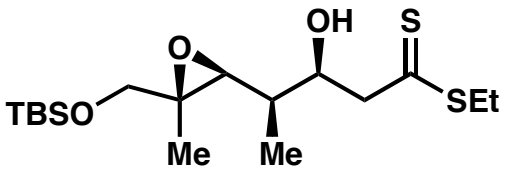
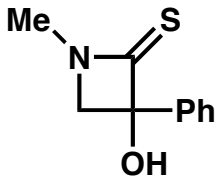
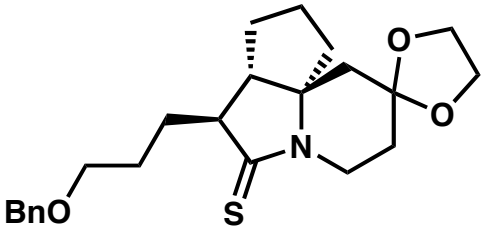






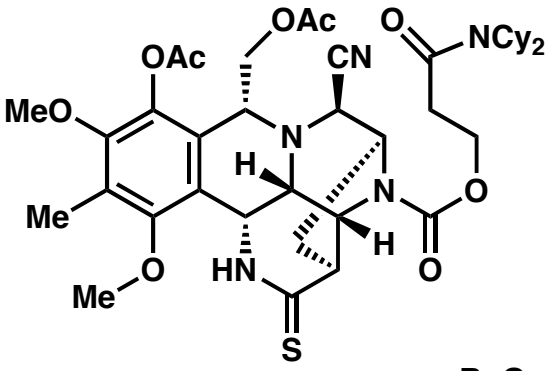
Selected Reactions of Thiocarbonyl Compounds

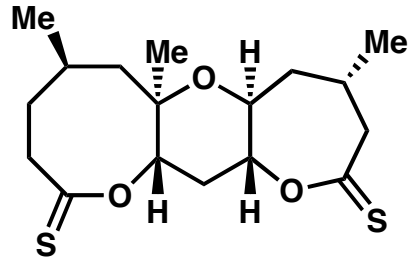
Shyam Krishnan

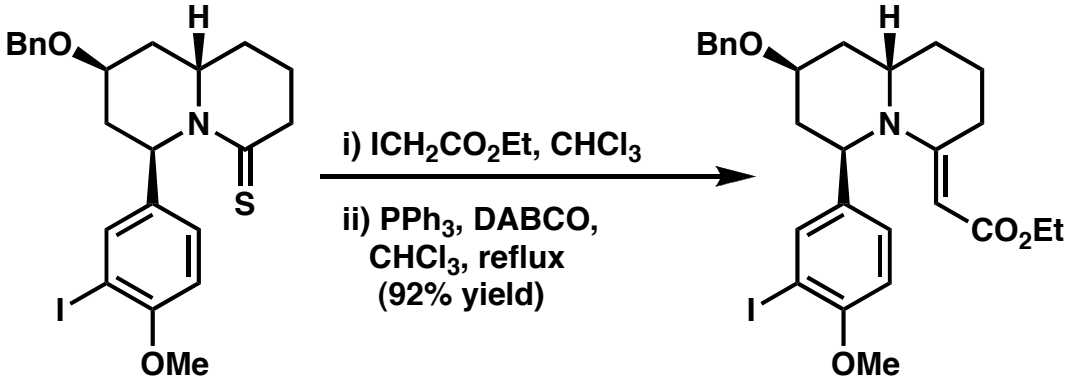
Monday, June 12, 2006

8 p.m.

147 Noyes







Selected Reactions of Thiocarbonyl Compounds

1) Thiocarbonyl compounds: nomenclature and structural properties

2) Methods of Synthesis

3) Reactions of thiocarbonyl compounds and their application in the synthesis of functionalized molecules

1) Reactions of carbanions derived from Thiocarbonyl compounds.
2) Carbanion addition to the thiocarbonyl group.
3) Reactions with electrophiles - the Eschenmoser sulfide contraction.
4) Radical mediated reactions.
5) [3,3] sigmatropic rearrangements - the thio-Claisen rearrangement.
6) [4+2] cycloaddition reactions.
7) [3+2] Dipolar cycloadditions.
8) Summary and future directions.

Reviews:

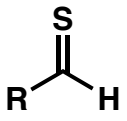
General review: Metzner, P. *Top. Curr. Chem.* **1999**, *204*, 127.
General review: Metzner, P. *Synthesis* **1992**, 1185.
Synthesis of heterocycles: Jagodzinski, T.S. *Chem. Rev.* **2003**, *103*, 197.
Radical chemistry: Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.
Photochemistry: Coyle, J. D. *Tetrahedron* **1985**, *41*, 5393.

Thiocarbonyl Compounds

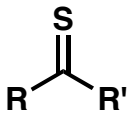
Structures, Nomenclature and Stability

Thiocarbonyl compounds possess a carbon-sulfur double bond

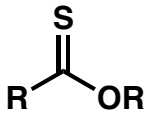
Thiocarbonyl compounds with at least one organic group bound to the thiocarbonyl carbon:



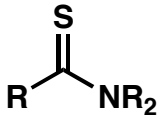
Thioaldehyde



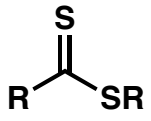
Thioketone



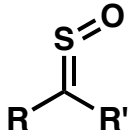
Thionoester



Thioamide



Dithioester



Sulfine/Thiocarbonyl oxide

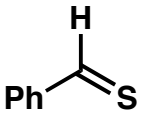
Typically display greater reactivity than their carbonyl (oxygen) analogs

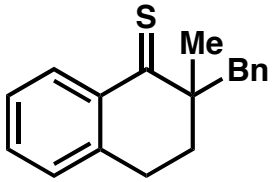
- **Larger covalent radius of sulfur vs oxygen (104.9 nm vs 70.2 nm), less efficient overlap in S_{3p}-C_{2p} π-bond**
- **Dissociation energy of C=S (115 kcal/mol) is significantly lower than for C=O (162 kcal/mol).**
- **Higher Polarisability of sulfur relative to oxygen**
- **Sulfines/thiocarbonyl oxides do not have stable counterparts among their oxygen analogs.**
- **Thioaldehydes and many thioketones are very reactive towards dimer, trimer or oligomer formation; often need to be generated *in situ.***

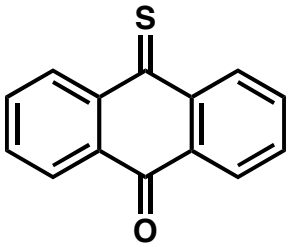
Thiocarbonyl Compounds

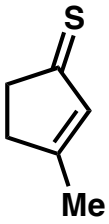
Spectroscopic Features

UV-vis spectroscopy: Many thiocarbonyl compounds are colored! This is likely due to an n → π* transition





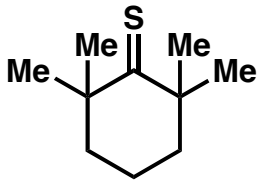


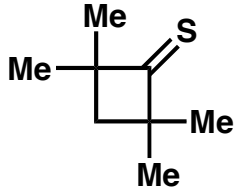


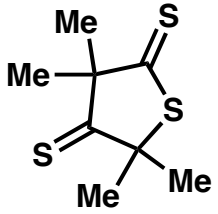
λ_{max}	575 nm	592 nm	697 nm	569 nm

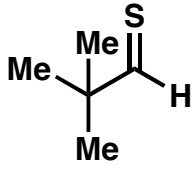
IR spectroscopy: C=S stretching vibration is only of medium intensity, 1100-1300 cm^{-1} .
Enethiols absorb around 2550 cm^{-1} (SH) and 1640 cm^{-1} (C=C).

^{13}C NMR: The thiocarbonyl carbon appears 35-63 ppm downfield relative to the carbonyl analog!









δ(C=S)	279.8	289.1	245.2, 267.7	255.6

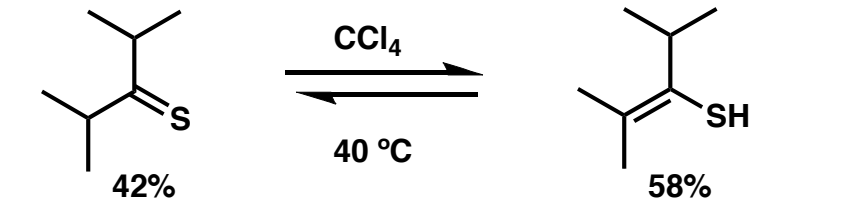
Chemical shift ~ 200 ppm for thioamide C=S

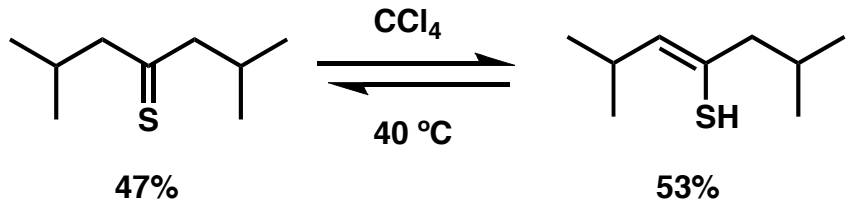
Schaumann, E. in *Supplement A, The Chemistry of double-bonded functional groups*. Patai, S. (ed.), **1989**, *Vol 2. Part 2*, p. 1269

Thiocarbonyl Compounds

Thial/Thione - Ene-thiol tautomerism

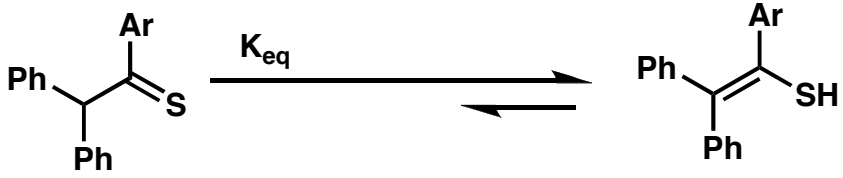
The enethiol tautomer is favored to a greater extent than in keto-enol tautomerism





Paquer, D. et al. *J. Bull. Soc. Chim. Fr.* **1971**, 4407

However, calculations on butane-2-thione suggest a high kinetic barrier to interconversion (85 kcalmol^{-1})
Thione and ene-thiol tautomers can be separated by GC (Lipscomb, R.D. et al, *J. Polym. Sci. Part 1* **1970**, *8*, 2187).



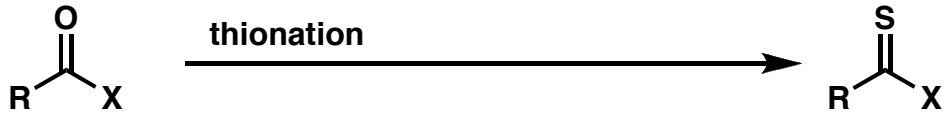
Ar = Ph, *p*-OMeC$_6$H$_4$

No thioketone observable even after 2 weeks of attempted equilibration
Authors estimate $K_{eq} \geq 10^6$ times that for the corresponding oxygen analogs!
Rappoport, Z. and co-workers, *J. Org. Chem.* **1996**, *61*, 5462.

Thiocarbonyl Compounds

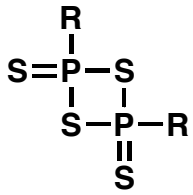
Synthesis Routes

Most generally-applicable route: thionation of the corresponding carbonyl compound:



R= alkyl, aryl.
X = alkyl, aryl, H, OR, NR_2, SR.

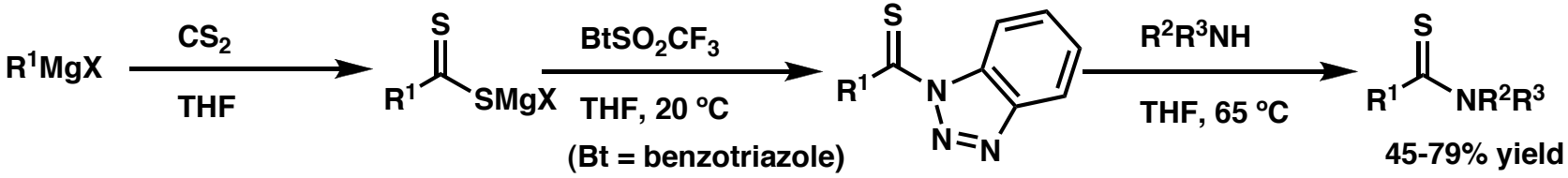
Commonly used thionation reagents:



P_4S_{10}

R = p-OMe-Ph (Lawesson's reagent)
SMe (Davy reagent)
PhOPh (Belleau reagent)

For a review of thionation using Lawesson's reagent: Jesberger, M. et al. *Synthesis* **2003**, *13*, 1929.

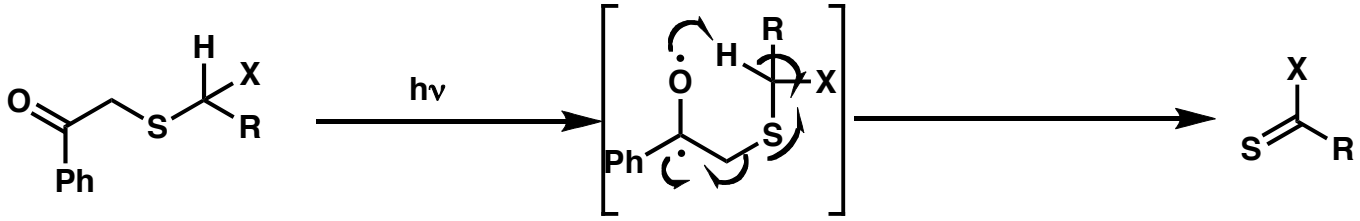


Katritzky, A.R., and co-workers, *Synthesis* **1995**, 1497.

Thiocarbonyl Compounds

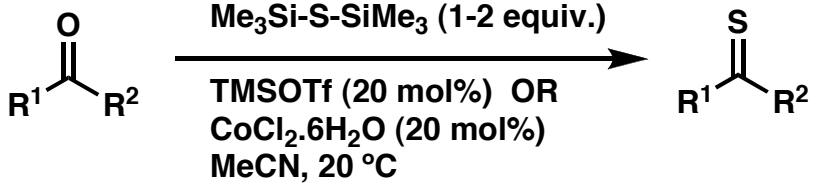
Synthesis Routes

Photolysis of phenacyl thioethers:



X = aryl, alkyl, H, OR
R = aryl, alkyl

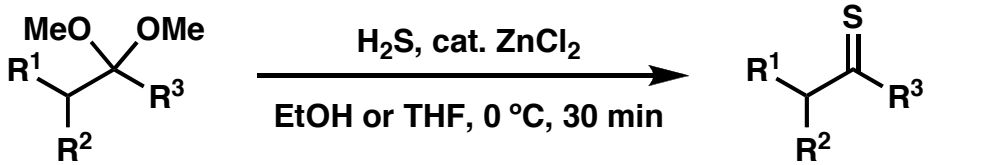
Mild conditions for formation of non-enethiolizable thioketones and thioaldehydes:



Thioaldehydes were generated in the presence of a trapping agent (diene)

Degl'Innocenti, A., and co-workers, *J. Org. Chem.* **1991**, *56*, 7323.

For enethiolizable thioketones:



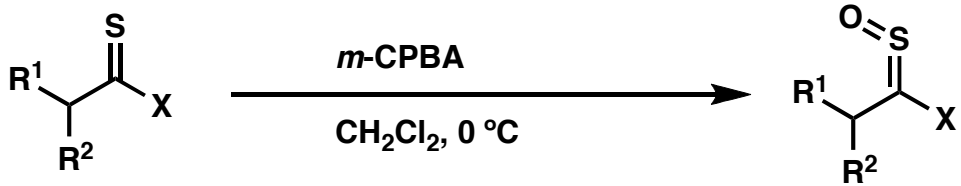
36-67% yields

Authors were able to isolate thioketones free from enethiols.
Metzner, P., and co-workers. *Tetrahedron Lett.* **1992**, *33*, 6151.

Thiocarbonyl Compounds

Synthesis Routes for Sulfines

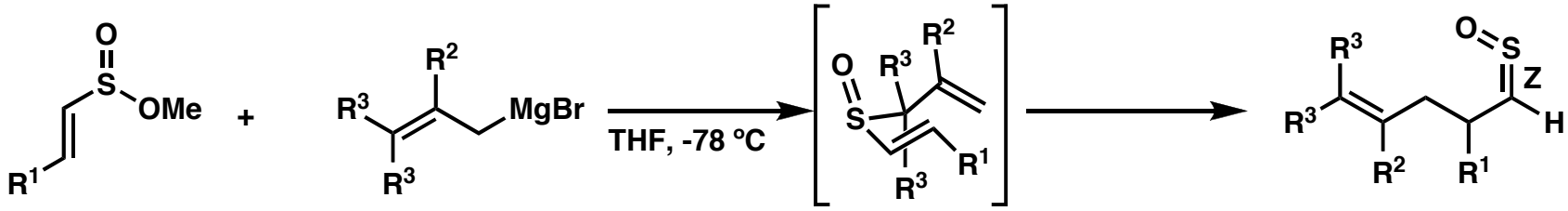
Peracid oxidation of thiocarbonyl compounds:



X = SR, OR, alkyl, aryl
R^1, R^2 = alkyl, aryl

Metzner, P., and co-workers, *Tetrahedron Lett.* **1991**, *32*, 747.

[3,3]-sigmatropic rearrangement of vinyl allyl sulfoxides:



R^1 = Alkyl

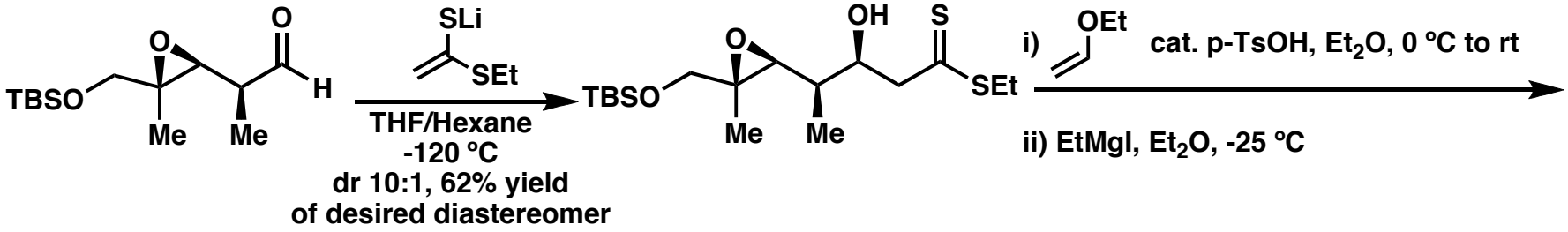
R^2 = Me, H
R^3 = Me, H

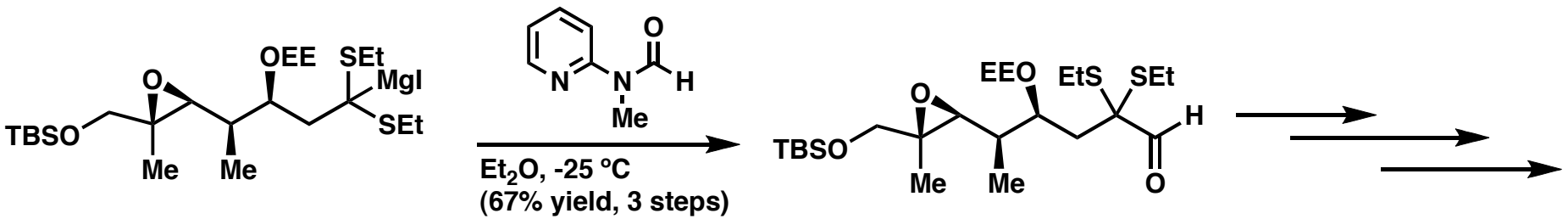
Z:E > 95:5
65-71% yields

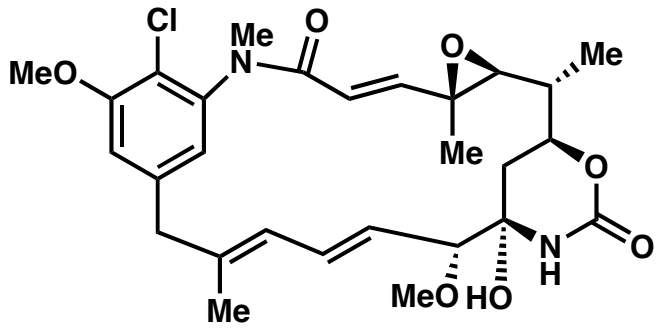
Reactions to form thioketone-S-oxides are less stereoselective
Baudin, J-B., et al *Synlett* **1992**, 909.

Aldol Reaction and Thiophilic Addition to Dithioesters

The Meyers approach to Maysine







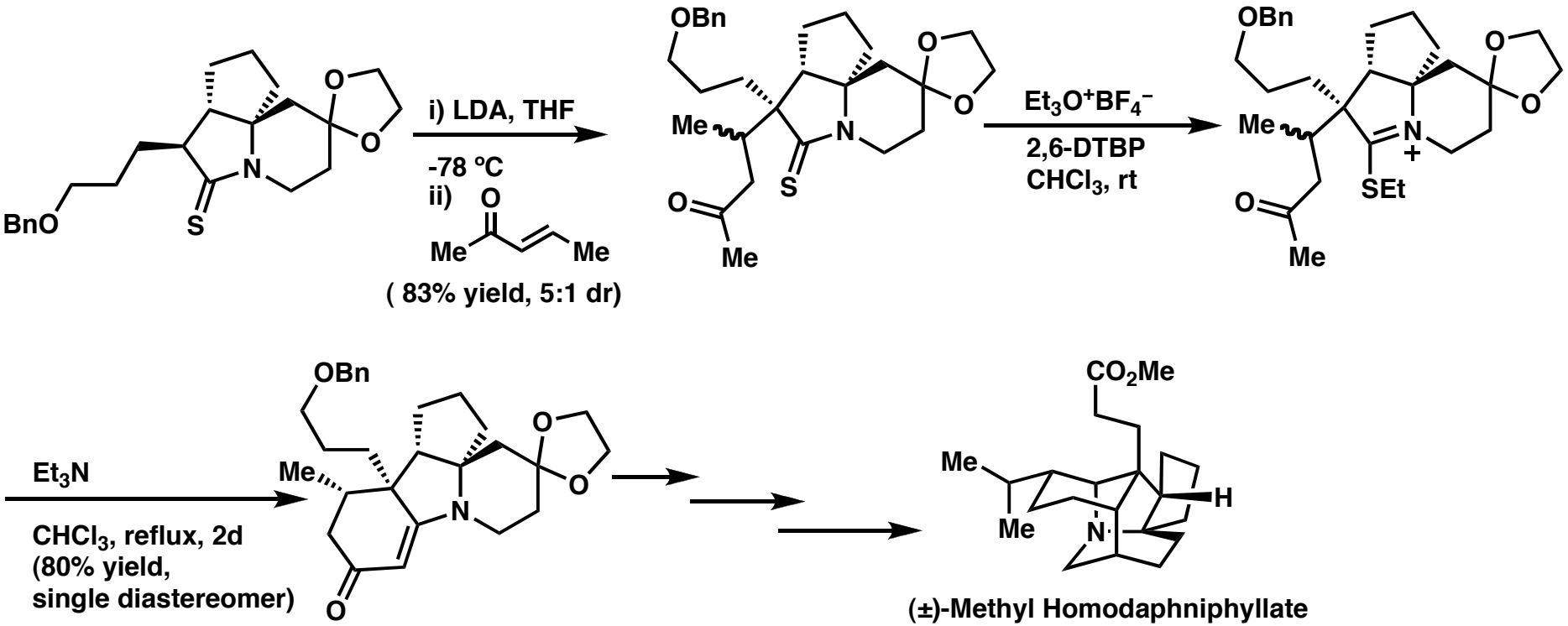
(–)-Maysine

- **Ester enolates result in poor dr in the aldol reaction.**
- **Reaction at -78 °C yields only 3:1 dr.**

Meyers, A.I., and co-workers, *J. Am. Chem. Soc.* **1983**, *105*, 5015.

Michael Addition of Thioamide Enolates

The Heathcock approach to Methyl Homodaphniphyllate

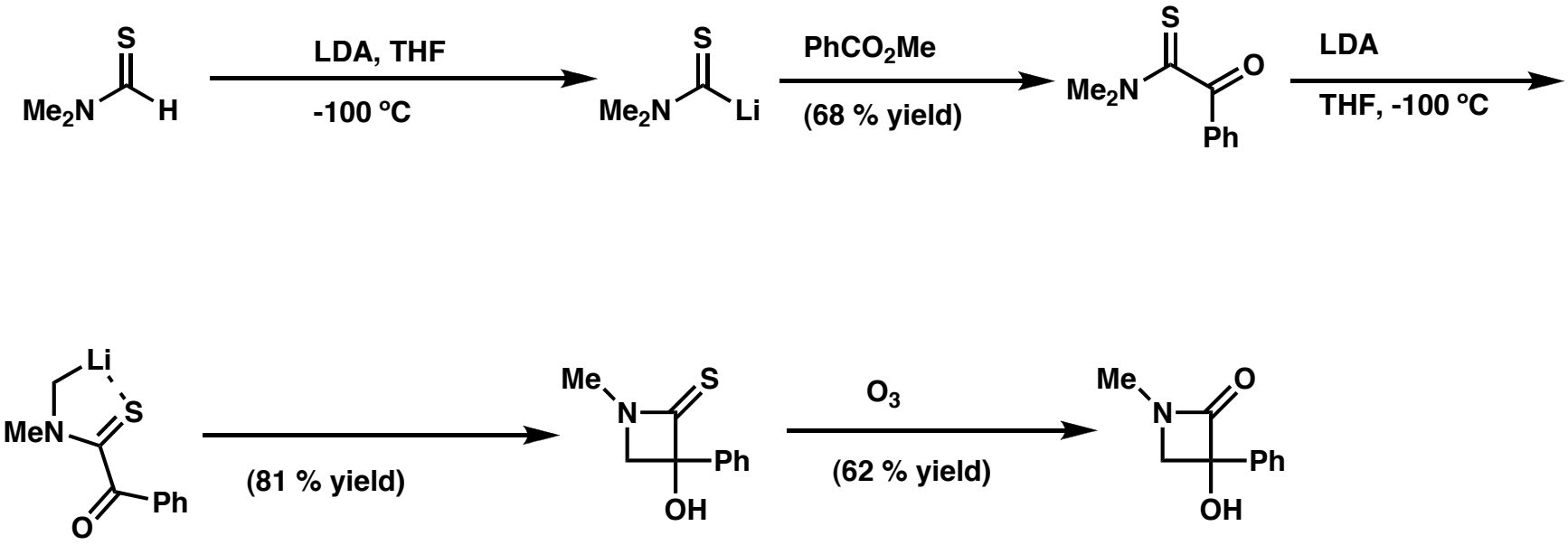


- **The enolate of the corresponding amide reacts predominantly 1,2-fashion.**
- **Major diastereomer undergoes efficient cyclization.**

Heathcock, C.H., and co-workers, *J. Org. Chem.* **1992**, *57*, 2531-2534.

Deprotonation of Acyl Thioamides

Synthesis of β-lactams

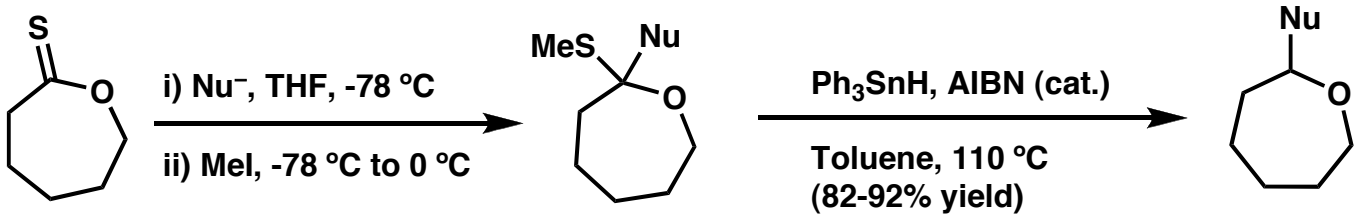


Other substituted benzoate esters can be used, as well as non-enolizable esters.

Creary, X., and co-workers, *J. Am. Chem. Soc.* **1995**, *117*, 5859.

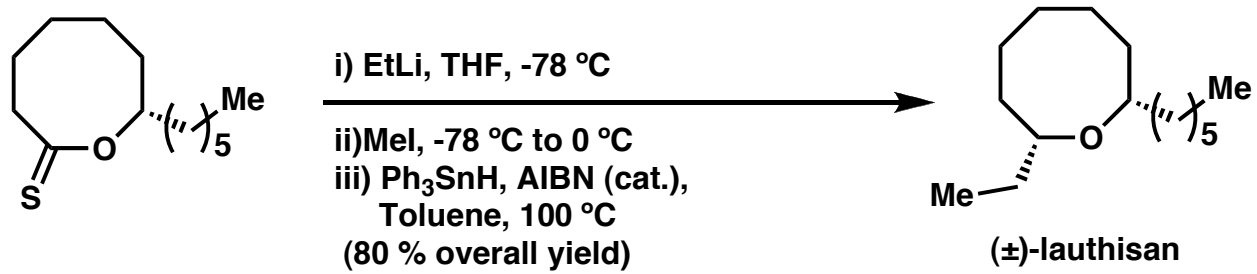
Addition of Nucleophiles to Thionolactones

Synthesis of Medium-ring Ethers



High yields of addition products with organolithium reagents (79-92% yield). Organomagnesium reagents (except allyl magnesium bromide) react poorly.

Reduction of the mixed thioketal is frequently highly diastereoselective:

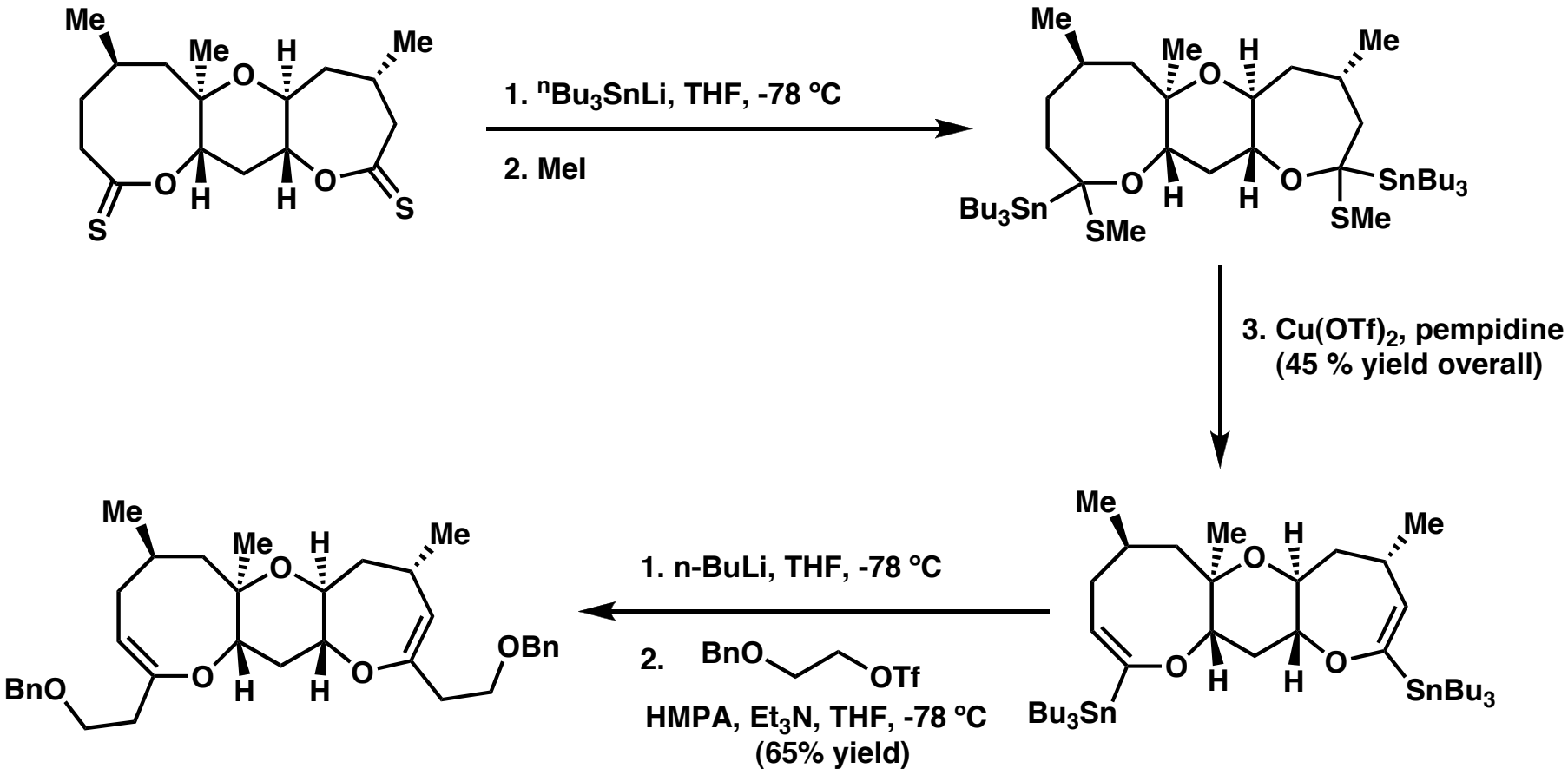


(±)-lauthisan

Nicolaou, K.C., and co-workers, *J. Am. Chem. Soc.* **1990**, *112*, 6263.

Addition of Nucleophiles to Thionolactones

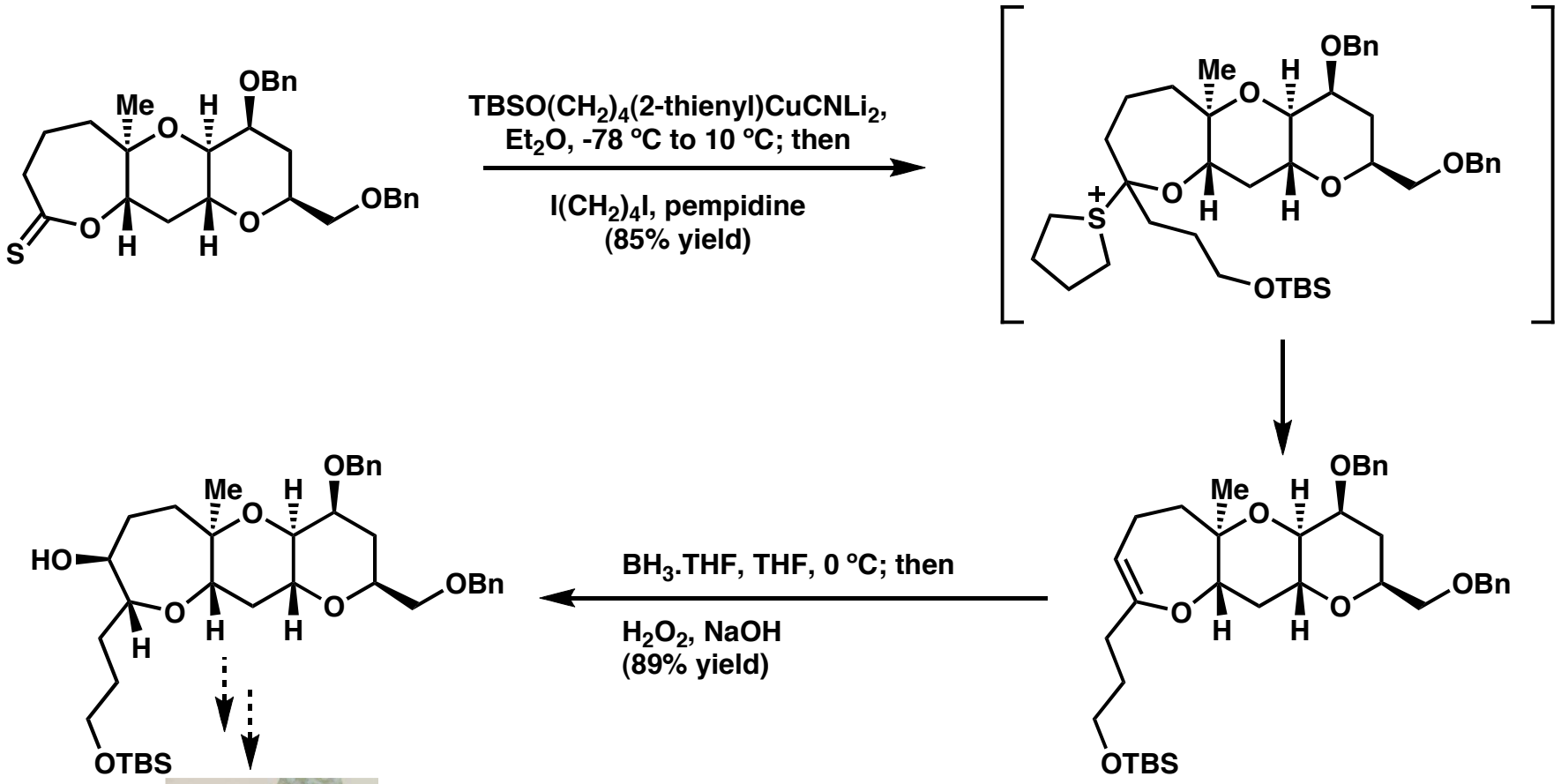
Synthesis of Polyethers



Nicolaou, K.C., and co-workers. *J. Am. Chem. Soc.* **1990**, *112*, 3696.

Addition of Nucleophiles to Thionolactones

Synthesis of Polyethers



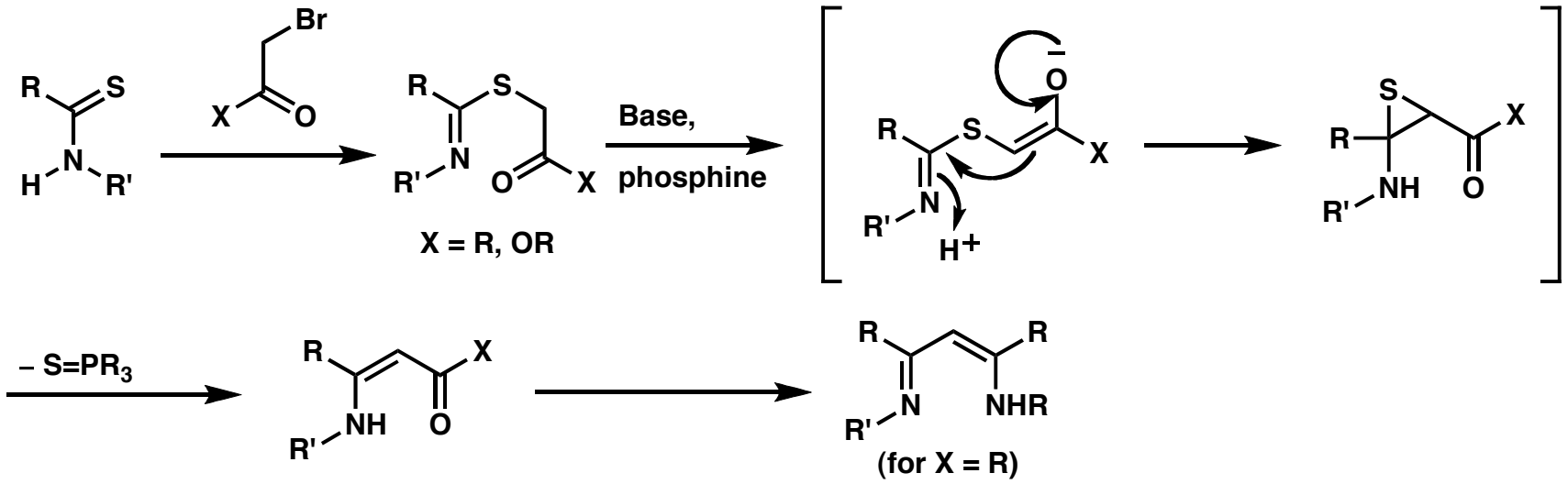
Brevetoxins

Nicolaou, K.C., and co-workers:
J. Am. Chem. Soc. **1993**, *115*, 3558.
J. Am. Chem. Soc. **1992**, *114*, 7935.
J. Am. Chem. Soc. **1990**, *112*, 4988.

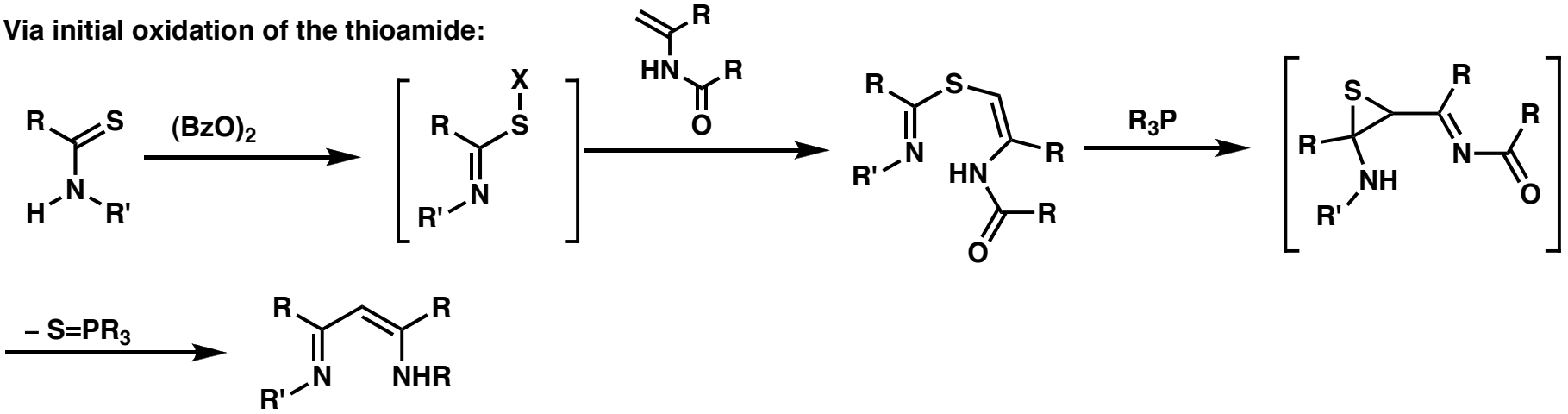
Eschenmoser Sulfide contraction

Synthesis of vinylogous amides, urethanes and amidines

Via initial alkylation on the thioamide:



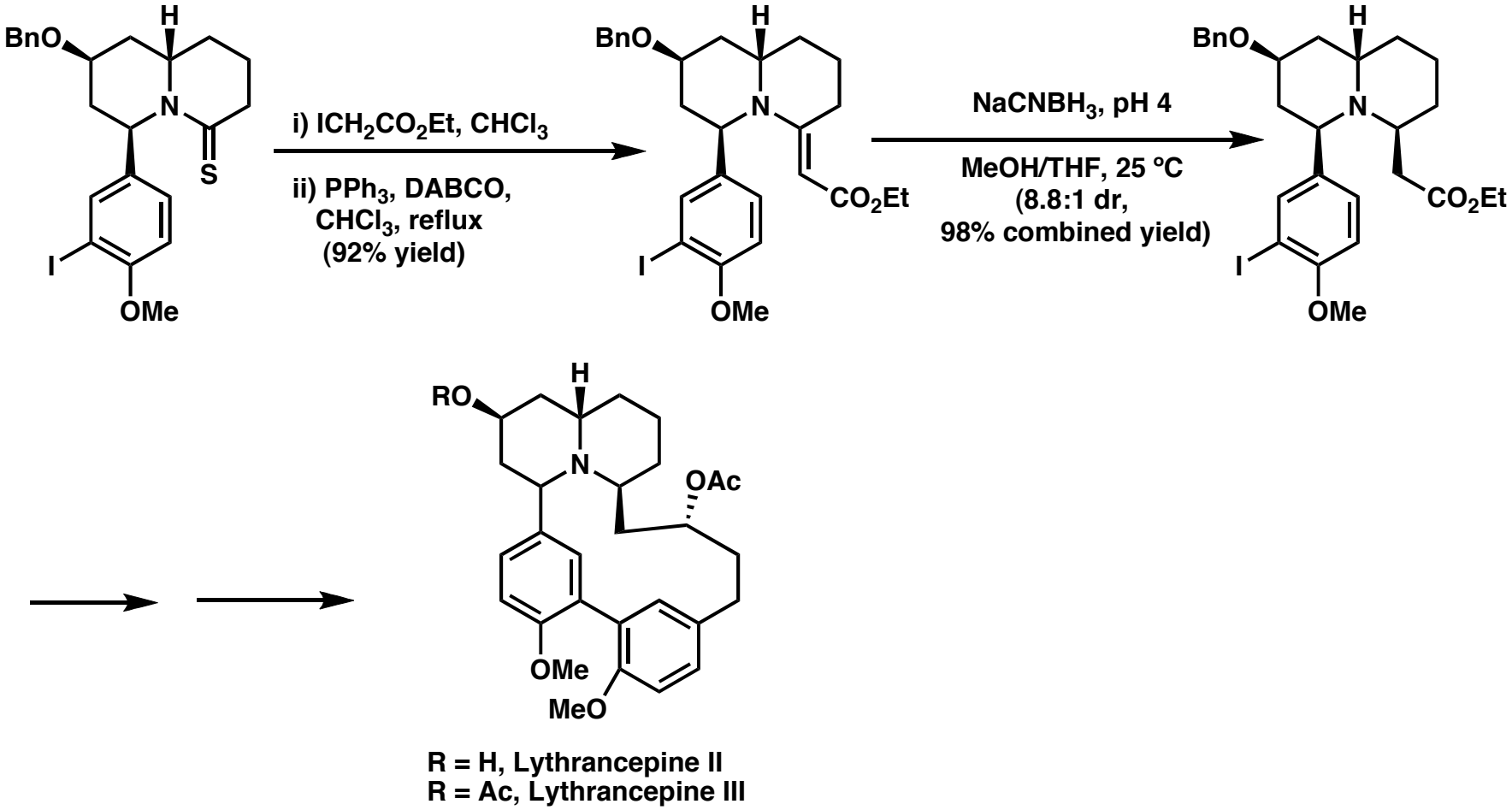
Via initial oxidation of the thioamide:



Eschemoser, A., and co-workers, *Angew. Chem. Intl. Ed. Engl.* **1973**, *12*, 910.
For a review, see Shiosaki, K. in *Comprehensive Organic Synthesis*, Trost, B.M., Fleming, I., Eds., Pergamon Press, Oxford, Vol.2. 865.

Eschenmoser Sulfide Contraction

Application in Synthesis of the Lythrancepines II & III

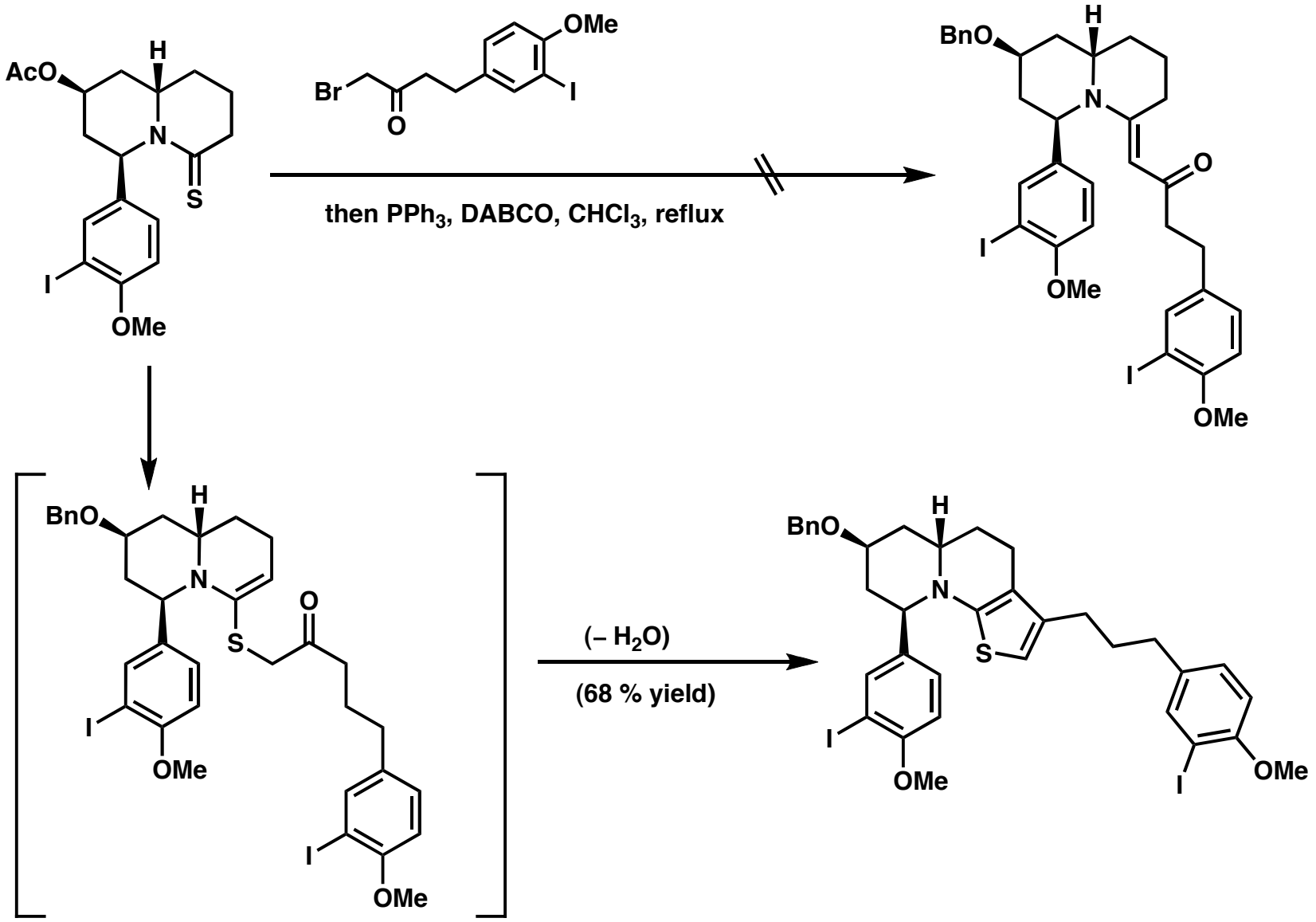


R = H, Lythrancepine II
R = Ac, Lythrancepine III

Hart, D.A., and co-workers, *J. Org. Chem.* **1987**, *52*, 4665.

Eschenmoser Sulfide Contraction

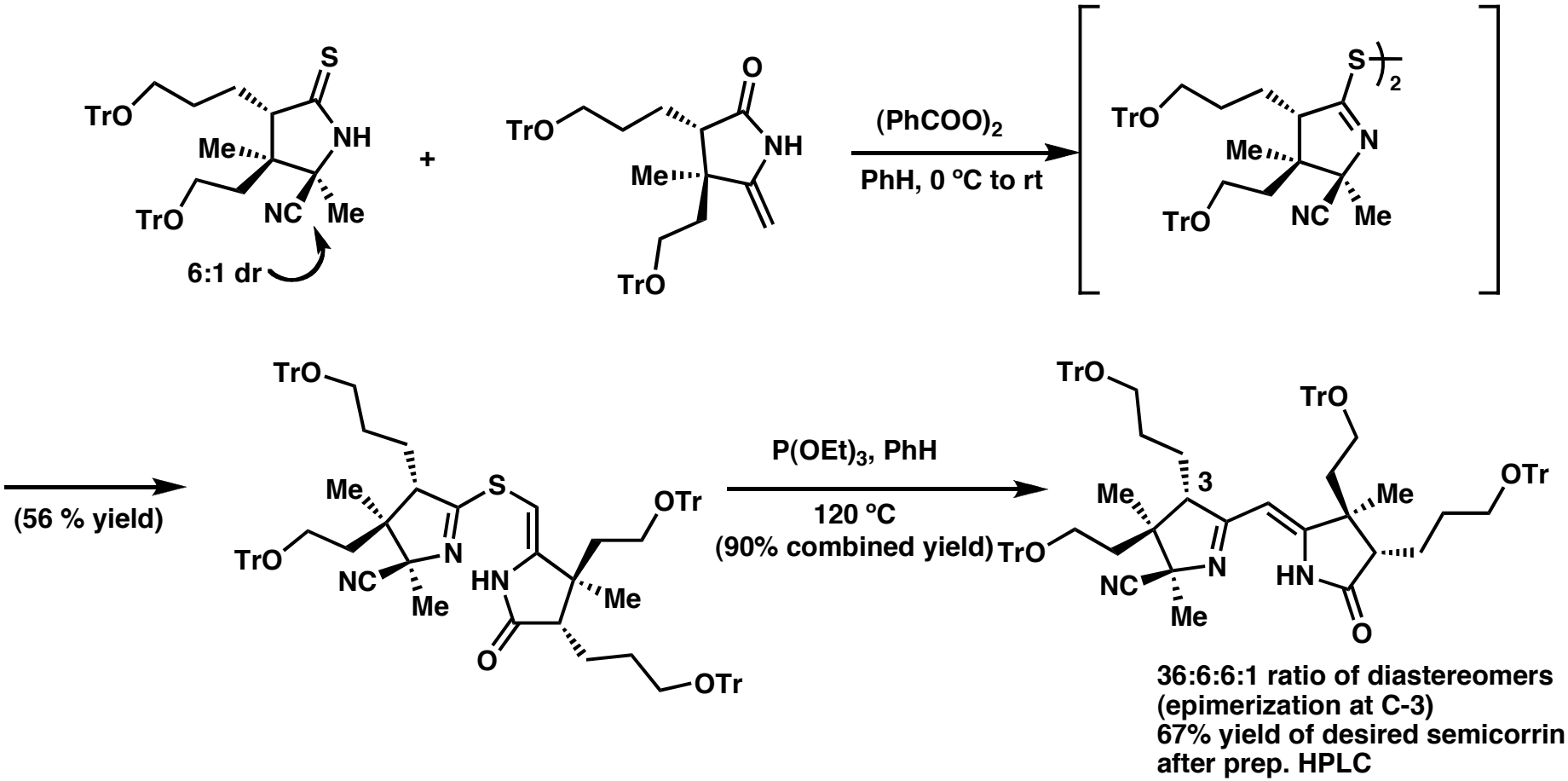
Synthesis of the Lythrancepines - a more convergent approach fails



Hart, D.A., and co-workers, *J. Org. Chem.* **1987**, *52*, 4665.

Eschenmoser Sulfide Contraction

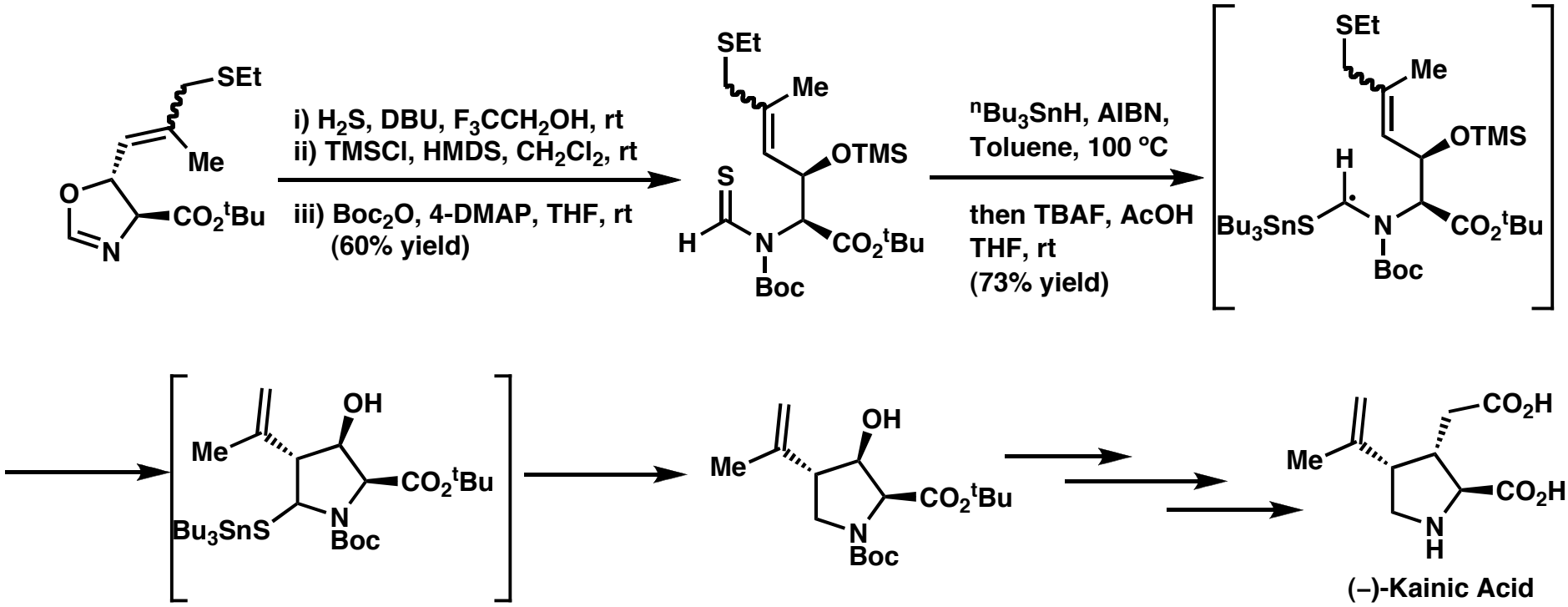
Application in Semicorrin synthesis



Mulzer, J., and co-workers, *J. Am. Chem. Soc.* **1997**, *119*, 5512.

Reactions via Radical Intermediates

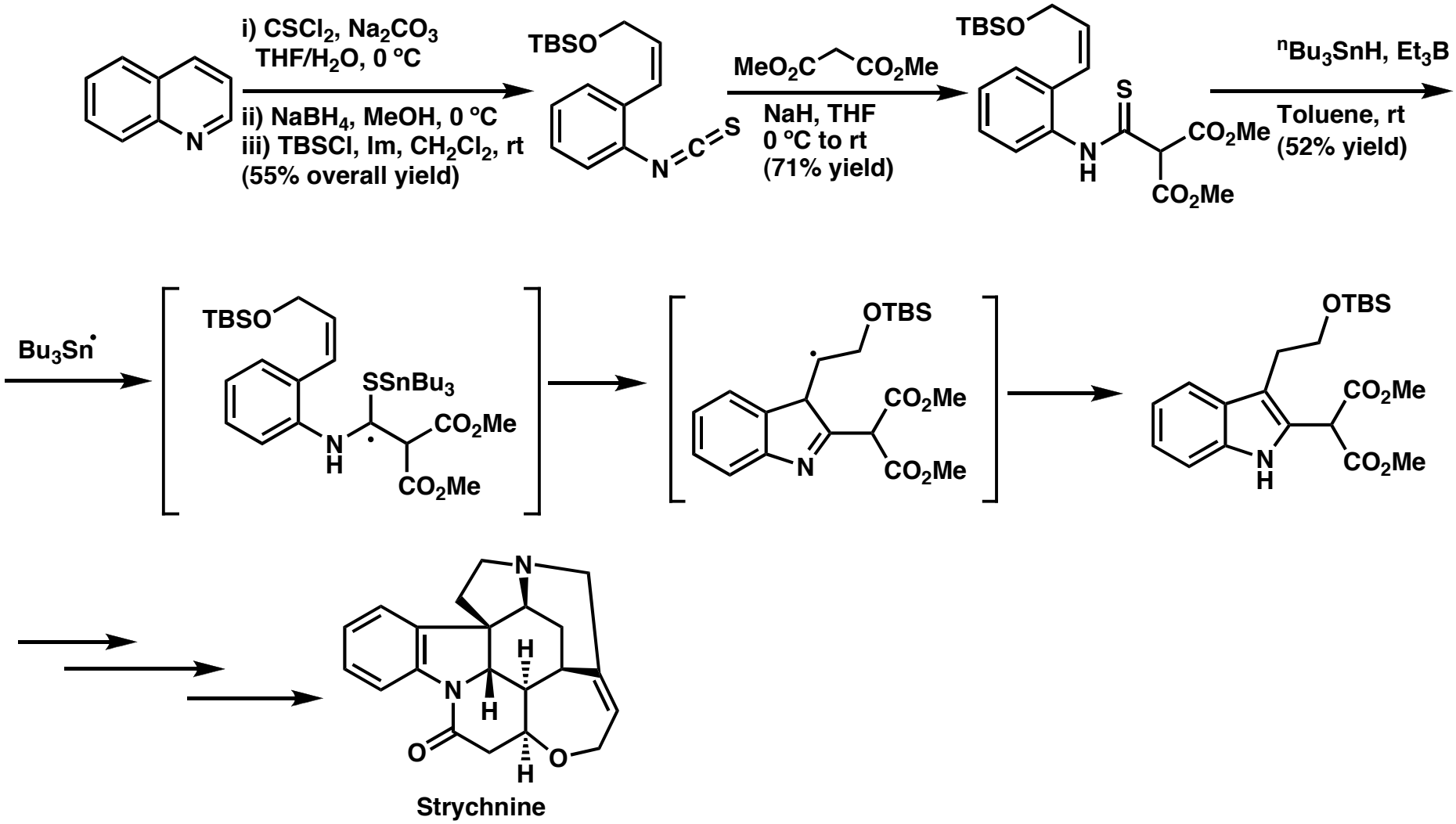
Synthesis of Kainic Acid



Bachi, M.D., and co-workers, *J. Org. Chem.* **1997**, *62*, 1896.

Reactions via Radical Intermediates

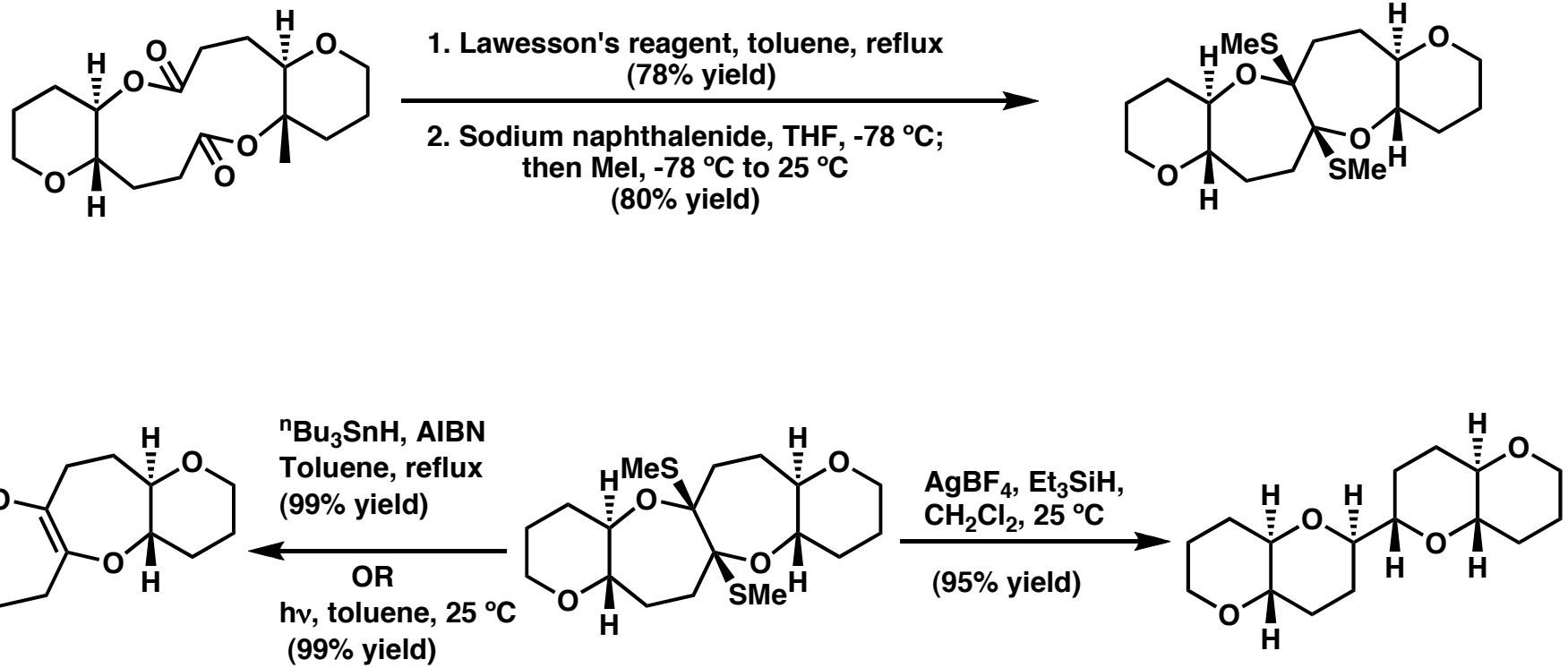
The Fukuyama Synthesis of Indoles - Application to the Synthesis of Strychnine



Fukuyama, T., and co-workers, *J. Am. Chem. Soc.* **2004**, *126*, 10246.

Transannular Bis-Thionolactone Cyclization

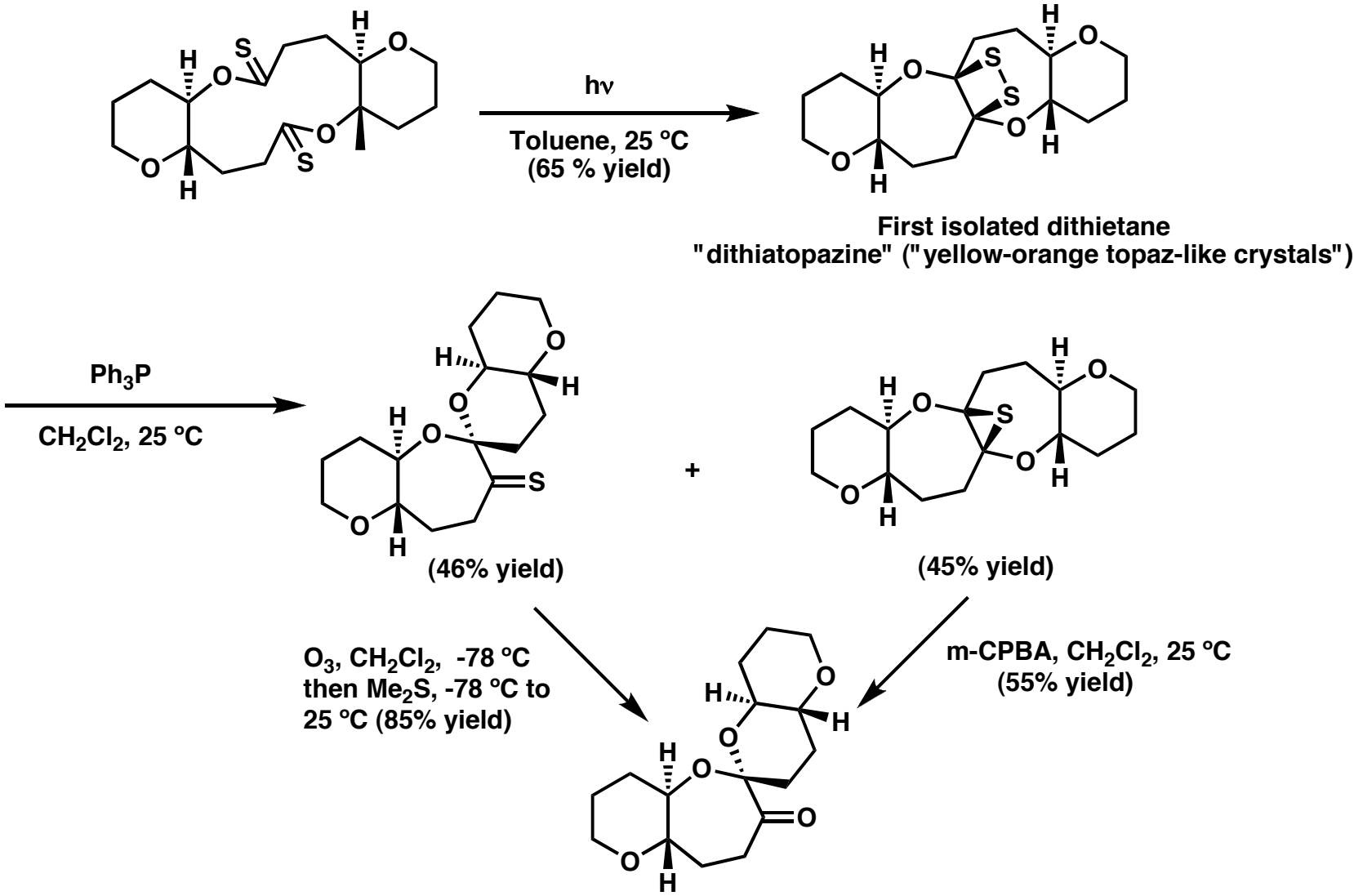
Synthesis of Polyethers



Nicolaou, K.C., and co-workers:
J. Am. Chem. Soc. **1986**, *108*, 6800.
J. Am. Chem. Soc. **1990**, *112*, 3040.

Transannular Bis-Thionolactone Cyclization

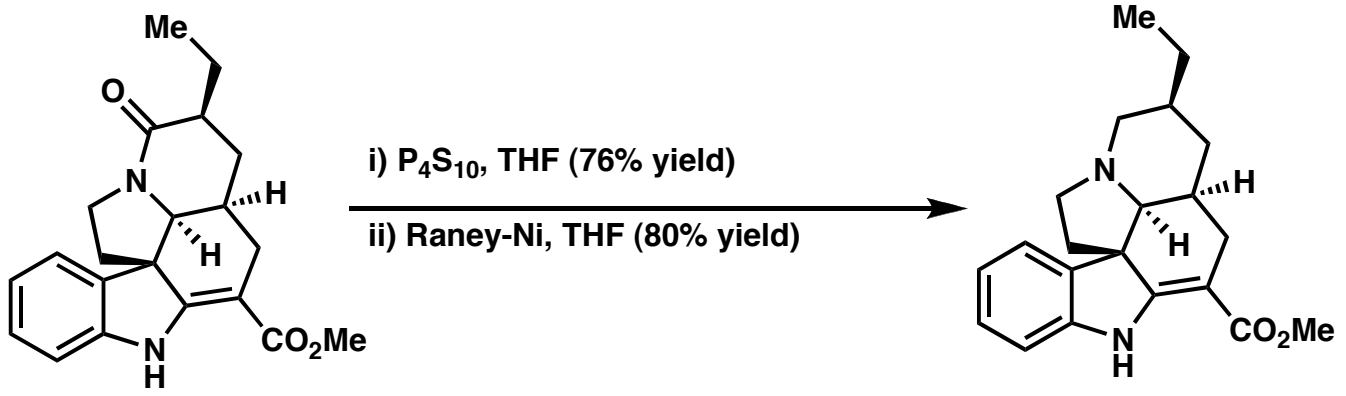
Synthesis of Polyethers



Nicolaou, K.C., and co-workers. *J. Am. Chem. Soc.* **1990**, *112*, 3029.

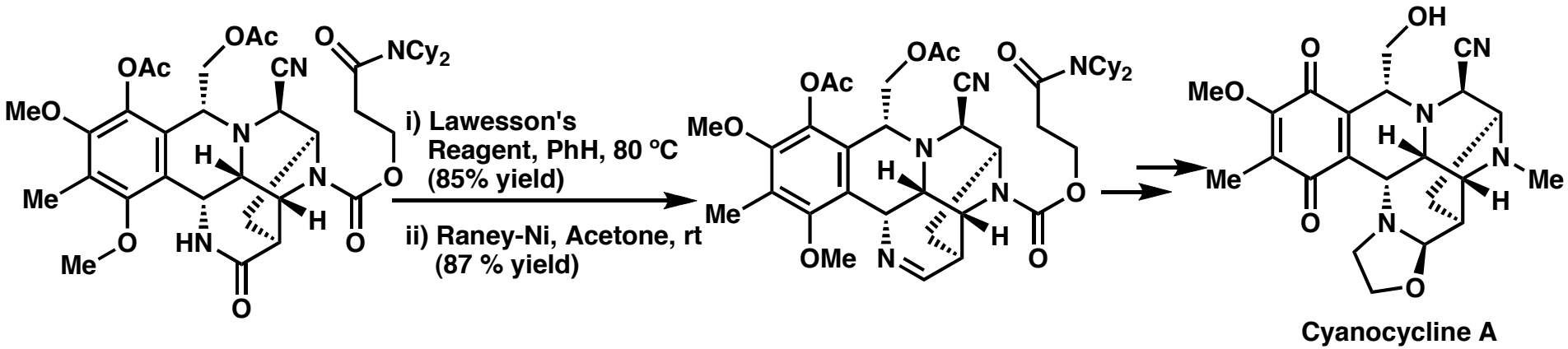
Desulfurization of Thioamides

Applications in alkaloid synthesis



pseudovincadifformine

Szantay, C., and co-workers, *J. Org. Chem.* **1993**, *58*, 6076.

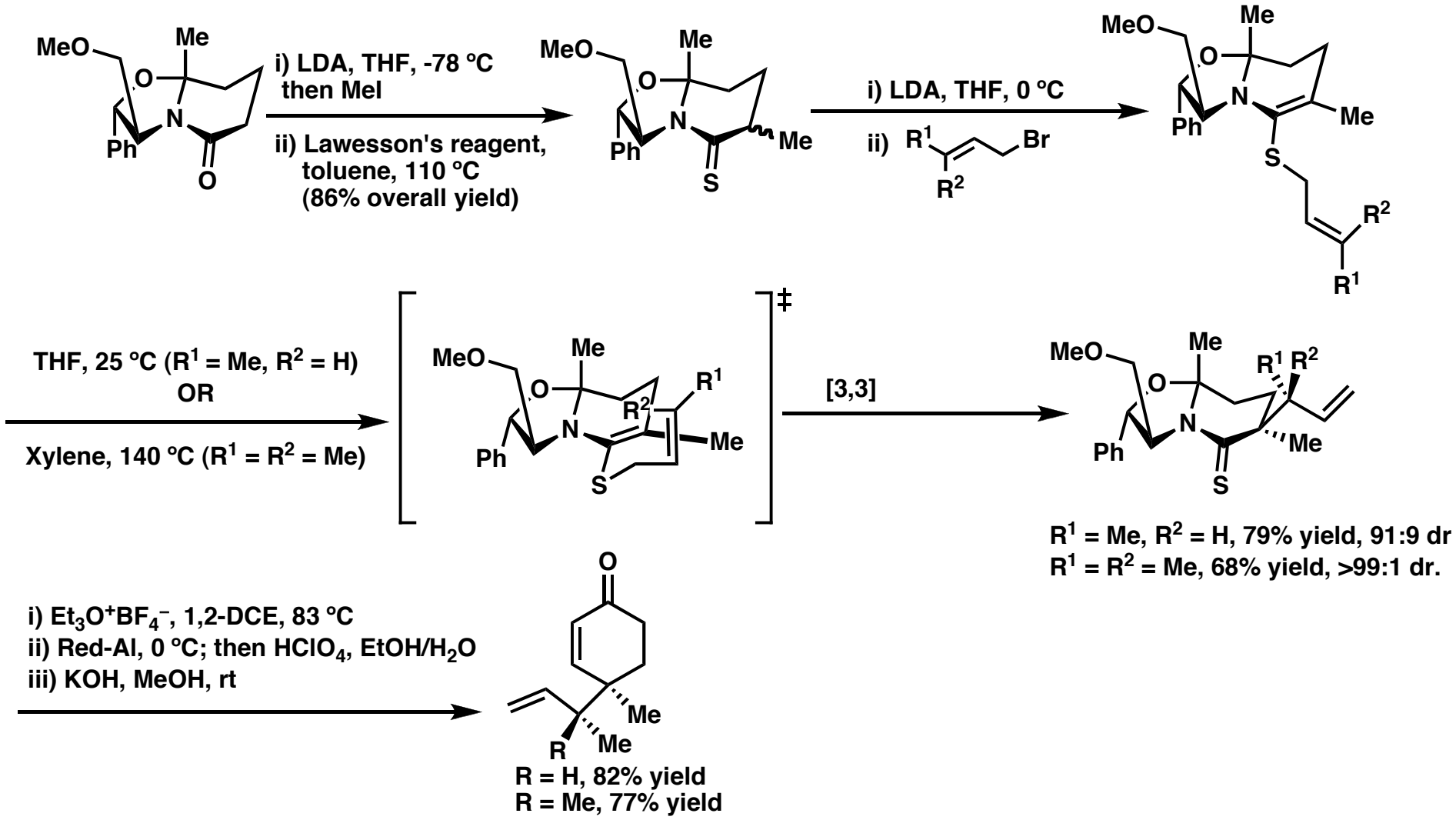


Cyanocycline A

Fukuyama, T., and co-workers, *J. Am. Chem. Soc*. **1987**, *109*, 1587.

Asymmetric Thio-Claisen Rearrangement

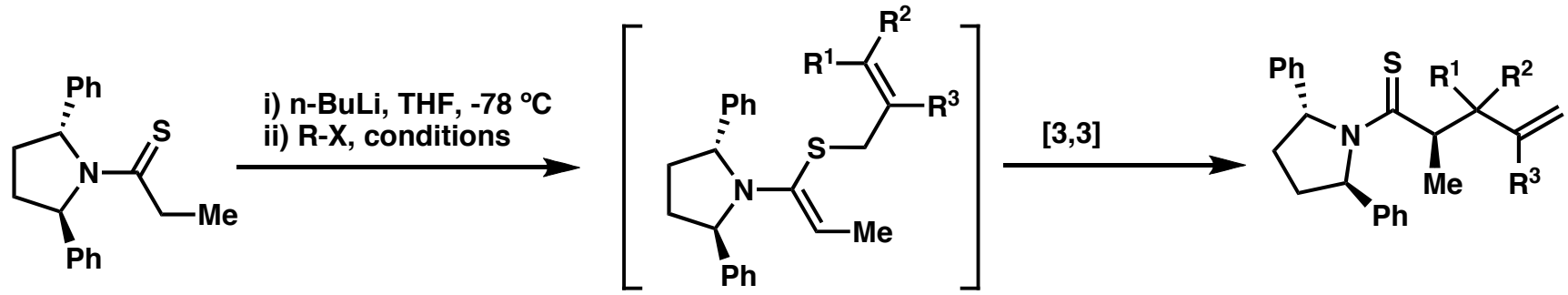
Meyers' approach

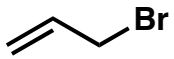
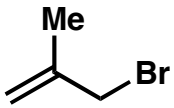
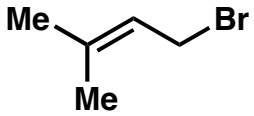
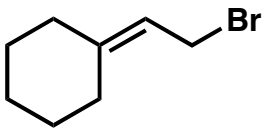


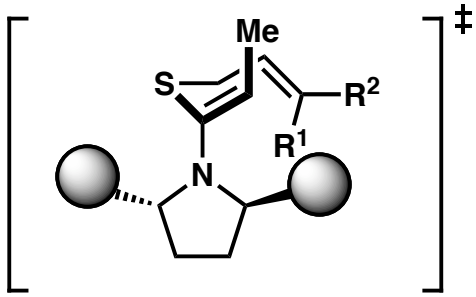
Meyers, A.I., and co-workers, *J. Am. Chem. Soc.* **1994**, *116*, 2633

Asymmetric Thio-Claisen Rearrangement

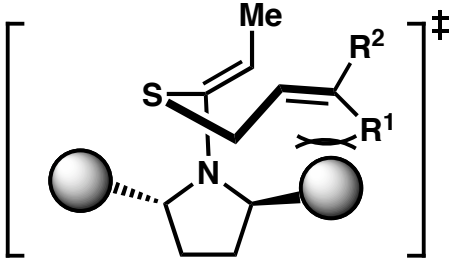
Use of C_2–Symmetric Diamines as Chiral Auxilliaries



R-X	Conditions	Yield (%)	dr
	-78 °C to rt	98	9.8:1
	-78 °C to rt	100	7.7:1
	reflux, 6h	89	>200:1
	reflux, 6h	91	>100:1



Favored

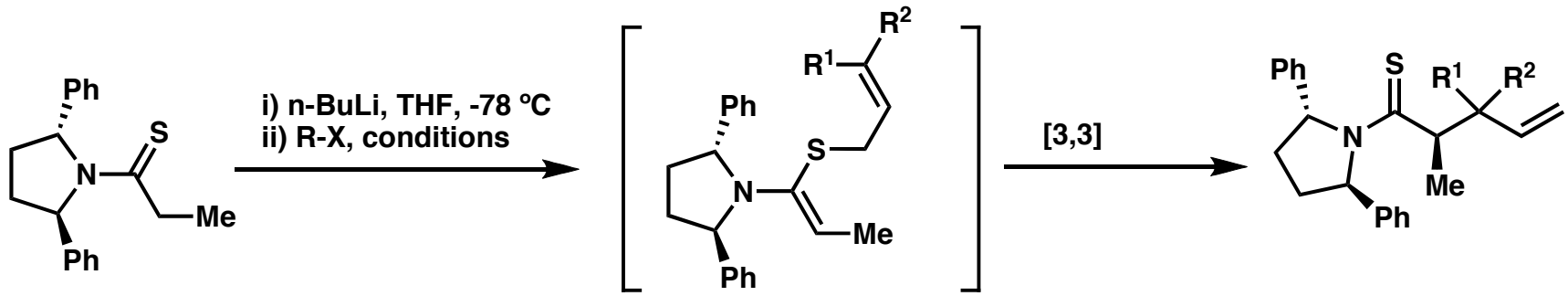


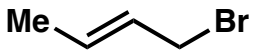
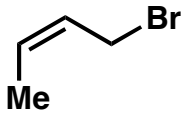
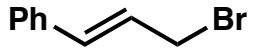
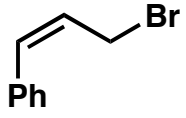
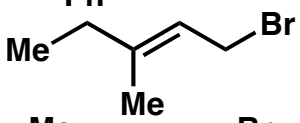
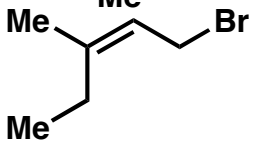
Disfavored

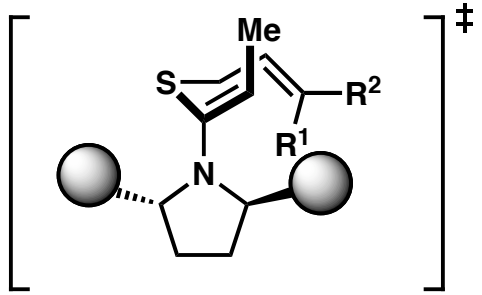
Rawal, V., and co-workers, *J. Am. Chem. Soc.* **2000**, *122, 190.*

Asymmetric Thio-Claisen Rearrangement

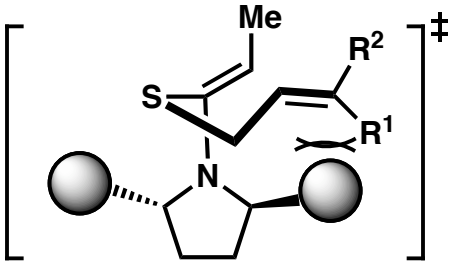
Use of C_2–Symmetric Diamines as Chiral Auxilliaries



R-X	Conditions	Yield (%)	syn:anti	dr
	-78 °C to rt	93	1:41	88:12
	reflux, 3h	92	>30:1	>99:1
	-78 °C to rt	100	<1:100	83:17
	reflux, 8h	86	>30:1	>99:1
	reflux, 9h	81	<1:50	>99:1
	reflux, 9h	88	>50:1	>99:1



Favored



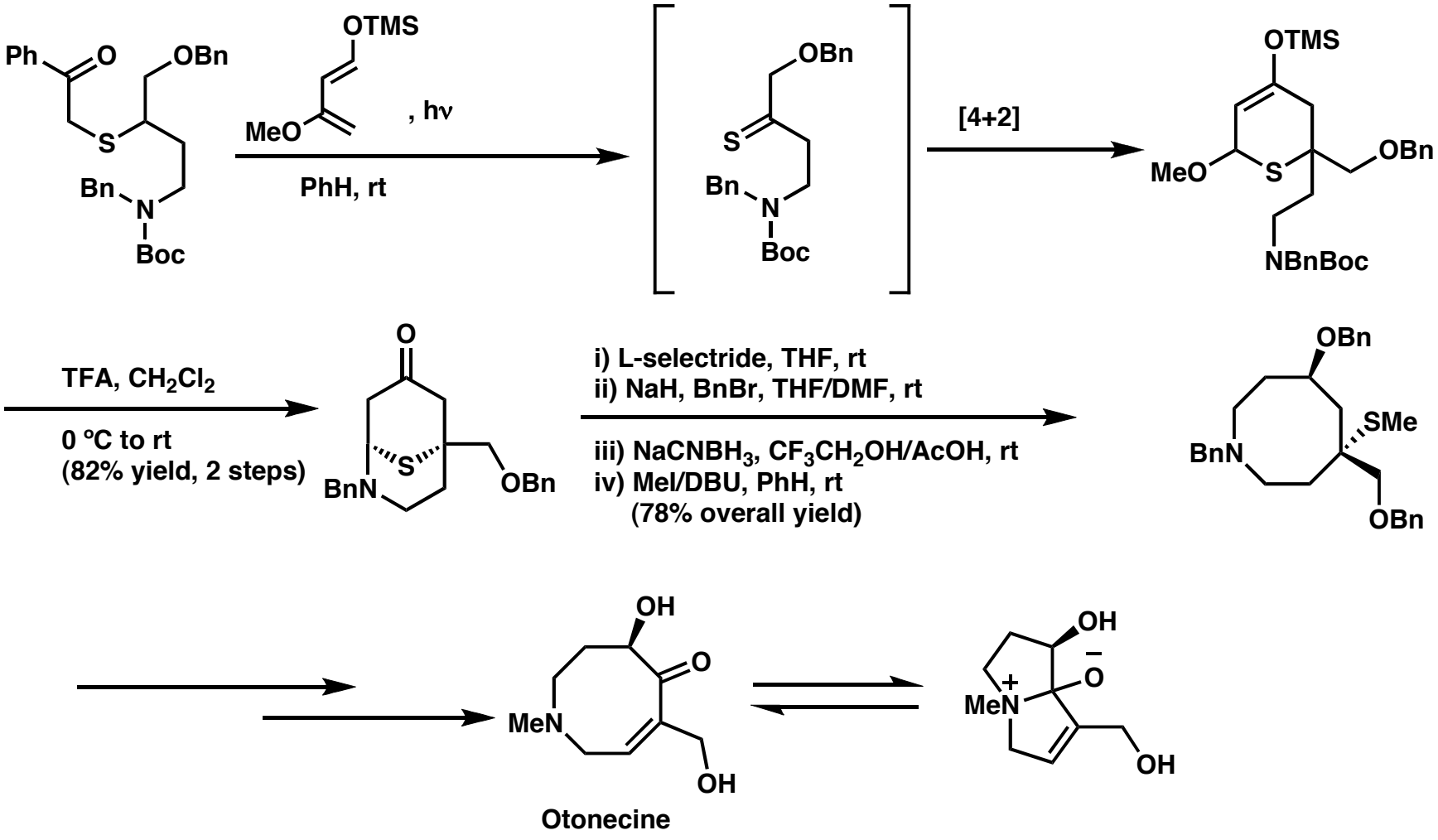
Disfavored

Z-oriented substituent (i.e. R^1) on allyl fragment results in higher dr.

Rawal, V., and co-workers, *J. Am. Chem. Soc.* **2000**, *122, 190.*

Diels-Alder Reactions

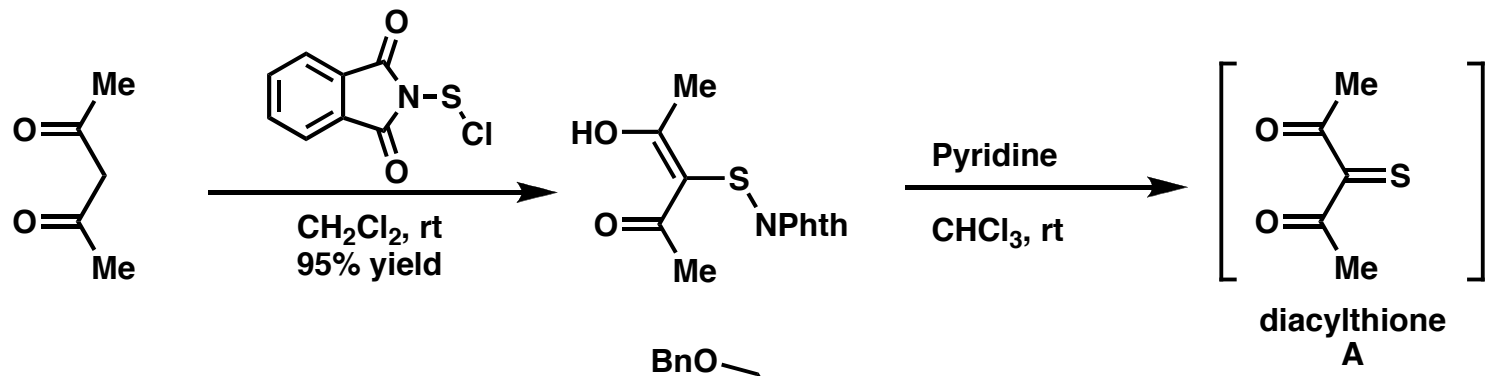
Thiocarbonyl compounds as dienophiles: Vedejs' synthesis of Otonecine

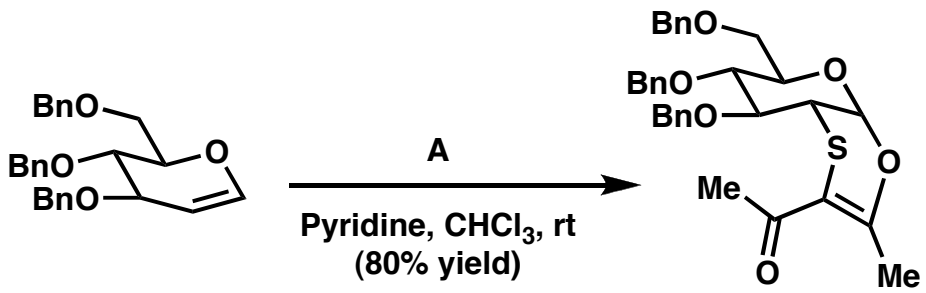


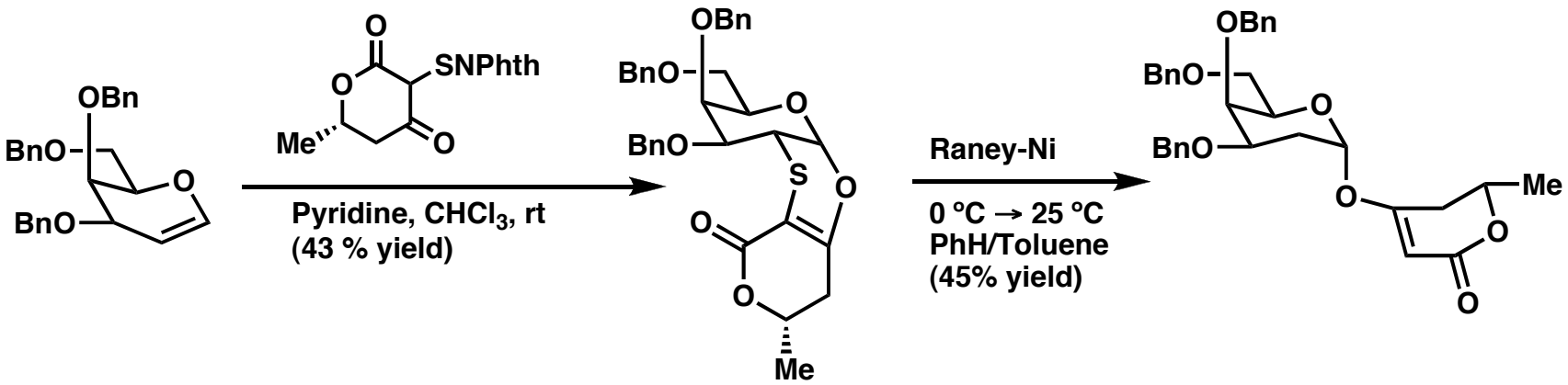
Vedejs, E., and co-workers, *J. Am. Chem. Soc.* **1998**, *120*, 3613.

Diels-Alder Reactions

Thiocarbonyl compounds as heterodienes - an alternate glycosylation strategy







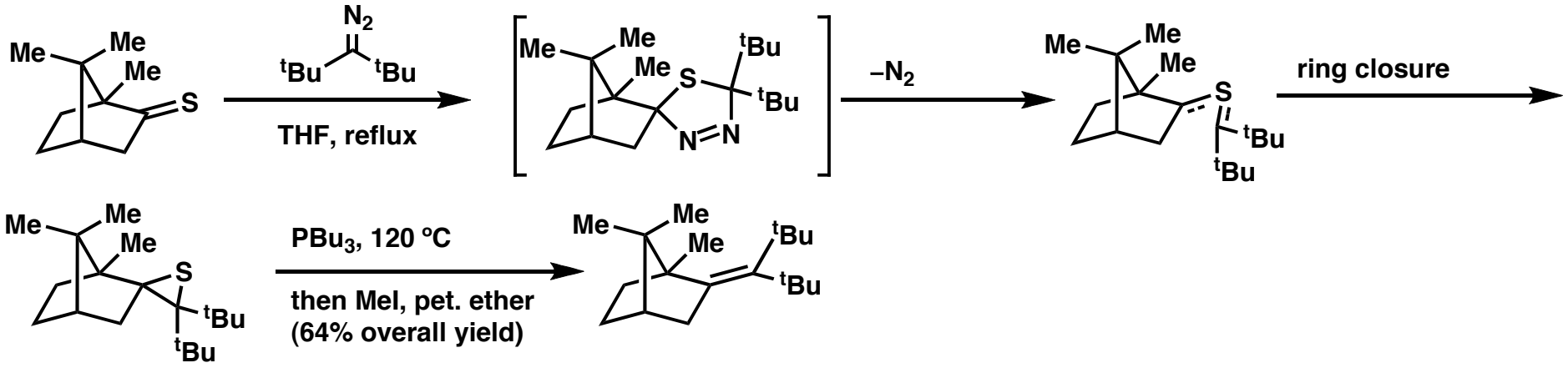
Desulfurization complicated by competing olefin reduction

Capozzi, G., and co-workers, *Angew. Chem. Intl. Ed. Engl.* **1996**, *35*, 777.

[3+2] Cycloadditions

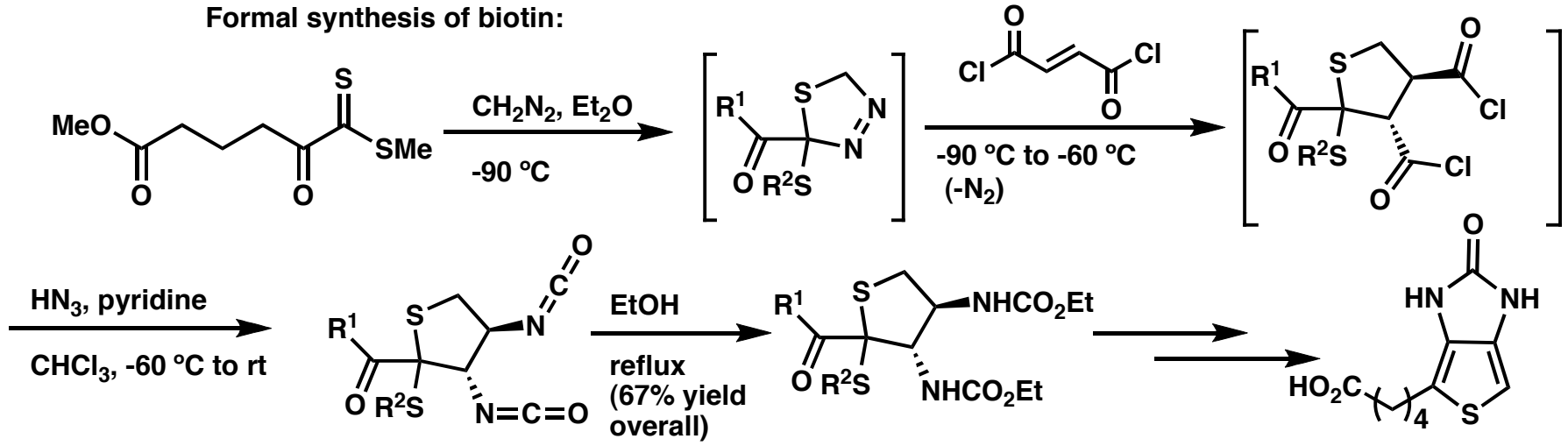
Thiocarbonyl compounds function as excellent dipolarophiles in dipolar cycloadditions. However, applications in complex molecule syntheses have been limited thus far.

Synthesis of sterically-hindered olefins:



Barton, D.H.R., and co-workers, *J. Chem. Soc. Perkin Trans.1* **1974**, 1794.

Formal synthesis of biotin:



Moran, J.R., and co-workers, *Tetrahedron* **1990**, *46*, 1057.

Summary and Future Directions

1. **Thiocarbonyl compounds display diverse reactivity towards nucleophiles, electrophiles, free radicals, sigmatropic rearrangements and cycloadditions.**

2. **They are often readily accessible from the corresponding carbonyl compounds (more familiar to organic chemists!), therefore reactivity can be readily evaluated in a bid to solve problems posed by complex molecule synthesis.**

3. **Future directions: Transition metal-catalyzed reactions, multi-component couplings.**

When in doubt, bleach!