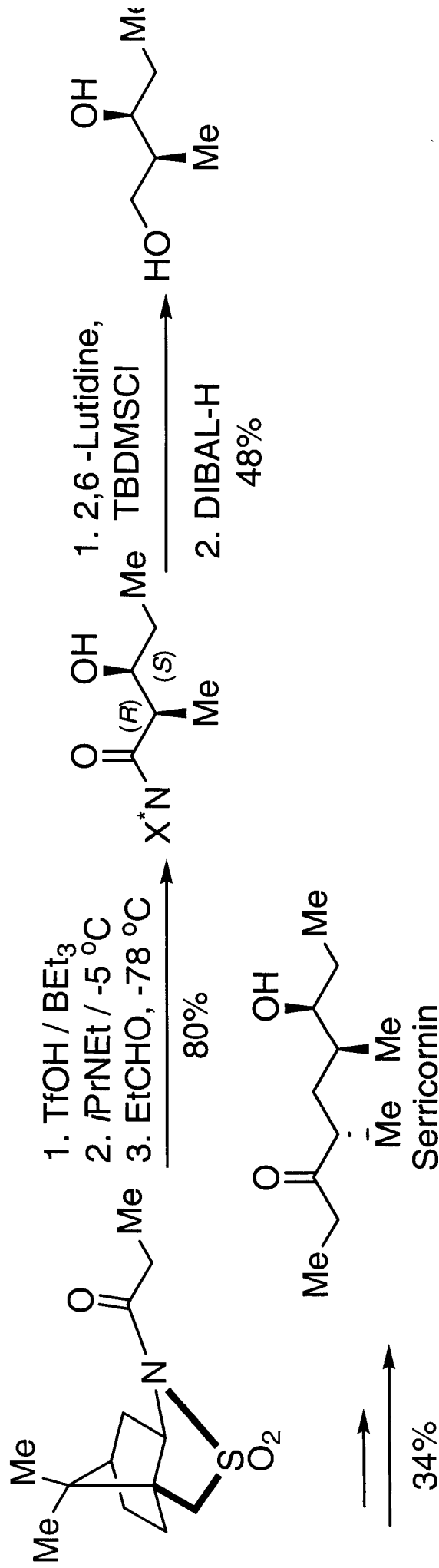
a: R = H, b: R = CH₃



Chiral Auxiliaries: Auxiliary controlled Aldol



Chiral Auxiliaries: Auxiliary controlled Aldol



Summary

- Intramolecular cyclization dominated Oppolzer's career
- Pioneered metallocene chemistry and developed a catalytic general process with palladium and nickel
- Oppolzer's work of chiral auxiliaries has influenced modern developments in asymmetric synthesis

