

A Scrutiny of the Total Synthesis of (-)-Cylindrocyclophane F

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Evans Group Seminar
November 23, 1999

- I. The Cyclophanes
 - A. Natural
 - B. Biosynthesis
 - C. Synthetic
- II. Smith Total Synthesis of (-)-Cylindrocyclophane F and Reactions Therein
 - A. Kowalski Ester Homologation
 - 1. Reaction conditions, mechanism, and scope
 - 2. Other homologation methods
 - B. Danheiser Benzannulation
 - 1. Reaction conditions, mechanism, and scope
 - 2. Variations and other aromatic annulations
 - C. Myers Reductive Coupling
 - 1. Reaction conditions, mechanism, and scope
 - 2. State-of-the-art in sp^3 - sp^3 C-C coupling

Primary References

Synthesis of (-)-Cylindrocyclophane F:

Smith, A. B. III *J. Am. Chem. Soc.* **1999**, *121*, 7423

Kowalski ester chain homologation:

Kowalski, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1429
J. Org. Chem. **1992**, *57*, 7194

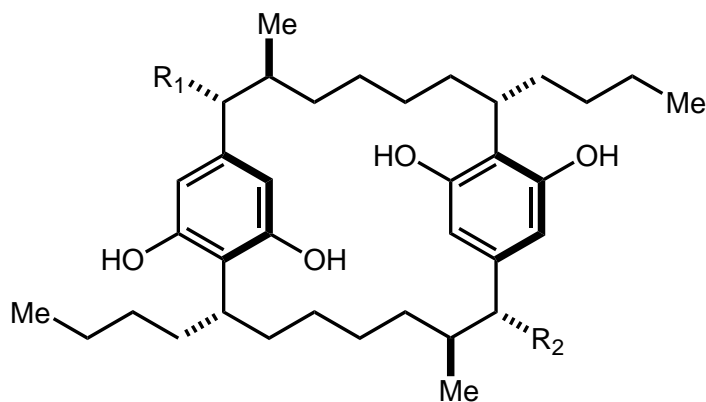
Danheiser benzannulation:

Danheiser, R. L. *J. Org. Chem.* **1984**, *49*, 1672

Myers reductive coupling:

Myers, A. G. *J. Am. Chem. Soc.* **1998**, *120*, 8891

The Cylindrocyclophanes



Cylindrocyclophane	R ₁	R ₂
A	OH	OH
B	OH	OAc
C	OH	H
D	OAc	OAc
E	OAc	H
F	H	H

n Isolated by Moore and co-workers from *Cylindrospermum licheniforme*, a species of the Nostocaceae cyanobacteria (blue-green algae)

Moore, R. E. *J. Am. Chem. Soc.* **1990**, *112*, 4061

Tetrahedron **1992**, *48*, 3001

Tetrahedron **1993**, *49*, 7615

n Along with the nostocyclophanes, the first example of [n,n]paracyclophanes isolated from a natural source

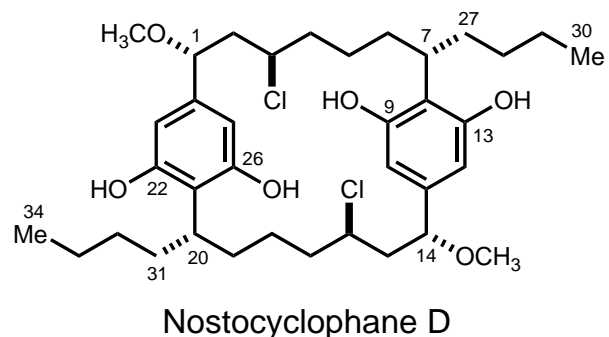
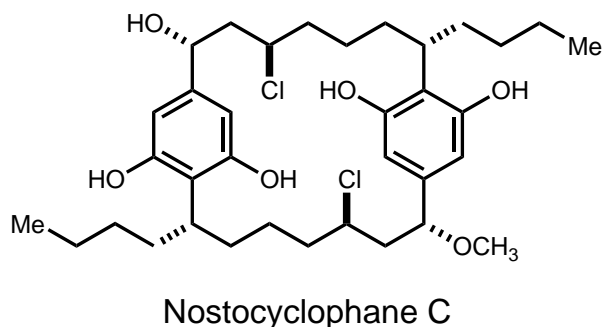
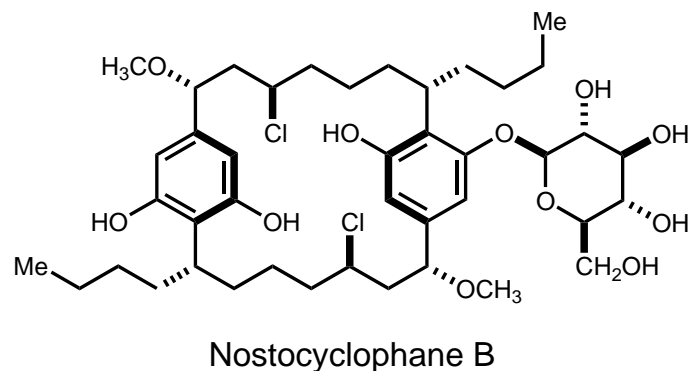
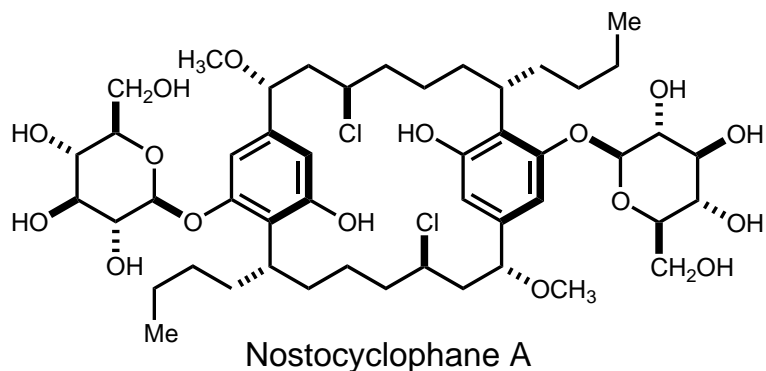
n Structural assignments based on NMR studies, CD spectroscopy, and X-ray crystallography

n Cylindrocyclophanes exhibit moderate cytotoxicity in KB and LoVo human tumor cell lines, but are not toxic selectively to tumor cells

n First total synthesis: (-)-Cylindrocyclophane F, in 20 steps and 8.3% overall yield

Smith, A. B. III *J. Am. Chem. Soc.* **1999**, *121*, 7423

Other Natural Cyclophanes: The Nostocyclophanes



Isolated from *Nostoc linckia*, a species of Nostocaceae (blue-green algae)

Moore, R. E. *J. Am. Chem. Soc.* **1990**, *112*, 4061

J. Org. Chem. **1991**, *56*, 4360

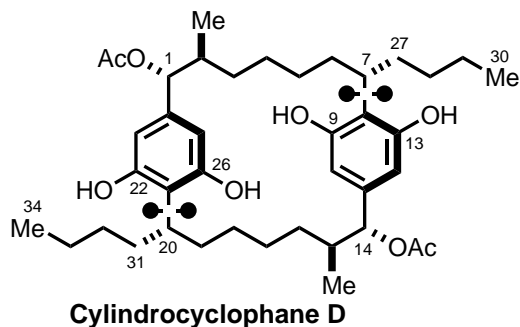
Biosynthetic pathway of Nostocyclophane D (the most abundant product) determined to be dimerization of acetate-derived nonaketides

Moore, R. E. *Tetrahedron* **1993**, *49*, 7615

Differ from cylindrocyclophanes in chlorination at C-3 and C-16, and lack of C-2 and C-15 methyl substituents

Exhibit moderate, nonselective cytotoxicity in LoVo and KB human tumor cell lines

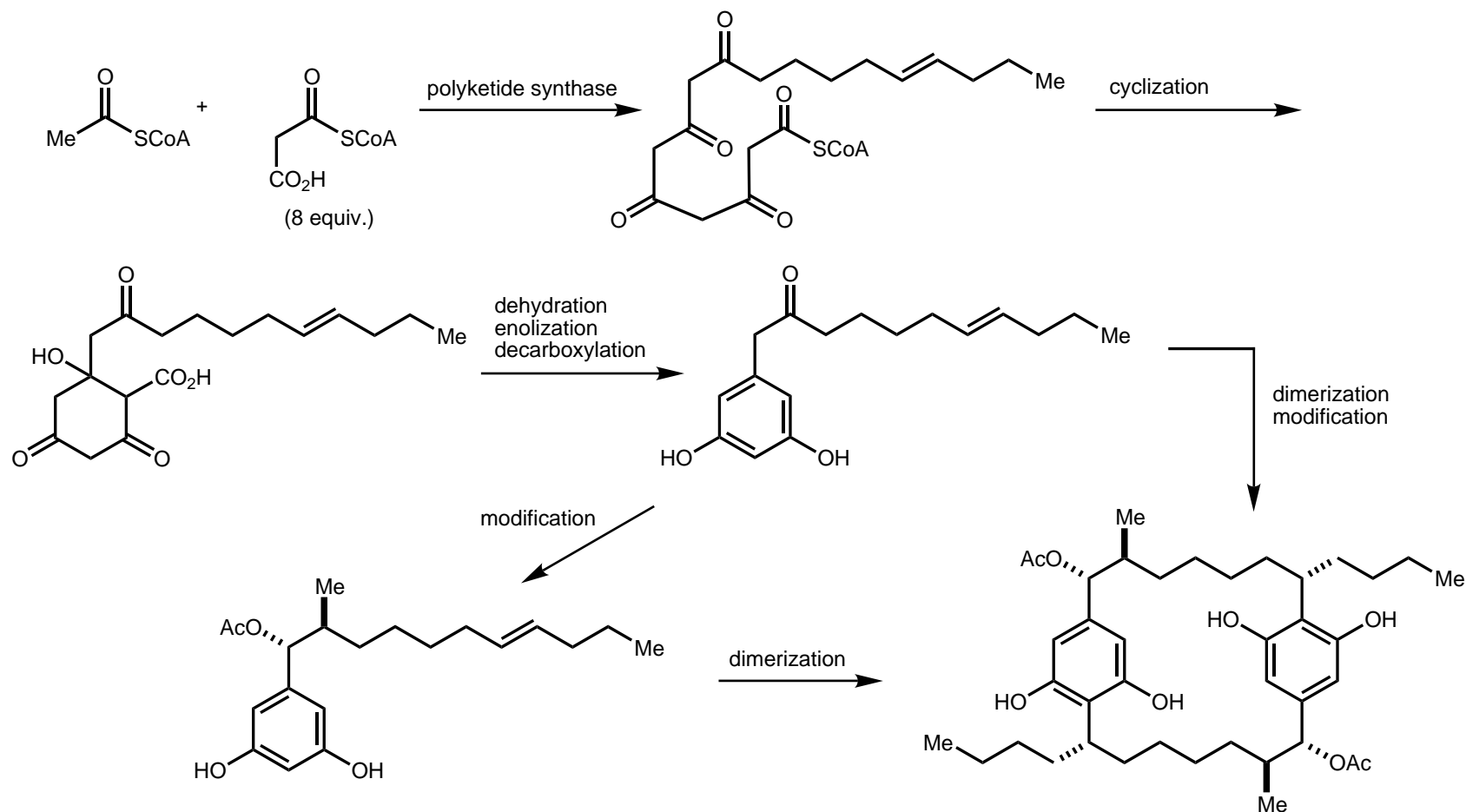
Proposed Biosynthetic Pathway of Cylindrocyclophane D



n dimer of two nonaketides, linked at C-7,8 and C-20,21

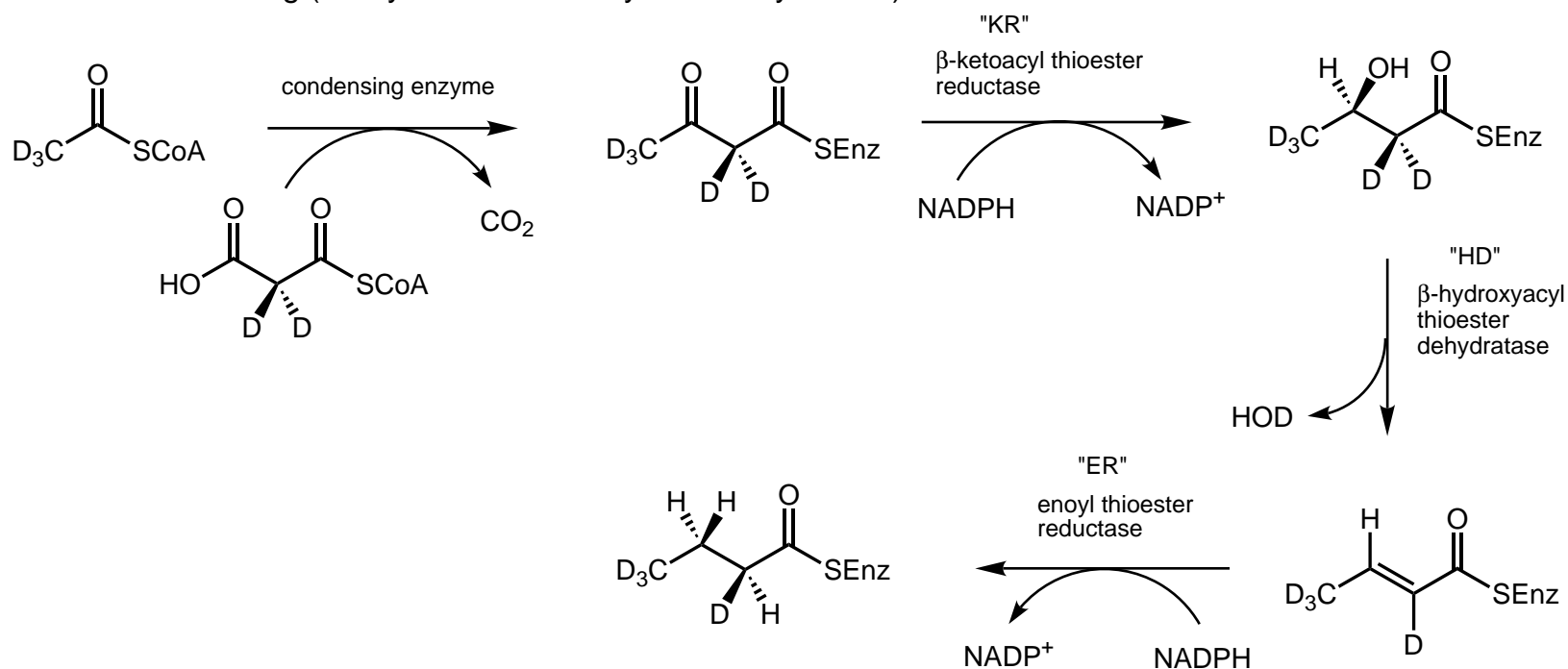
n backbone entirely acetate-derived, as determined by feeding isotopically-labeled sodium acetate to *Cylindrospermum licheniforme*

n phenolic oxygens also acetate-derived

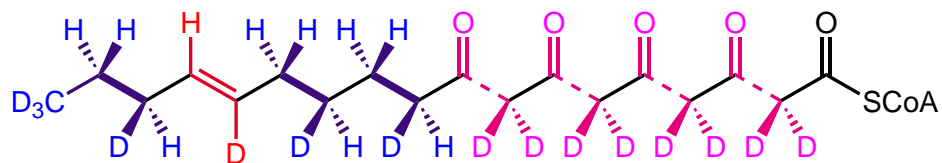


Action of Polyketide Synthase, A Modular Enzyme

One Cycle of Full Processing (i.e. cyanobacteria fatty acid biosynthesis)



Biosynthesis of Cylindrocyclophane D involves eight PKS cycles:



blue units (bold): KR, HD, ER
red unit (alkene): KR, HD
magenta units (dashed): no reduction

Synthetic Paracyclophanes - Why??

- n To study aromatic stacking interactions
- n To study ring strain in hydrocarbon rings
- n To gain insight into host-guest chemistry related to these structures

Dale's Postulate: Cycloalkanes with diametrically opposed alkene, alkyne, or phenylene functions linked by chains with an odd number of methylene units are nearly strain-free, while those with an even number are conformationally unstable.

- n Cycloalkanes with diametrically opposed 1,3-diene units connected by saturated carbon chains consisting of the same odd number of n methylene units have higher melting points than their even-numbered counterparts, indicating more rigid conformations
- n Two acetylenic bonds diametrically placed in 14-, 18-, and 22-membered rings can give strain-free, stable conformations, whereas in 12-, 16-, and 20-membered rings this is not possible, as evidenced by strong melting point alternation
- n For $[n,n]$ paracyclophanes, the melting point trend is weaker, but still observable
- n In the case of $[2,2]$ and $[3,3]$ paracyclophanes, ring strain and pi-electron repulsion causes the benzene rings to bend outward, as observed in the X-ray crystal structures

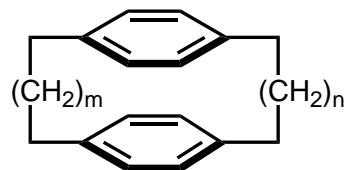
Dale, J. *Angew. Chem., Int. Ed. Engl.* **1966**, 5, 1000

Books:

Keehn, P. M. & Rosenfeld, S. M. *Cyclophanes*. Academic Press: New York, **1983**.
Boekelheide, V. et al. *Topics in Current Chemistry: Cyclophanes*, **1983**, 113
Hart, H. et al. *Topics in Current Chemistry: Cyclophanes*, **1994**, 172

Synthetic Cyclophanes

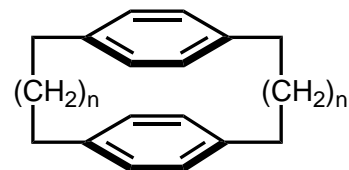
[m,n]Paracyclophanes



$m=2, n=2$ $m=2, n=3$ $m=2, n=4$ $m=3, n=6$
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Cram, D. J. *J. Am. Chem. Soc.* **1951**, 73, 5691

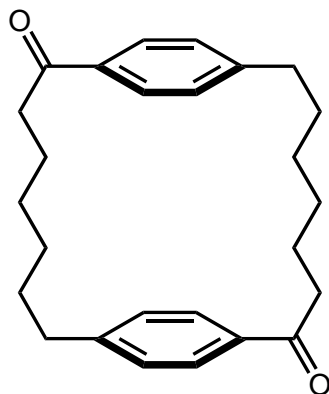
[n,n]Paracyclophanes



$n=7, 8, 9, 10, 11$

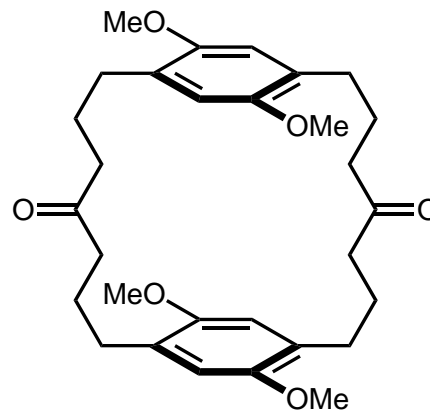
Mascal, M. J. *Chem. Soc., Perkin Trans. I* **1996**, 11, 1141

Friedel-Crafts Dimer



Schubert, W. M. *J. Am. Chem. Soc.* **1954**, 76, 5462
 Huisgen, R. *Chem. Ber.* **1957**, 90, 1946

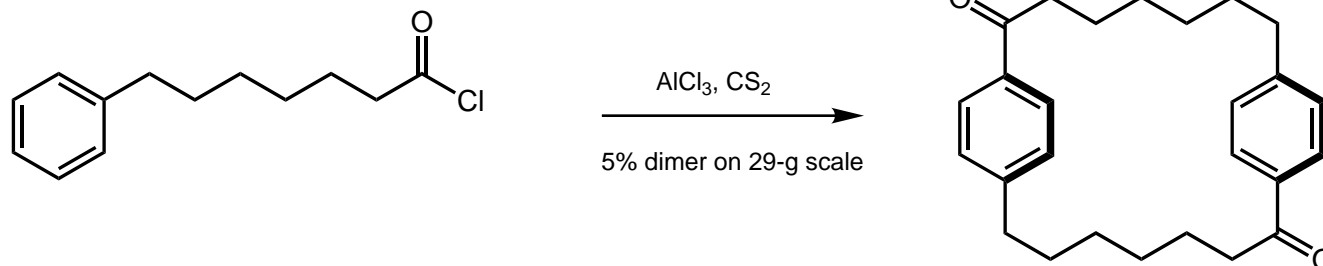
[7,7]Paracyclophane-4,17-dione via Bis(dithiane) Alkylation



Staab, H. A. *Chem. Ber.* **1987**, 120, 89

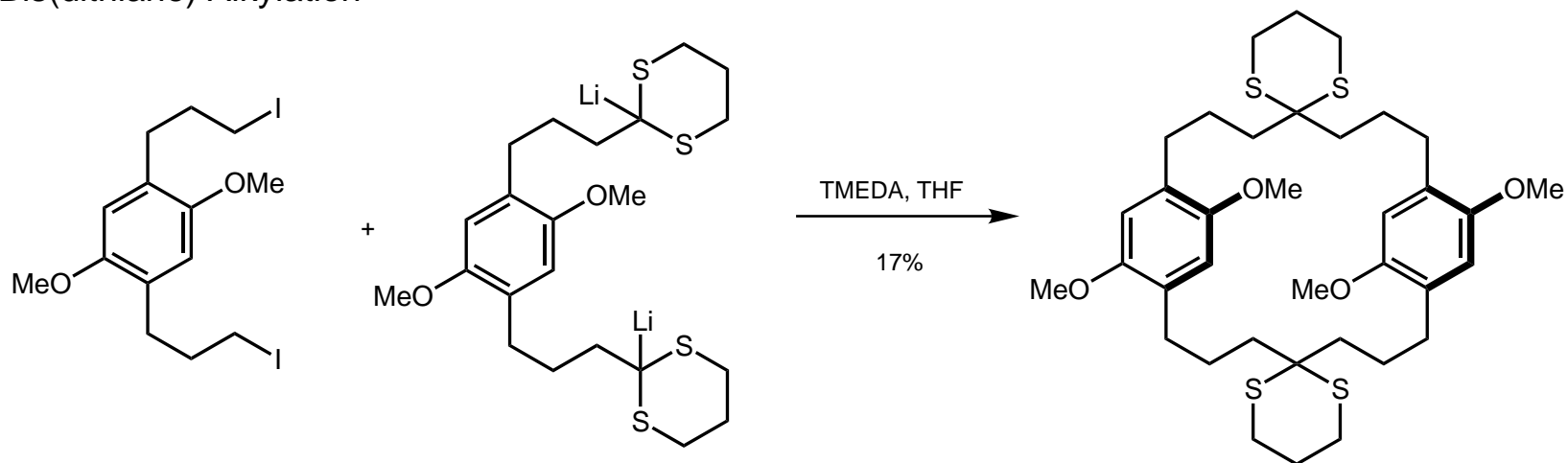
Previous Approaches to Synthetic [7,7]Paracyclophanes

High-Dilution Friedel Crafts Reaction



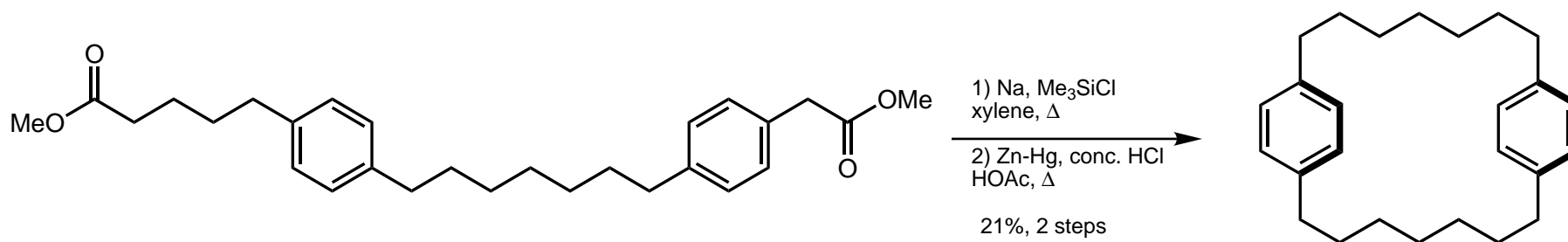
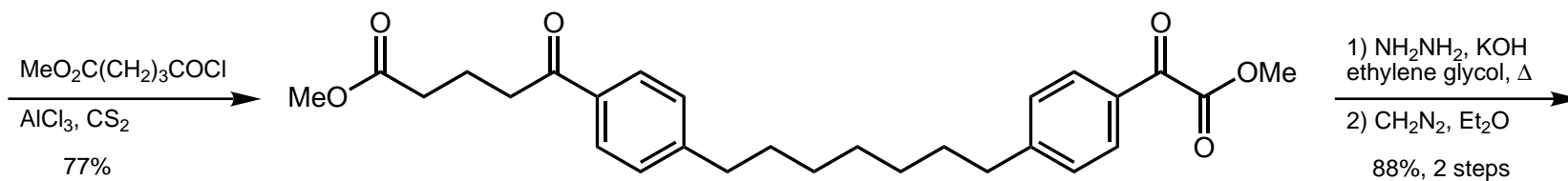
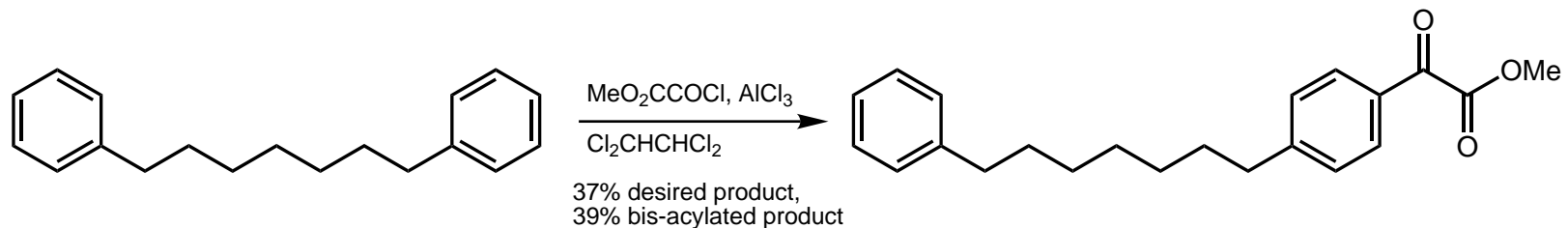
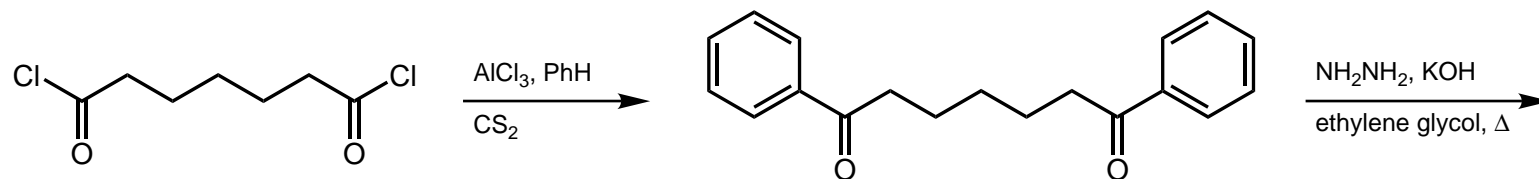
Schubert, W. M. *J. Am. Chem. Soc.* **1954**, 76, 5462
Huisgen, R. *Chem. Ber.* **1957**, 90, 1946

Bis(dithiane) Alkylation



Staab, H. A. *Chem. Ber.* **1987**, 120, 89

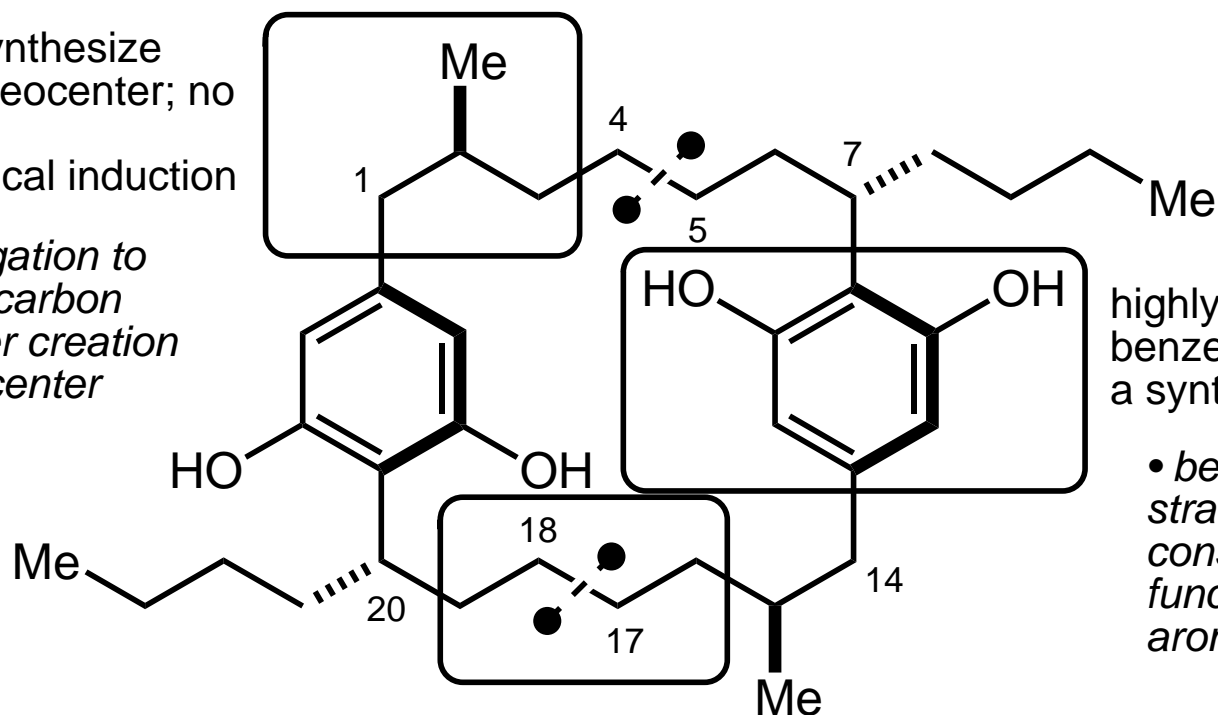
Mascal's [7,7]Paracyclophane Synthesis



(-)-Cylindrocyclophane F as a Synthetic Target

difficult to synthesize isolated stereocenter; no potential for stereochemical induction

- *homologation to lengthen carbon chain after creation of stereocenter*



highly functionalized benzene rings present a synthetic challenge

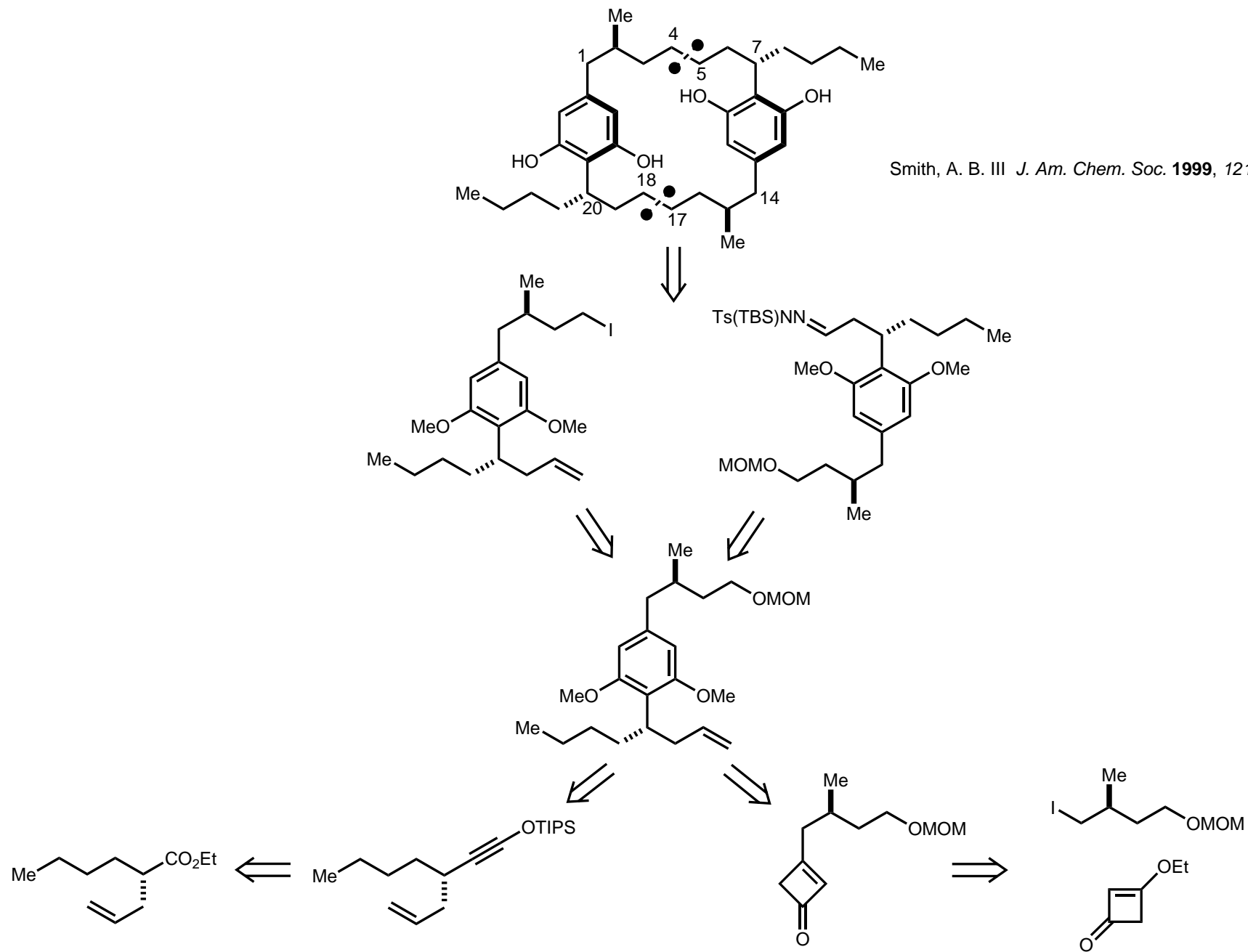
- *benzannulation strategy efficiently constructs highly functionalized aromatic rings*

ideal to construct $C(sp^3)-C(sp^3)$ bond, but little existing methodology for complex fragment coupling

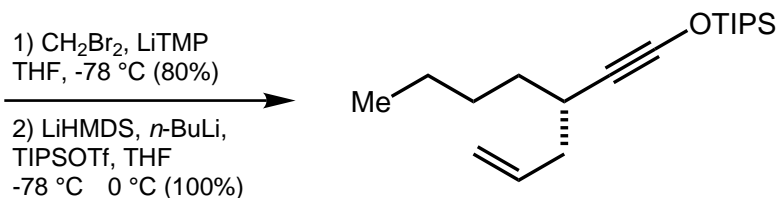
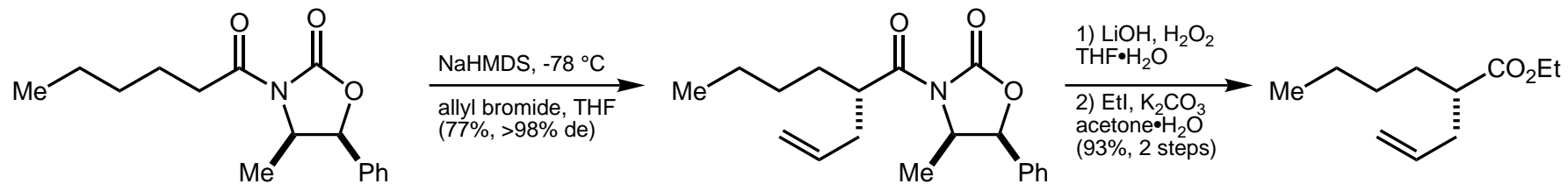
- *Myers reductive coupling presents viable alternative to direct C-C bond formation*

The Smith Retrosynthesis of (-)-Cylindrocyclophane F

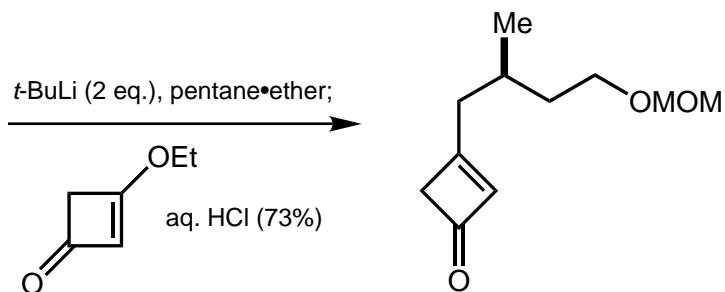
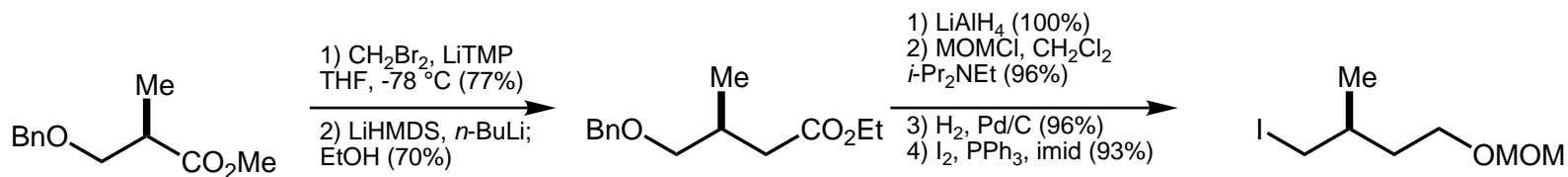
Smith, A. B. III *J. Am. Chem. Soc.* **1999**, *121*, 7423



The Synthesis of (-)-Cylindrocyclophane F - I



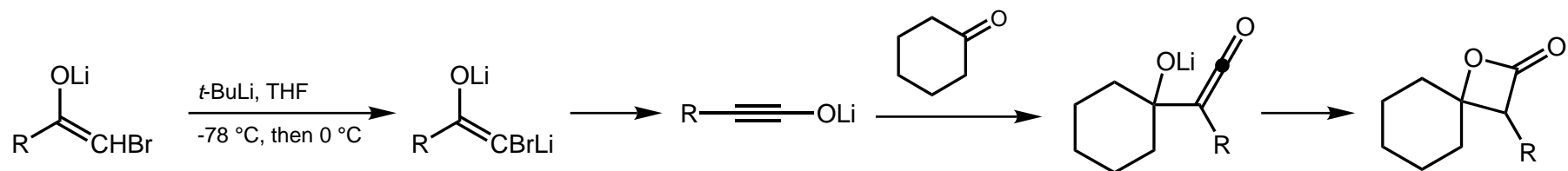
Alkylation: Evans, D. A. *J. Am. Chem. Soc.* **1982**, *104*, 1737
 Homologation: Kowalski, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1429;
 Kowalski, C. J. *J. Org. Chem.* **1992**, *57*, 7194
 Ynolate O-silylation: Kowalski, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 7127



Synthesis of methyl ester: White, J. D. *J. Org. Chem.* **1992**, *57*, 5292
 Synthesis of cyclobutenone: Wasserman, H. H. *J. Org. Chem.* **1973**, *38*, 1451

Kowalski Ester Homologation: Background

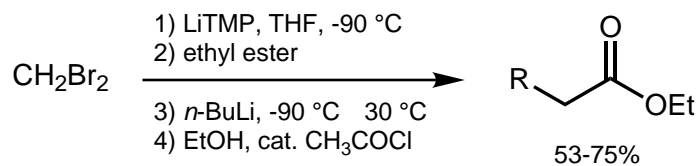
The Alkynolate Anion Clue



is an accidental discovery of a side reaction which occurred in THF, but not in Et_2O

Kowalski, C. J. *J. Am. Chem. Soc.* **1982**, 104, 321

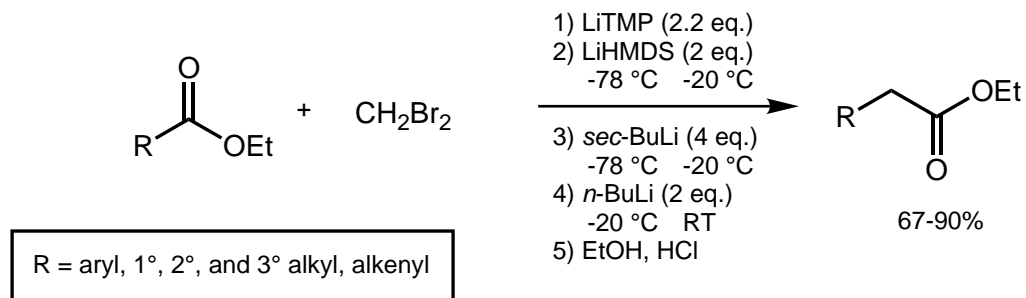
Initial Homologation Conditions



Kowalski, C. J. *J. Am. Chem. Soc.* **1985**, 107, 1429

Kowalski Ester Homologation

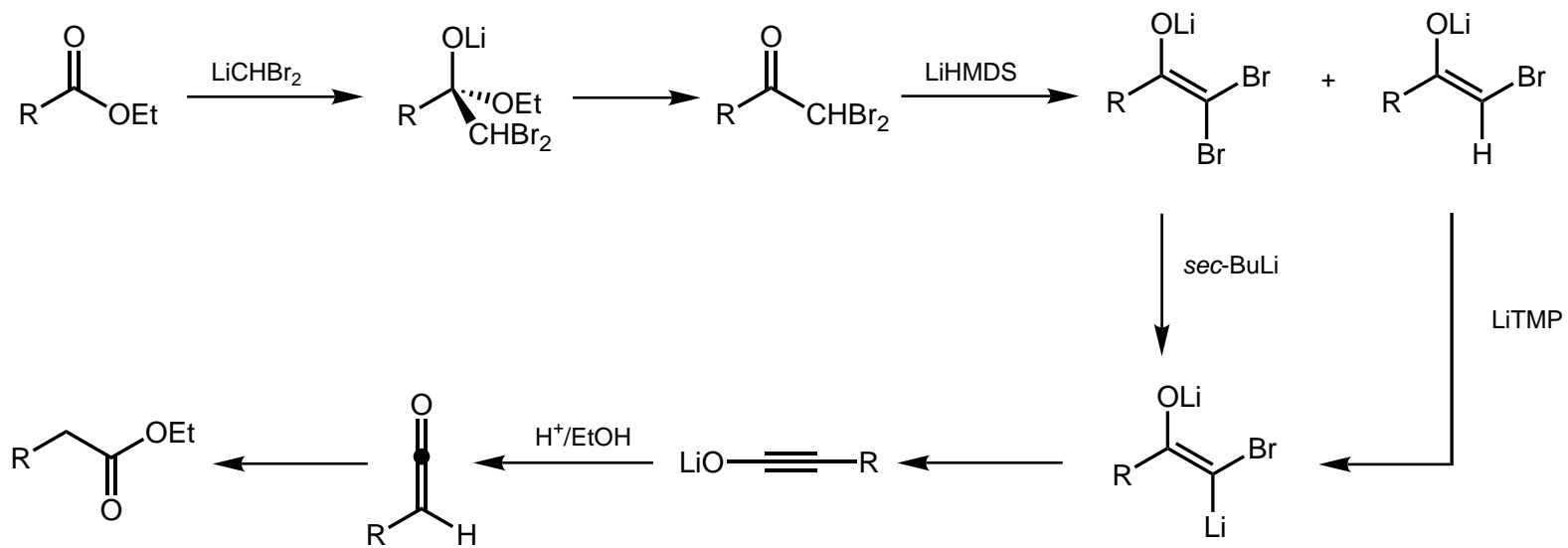
Optimized Procedure



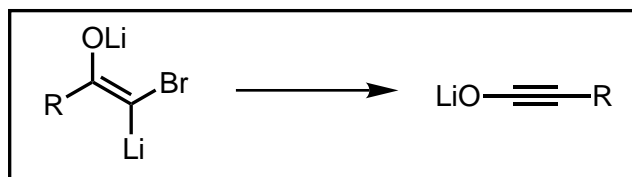
Kowalski, C. J. *J. Org. Chem.* **1992**, *57*, 7194

Note: An allylic methoxy stereocenter β to homologation site did not racemize under reaction conditions

Proposed Sequence of Intermediates:



Alkynolate Formation: Similarities to Other Rearrangements

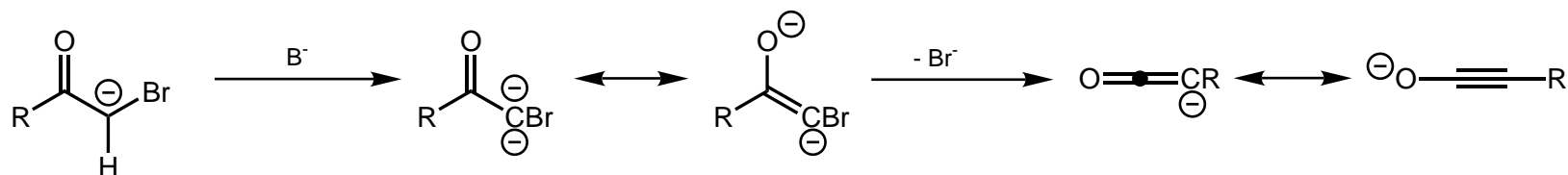


Hofmann rearrangement



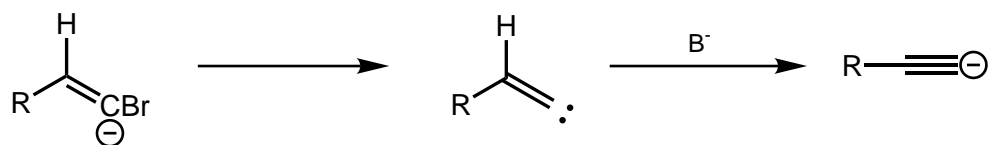
Wallis, E. S. & Lane, J. F. *Org. React.* **1946**, 3, 267

Kowalski ester homologation: isoelectronic with Hofmann

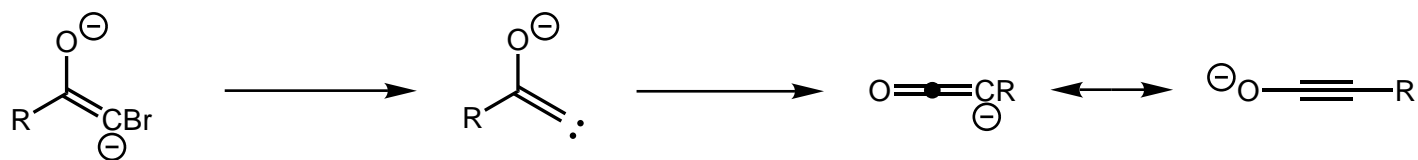


Kowalski, C. J. *J. Am. Chem. Soc.* **1982**, 104, 321

α -elimination: a possible alternative?

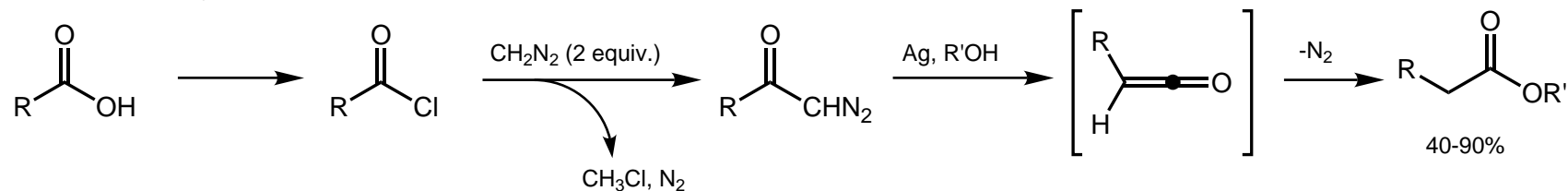


Corey, E. J. *Tet. Lett.* **1972**, 3769



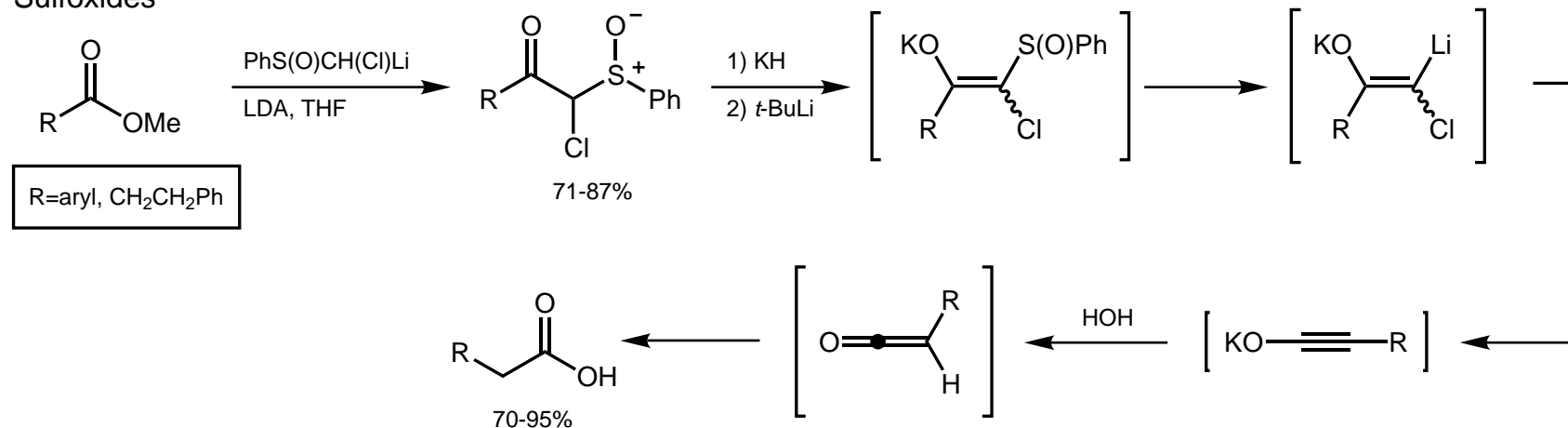
Other Homologation Methods - I

Arndt-Eistert Synthesis

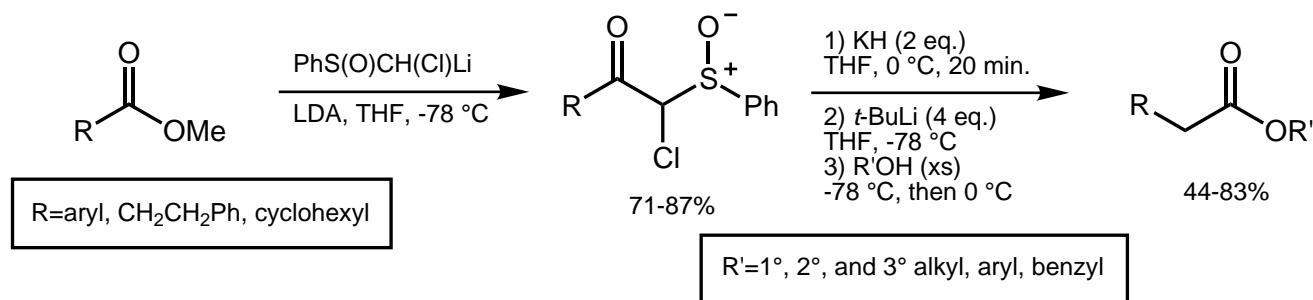


Bachmann, W. E. *Org. React.* **1942**, 1, 38

Sulfoxides



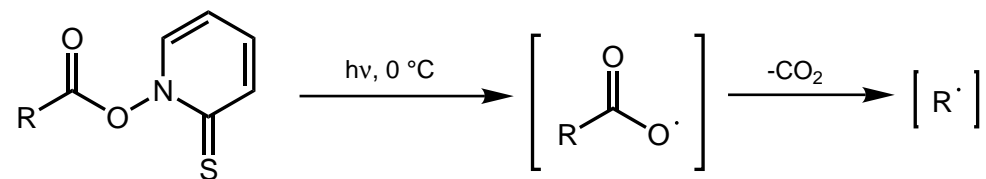
Yamakawa, K. *Tet. Lett.* **1994**, 35, 133



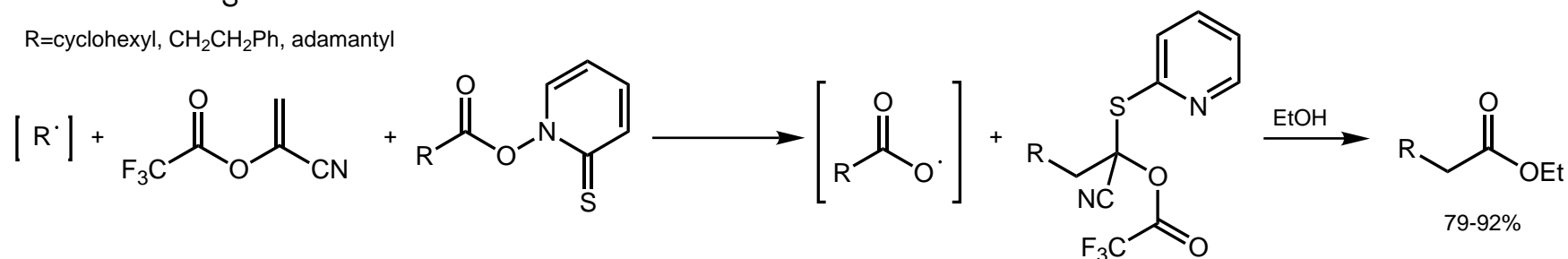
Sato, T. *Tetrahedron* **1997**, 53, 7843

Other Homologation Methods - II

Barton Ester

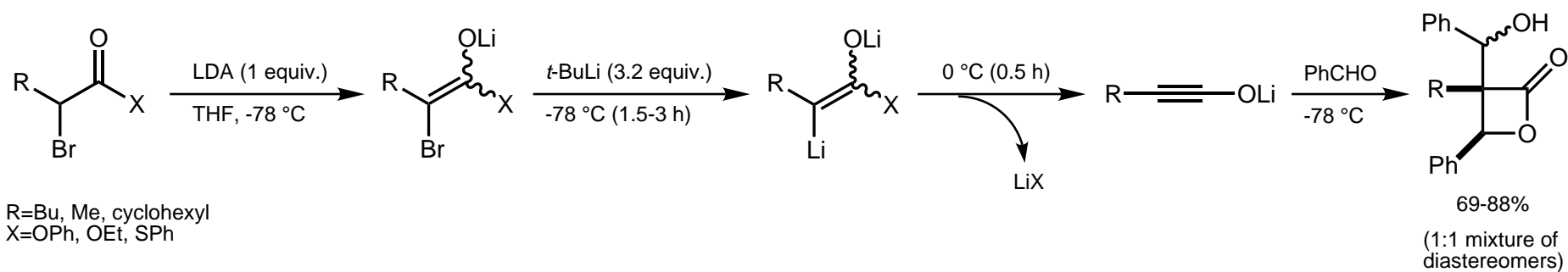


R=cyclohexyl, CH₂CH₂Ph, adamantyl



Jaszberenyi, J. C. *Tet. Lett.* **1993**, 34, 6505

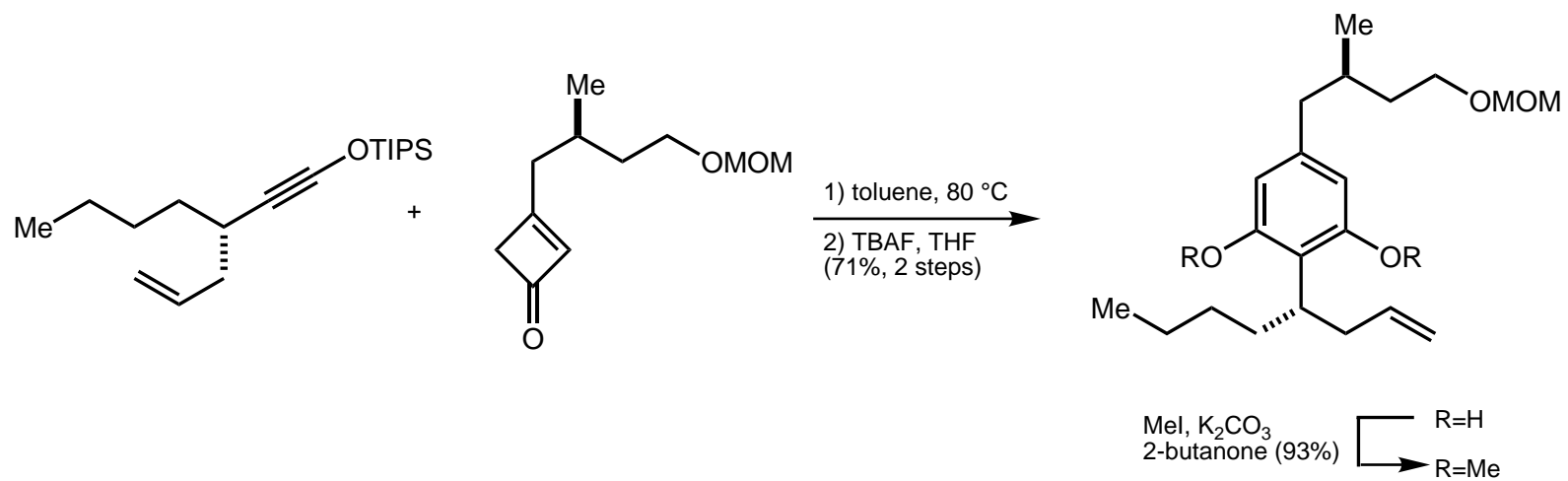
α-Bromo Ester



R=Bu, Me, cyclohexyl
X=OPh, OEt, SPh

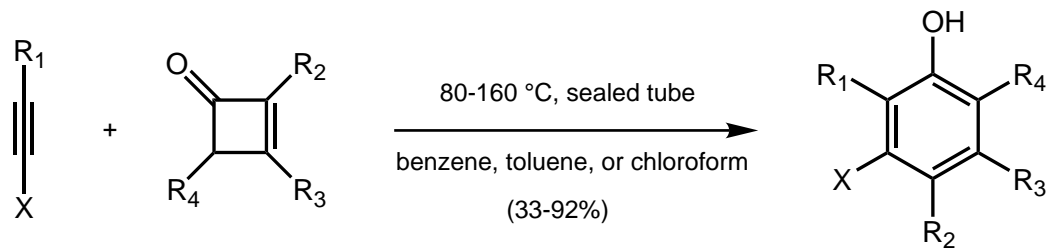
Shindo, M. *Tetrahedron* **1998**, 54, 2411

The Synthesis of (-)-Cylindrocyclophane F - II



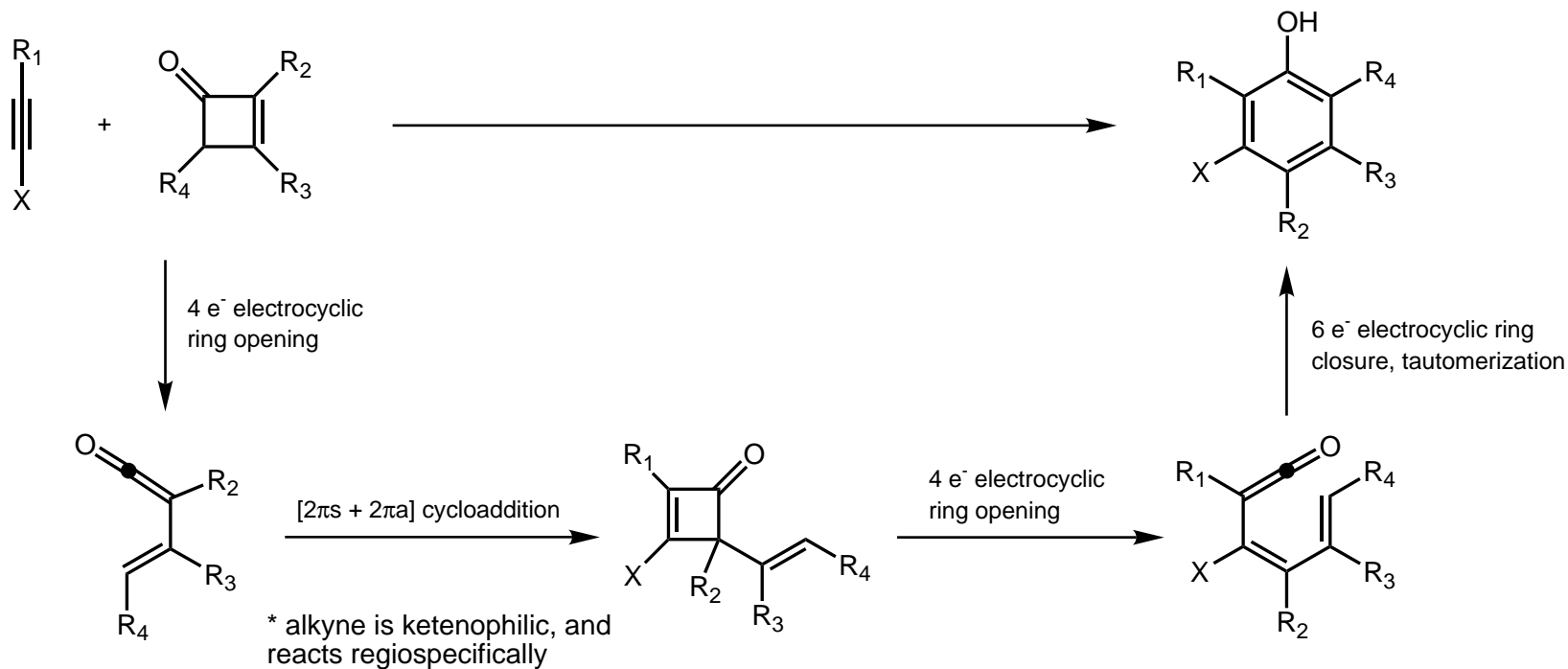
Benzannulation: Danheiser, R. L. *J. Org. Chem.* **1984**, *49*, 1672

Danheiser Benzannulation

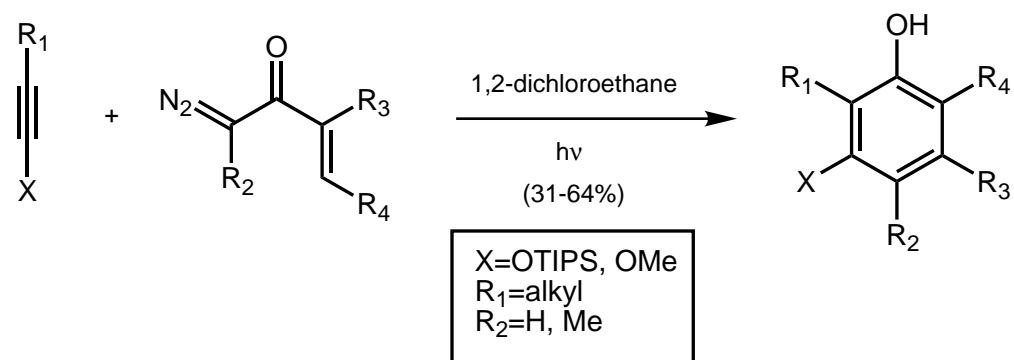


X=NR₂, OR, SR
 R₁=alkyl, H
 R₂=H, Me
 R₃=alkyl, OEt
 R₄=H, Me, Cl

Proposed Mechanism:

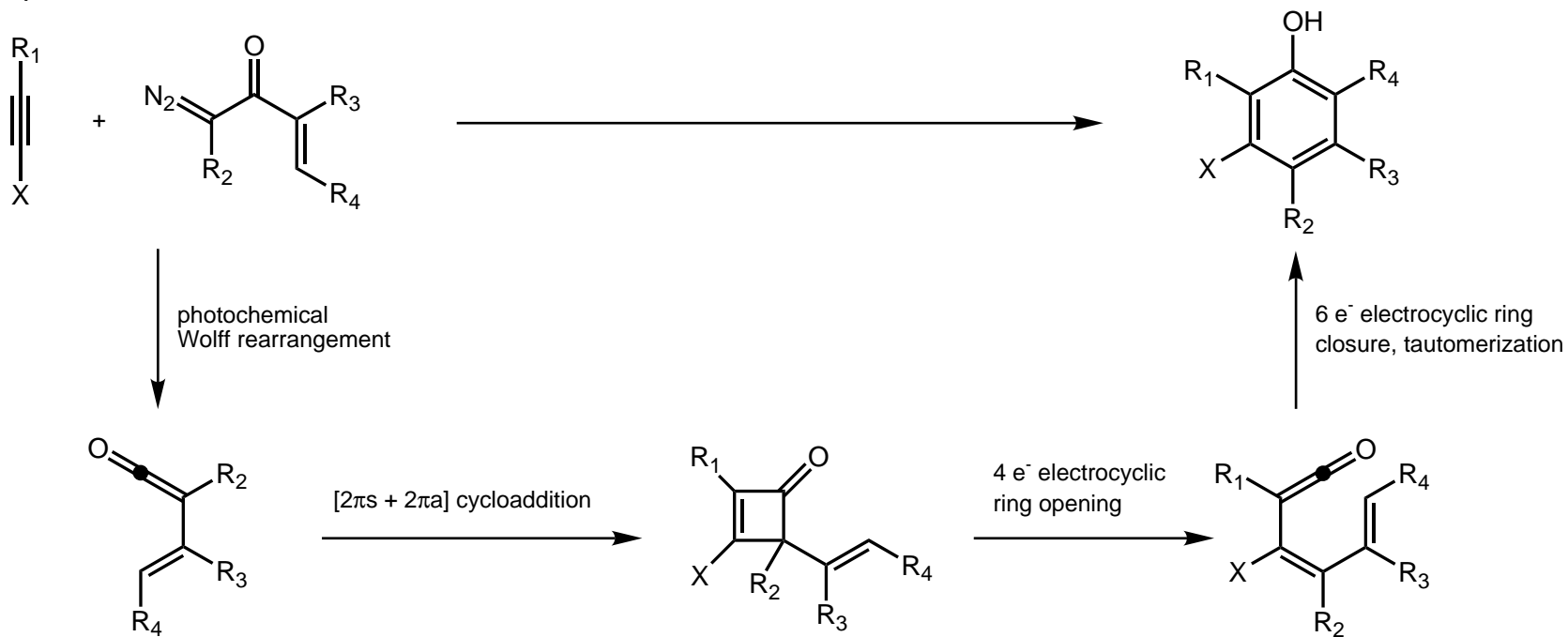


Annulation via Photochemical Wolff Rearrangement



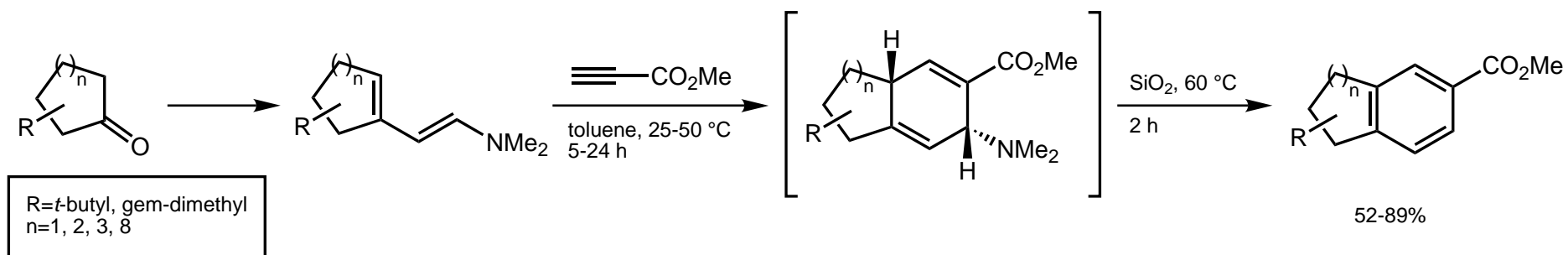
- n Provides access to polycyclic aromatic and heteroaromatic compounds
- n R_3 and R_4 can be linked in an aromatic or non-aromatic ring

Proposed Mechanism:

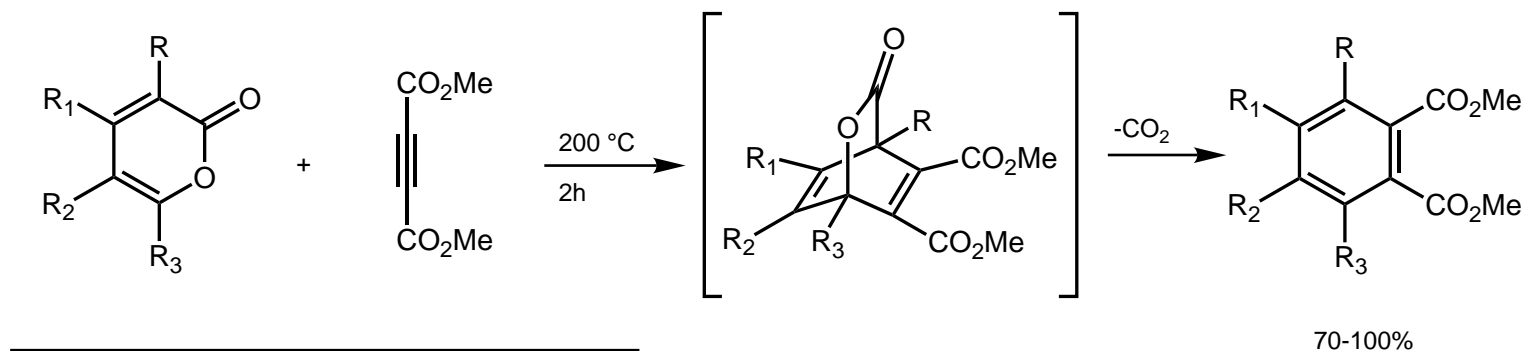


Other Benzannulations - I

Diels-Alder



Snowden, R. L. *Tet. Lett.* **1986**, 27, 703

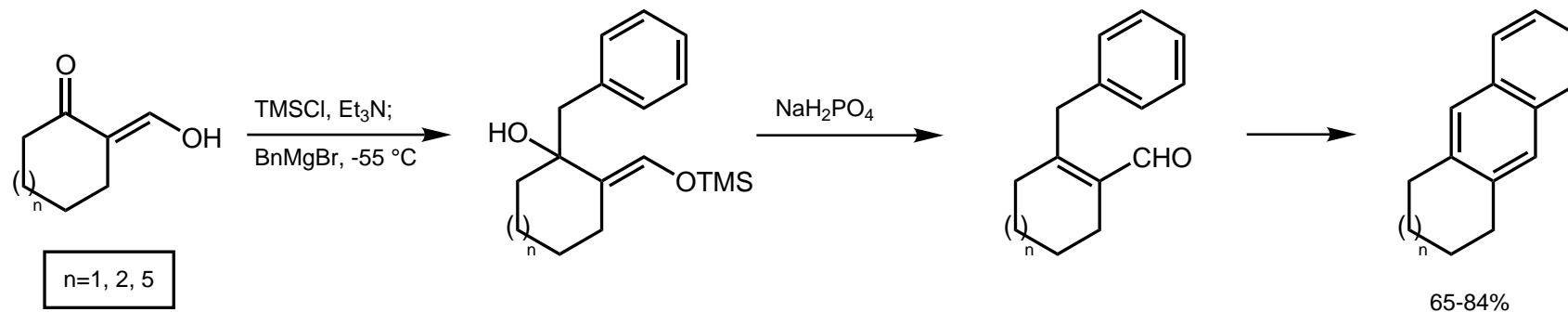


$R = \text{H, CO}_2\text{Me, OMe, Me, Et}$
 $R_1 = \text{OMe, H, Me, CO}_2\text{Me}$
 $R_2 = \text{H, 3,4,5,10-alkyl rings with R}_3, \text{CO}_2\text{R}$
 $R_3 = \text{H, 3,4,5,10-alkyl rings with R}_2, \text{Me, CO}_2\text{Me, OMe}$

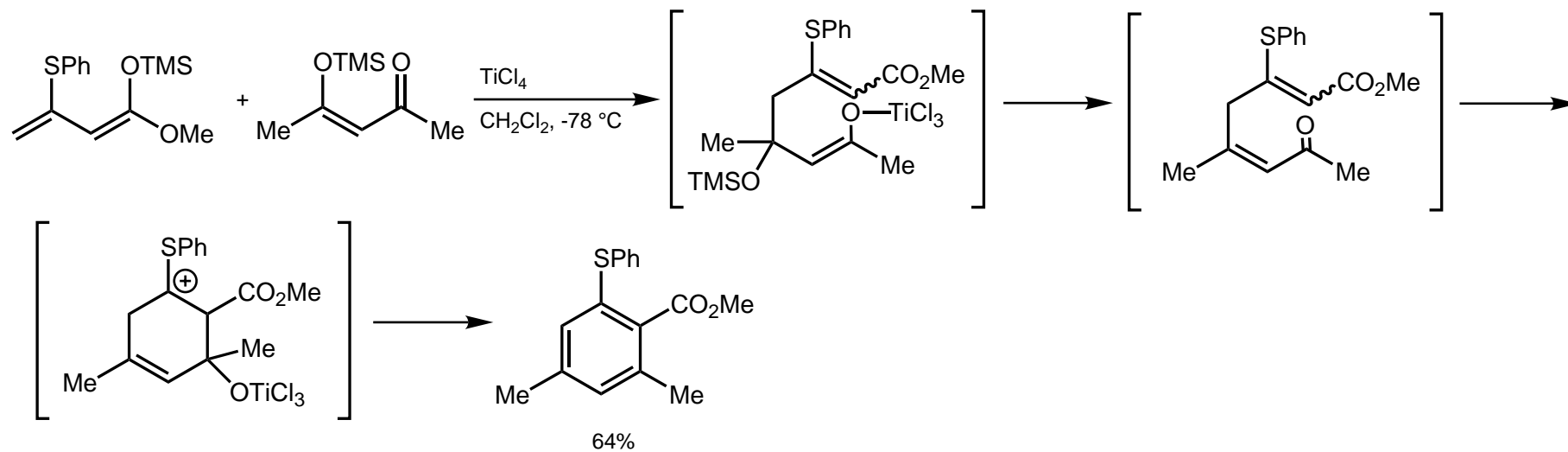
Effenberger, F. *Chem. Ber.* **1987**, 120, 1347

Other Benzannulations - II

Carbonyl Condensation



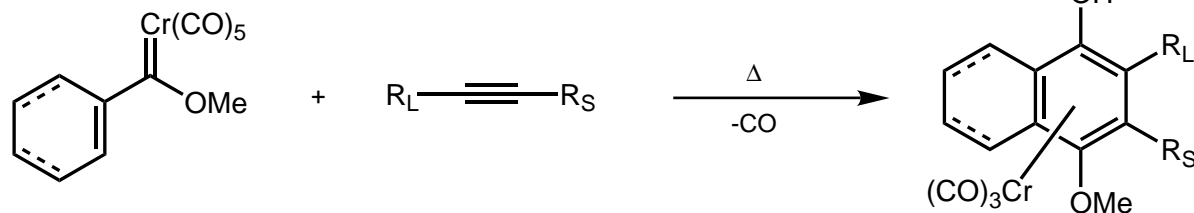
Tius, M. A. *Tet. Lett.* **1986**, 27, 2571



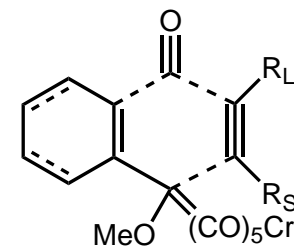
Chan, T. H. *J. Org. Chem.* **1986**, 51, 3012

Other Benzannulations - III

Dötz Reaction

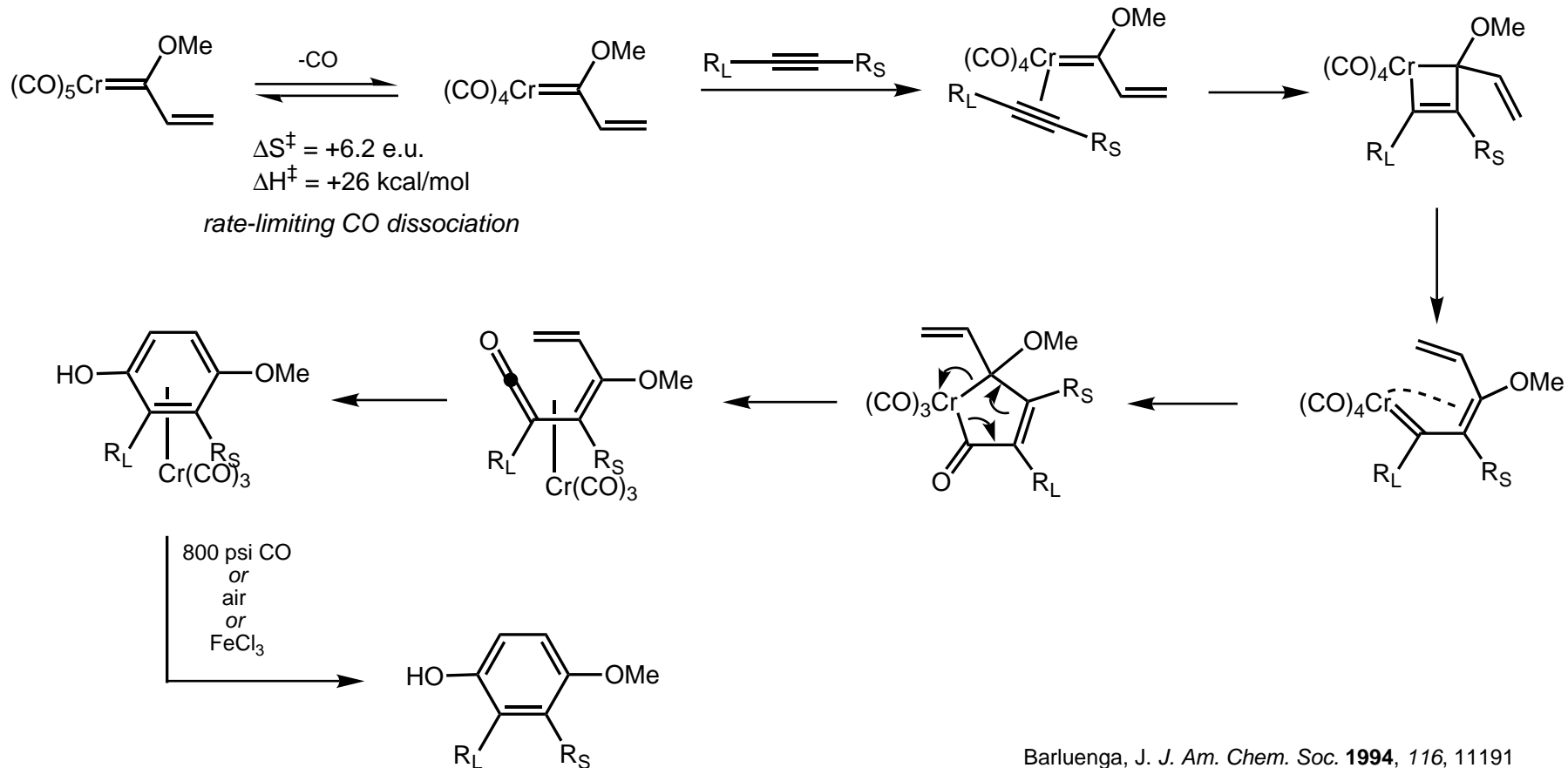


Observed Connectivity:



Dötz, K. H. *Angew. Chem. Int. Ed. Eng.* **1984**, 23, 587

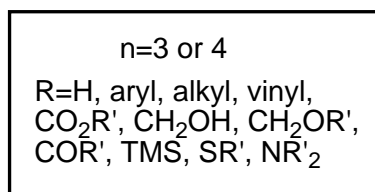
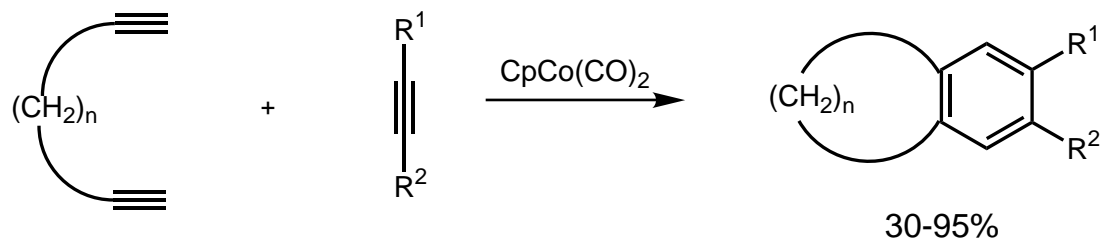
Proposed Mechanism:



Barluenga, J. *J. Am. Chem. Soc.* **1994**, 116, 11191
 Connell, B. Evans Group Seminar, Feb. 1999

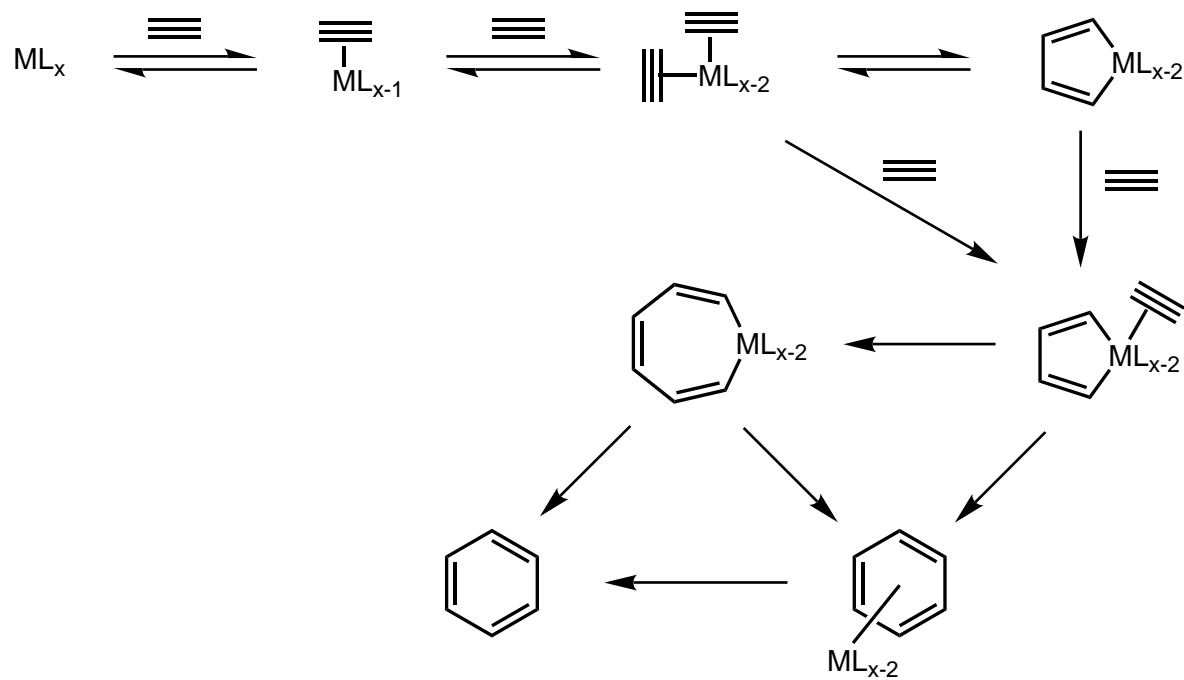
Other Benzannulations - IV

Co-mediated [2 + 2 + 2] Acetylene Cycloadditions

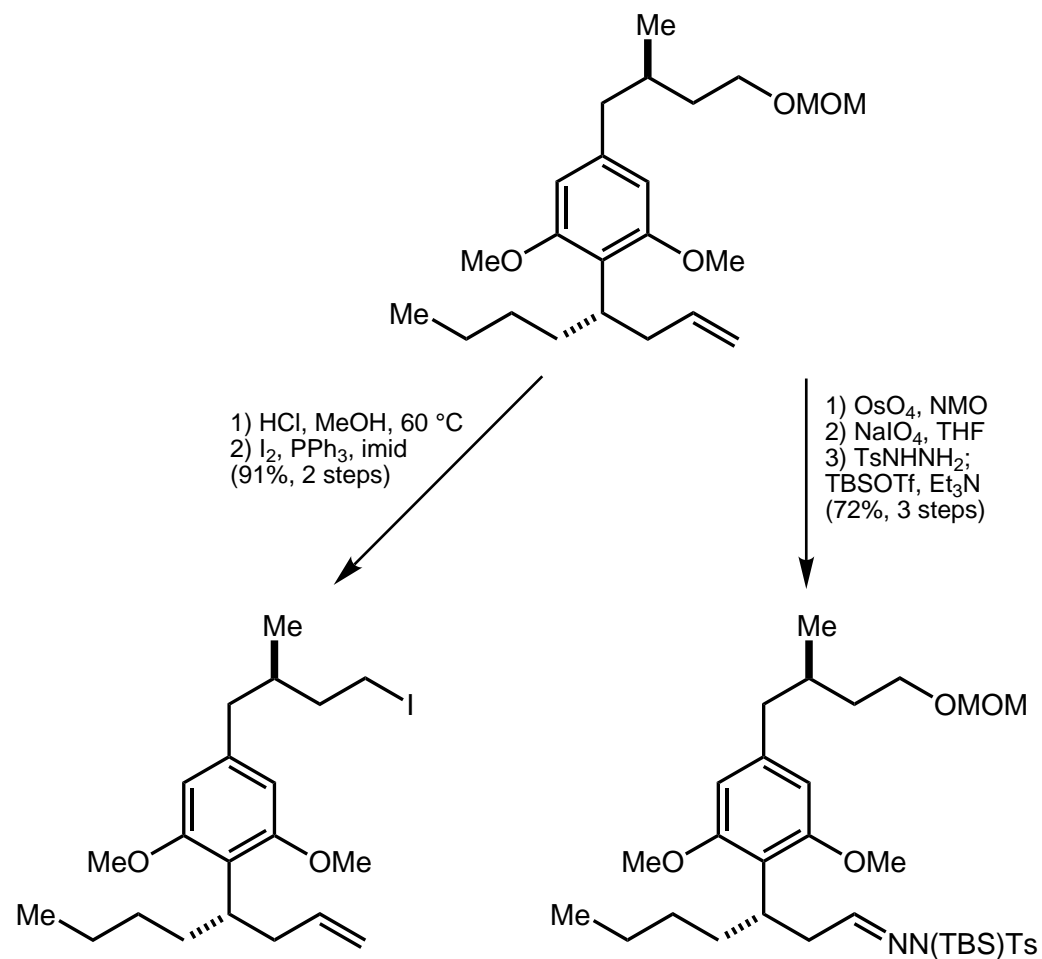


Vollhardt, K. P. C. *Angew. Chem. Int. Ed. Eng.* **1984**, 23, 539

Proposed Mechanism:

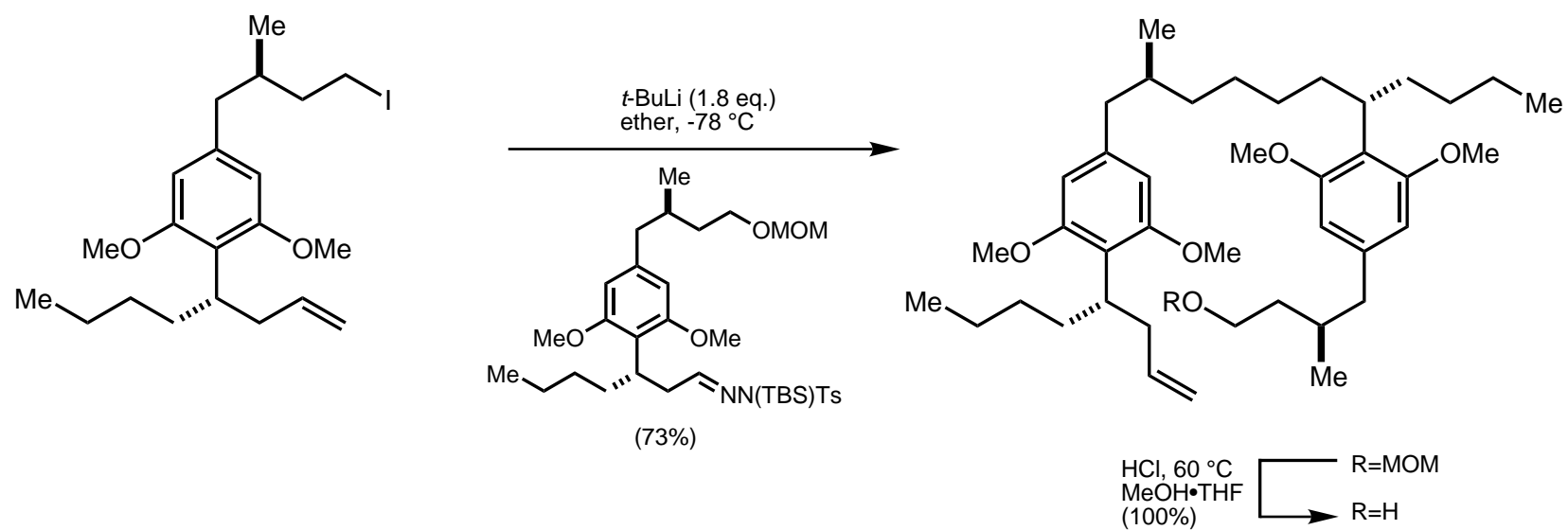


The Synthesis of (-)-Cylindrocyclophane F - III



Silylated tosylhydrazone formation: Myers, A. G. *J. Am. Chem. Soc.* **1990**, 112, 8208

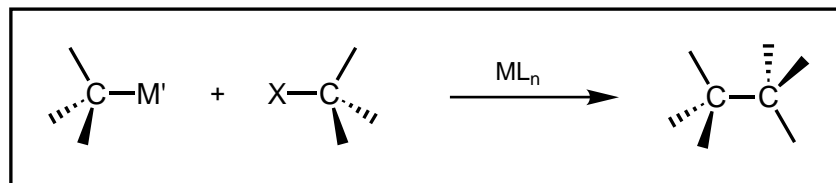
The Synthesis of (-)-Cylindrocyclophane F - IV



Reductive coupling: Myers, A. G. *J. Am. Chem. Soc.* **1998**, *120*, 8891

The State-of-the-Art in Alkyl-Alkyl Cross-Coupling Reactions

Mini-review: Cárdenas, D. J. *Angew. Chem. Int. Ed.* **1999**, 38, 3018



$\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ coupling between $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ centers has been poorly developed

$\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ coupling of organocuprates and alkyl halides has been known since 1960s, but functional group tolerance is poor

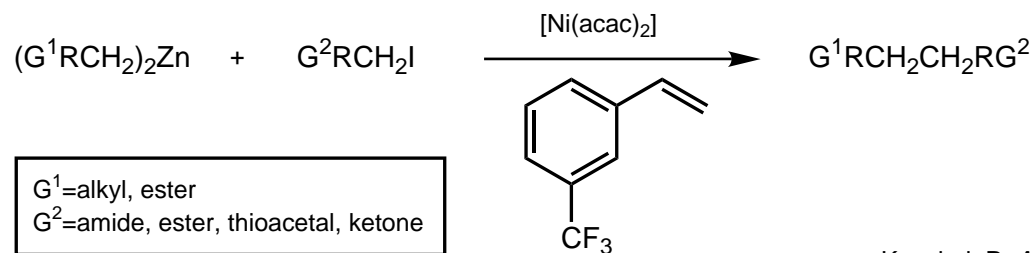
Main Difficulties:

- 1) Alkyl halides, even MeI, react slowly with Pd^0 complexes
- 2) β -Elimination of hydrogen competes with often-slower transmetalation
- 3) Reductive elimination is slow

Potential Solutions:

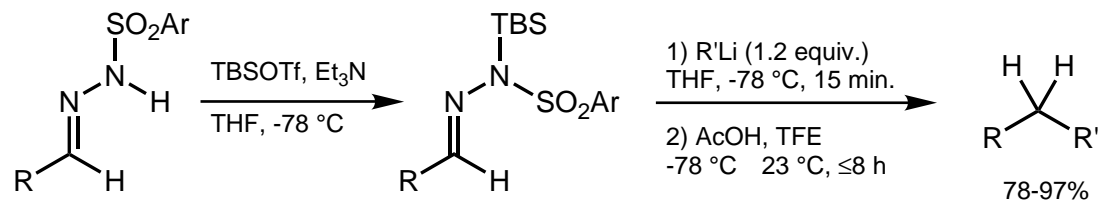
- 1) Use a different, more reactive metal, such as Ni^0
- 2) Faster transmetalation step?
- 3) Certain additives can accelerate reductive elimination

A potentially useful $1^\circ(\text{alkyl})\text{-}1^\circ(\text{alkyl})$ bond-forming reaction:



Knochel, P. *Angew. Chem. Int. Ed.* **1998**, 37, 2387

Myers Reductive Coupling



R=1°, 2°, or 3° alkyl, aryl, α-methyl, acetonide-protected sugar
R'=1° or 3° alkyl, phenyl, enolate, β-methyl

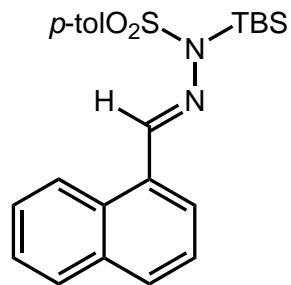
Myers, A. G. *J. Am. Chem. Soc.* **1998**, *120*, 8891

R Stipulations

- n where R=adamantyl, competitive *o*-lithiation of tolyl group occurs upon addition of BuLi: trisyl hydrazones solve problem
- n functionalities must be stable to addition of strong base

R' Stipulations

- n amides, TBS-protected hydroxyls, diethyl acetals stable to lithiation
- n lithium reagents prepared by either lithium-iodide exchange or deprotonation
- n liability of coupling: difficult to generate organolithium reagents with sensitive functionalities
- n lithium acetylides and Grignard reagents exhibit insufficient reactivity

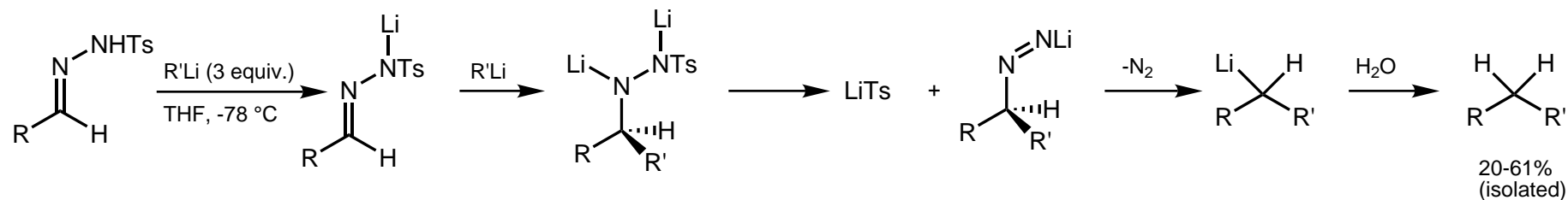


A

- n X-ray crystal structure of **A** reveals the TBS group adjacent to the imino lone pair
- n sulfonyl oxygens may be in good orientation to direct organolithium reagent to the imine group

Earlier Reductive Couplings of Aldehyde Tosylhydrazones

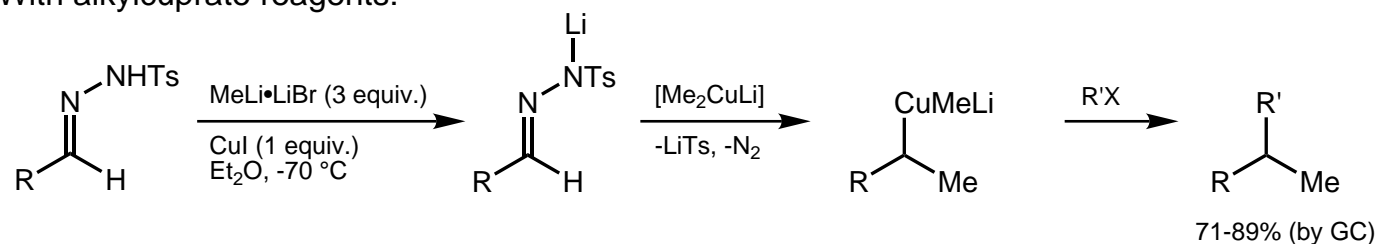
With alkyllithium reagents:



R=1° alkyl, benzyl, phenyl, alkenyl
R'=1° alkyl

Vedejs, E. *Tet. Lett.* **1977**, 135

With alkylcuprate reagents:

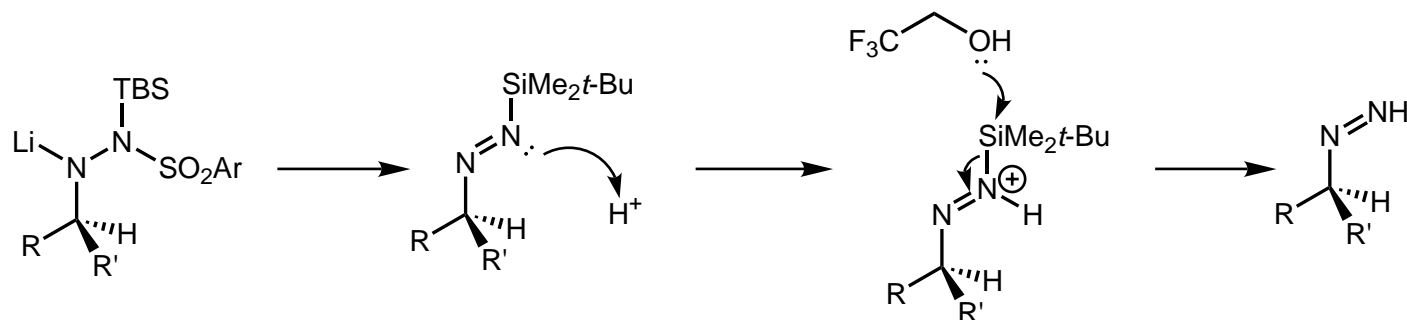
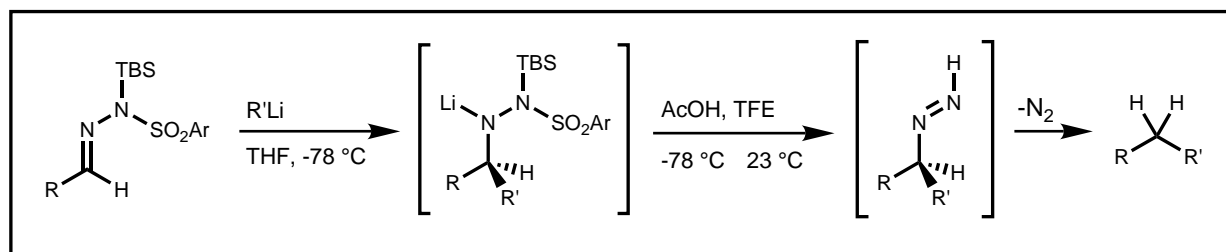


R=2° or 3° alkyl
R'X=MeI, *n*-BuBr, HCl

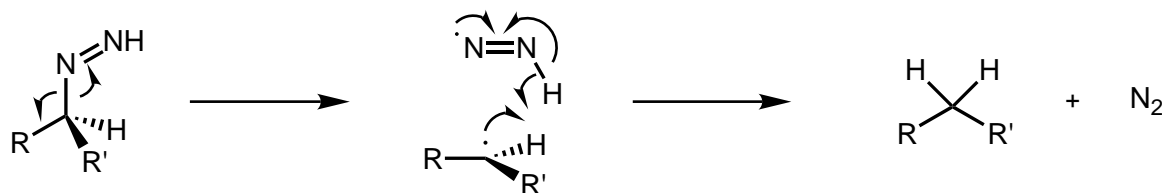
n for R=1° alkyl, conversion is 23% at best

Bertz, S. H. *Tet. Lett.* **1980**, 21, 3151

Myers Coupling - Mechanism



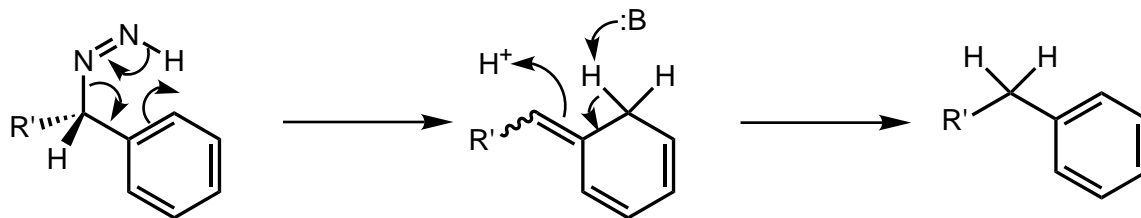
Radical pathway:



radical pathway established by trapping intermediate free radical with TEMPO

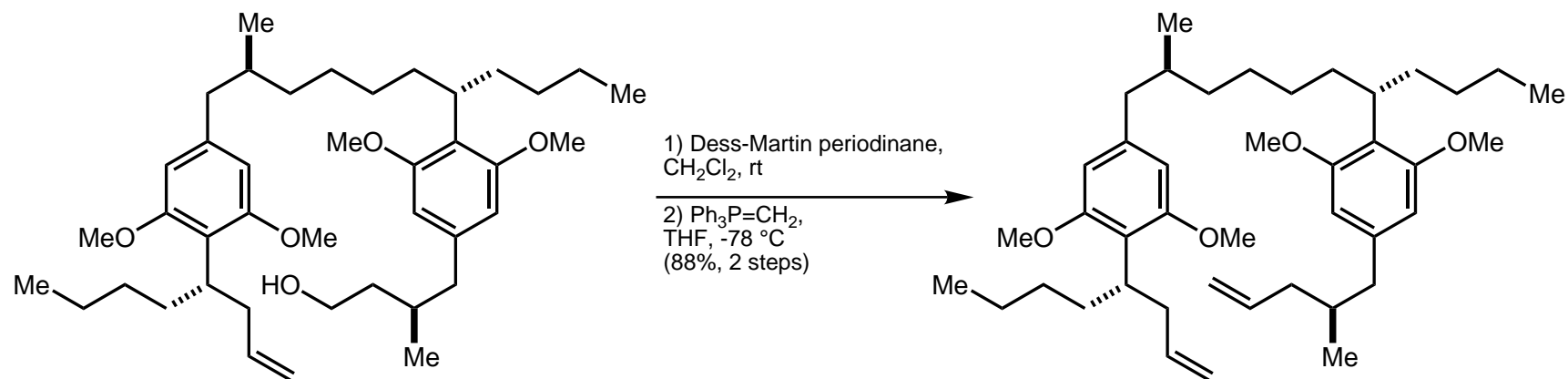
Myers, A. G. *J. Am. Chem. Soc.* **1998**, 120, 8891

[3,3]-Sigmatropic elimination of N_2 (R=aryl, vinyl):

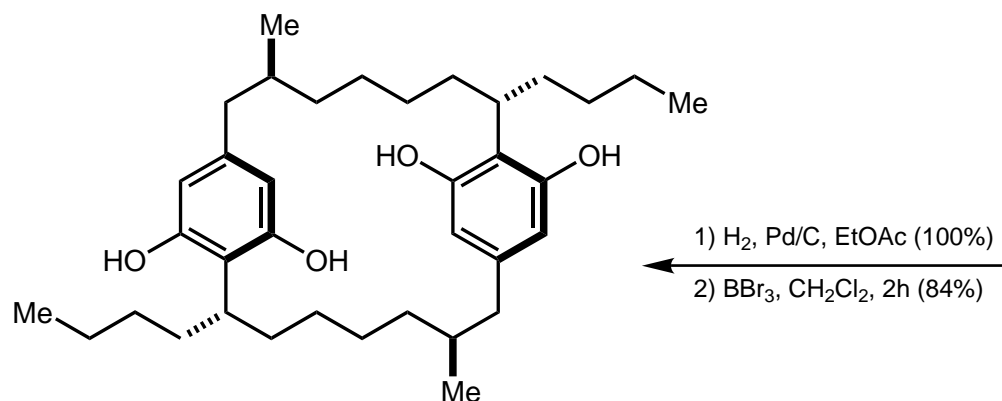
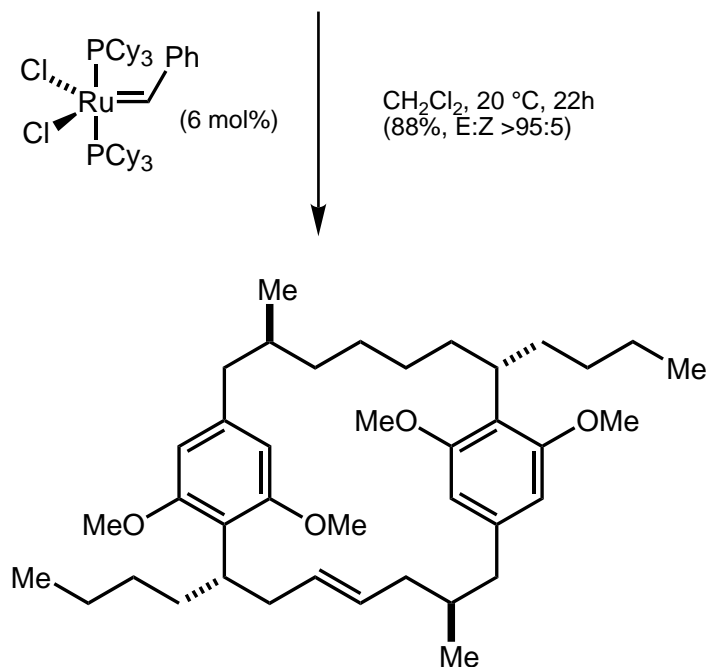


Myers, A. G. *J. Am. Chem. Soc.* **1997**, 119, 8572

The Synthesis of (-)-Cylindrocyclophane F - V



Ring-closing metathesis: Grubbs, R. H. *Tetrahedron* **1998**, *54*, 4413
Hu, E. Evans Group Seminar, Feb. 1999
Barrow, J. Evans Group Seminar, Jan. 1996



(-)-Cylindrocyclophane F

Summary

- n The cylindrocyclophanes are structurally unique natural products whose symmetry enables concise, convergent total syntheses
- n The nonselective cytotoxicity of the cylindrocyclophanes is potentially prohibitive for drug development
- n The Kowalski ester homologation requires further refinement and comprehension before it can emerge as a major homologation method
- n While the Danheiser benzannulation is a convenient method for creating highly functionalized aromatic compounds, it is one of many effective annulation strategies
- n The Myers reductive coupling may open some new avenues of alkyl-alkyl bond formation, although both coupling partners must be stable to strong base
- n Smith and co-workers completed the total synthesis of (-)-Cylindrocyclophane F in 20 linear steps and 8.3% overall yield