Umpolung: Carbonyl Synthons

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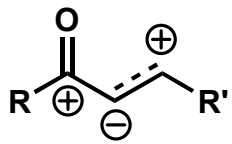
Organic Supergroup Meeting

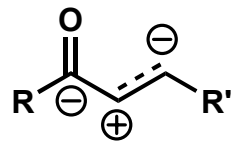
Princeton University

February 4, 2004

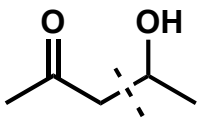
Umpolung - The Carbonyl Group

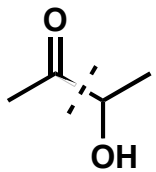


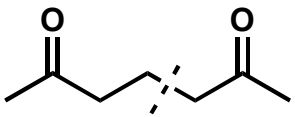
normal reactivity



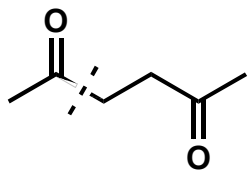
inverted reactivity
umpolung







odd number of carbons between functional groups



even number of carbons between functional groups

Seebach ACIEE 1979 239

Umpolung - Carbonyl Synthons

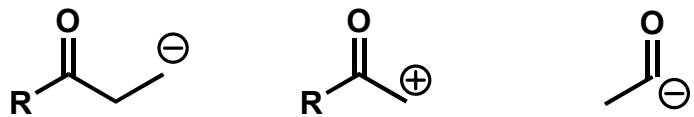
Polarity inversion is an old concept, but vigorous research in the area is of relatively recent origin.

The concept of synthons, or functional group equivalents, has spurred research.

Synthons: structural units within a molecule which are related to possible synthetic operations

Corey Pure Appl. Chem 1967 19

1. **homoenolates**
2. **α-electrophiles**
3. **acyl anions**



Umpolung - Carbonyl Synthons

Inversion reactions described as "symmetrization of reactivity"

Corey Pure Appl. Chem 1967 19

"charge affinity inversion"

Evans Acc. Chem. Res. 1974 147

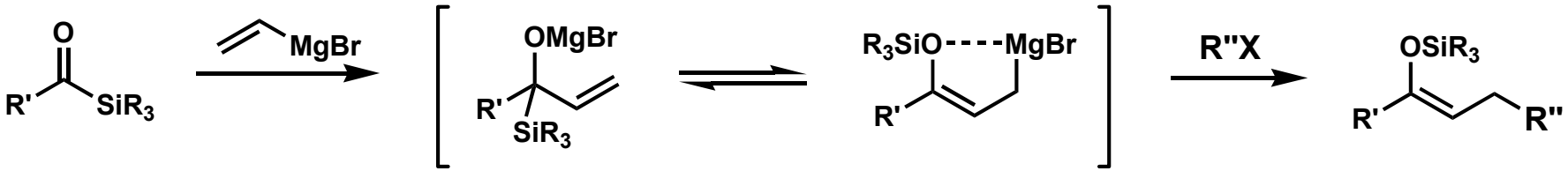
suggested the German word *umpolung* as a concise expression for the concept

Seebach Chem. Ind. 1974 687

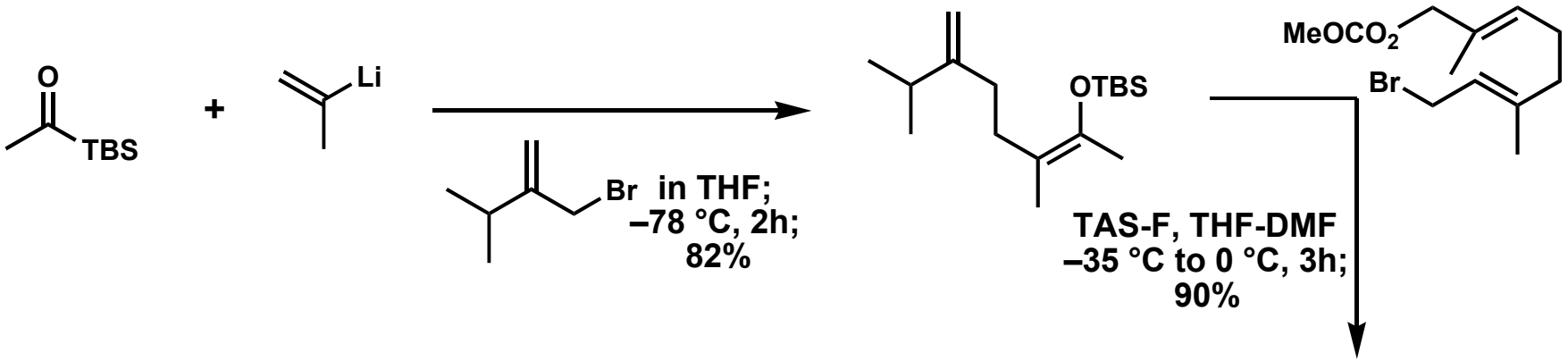
***umpolung*: pole reversal; reversion of polarity; turn-over**

(http://dictionaries.travlang.com/GermanEnglish/)

Homoenolates

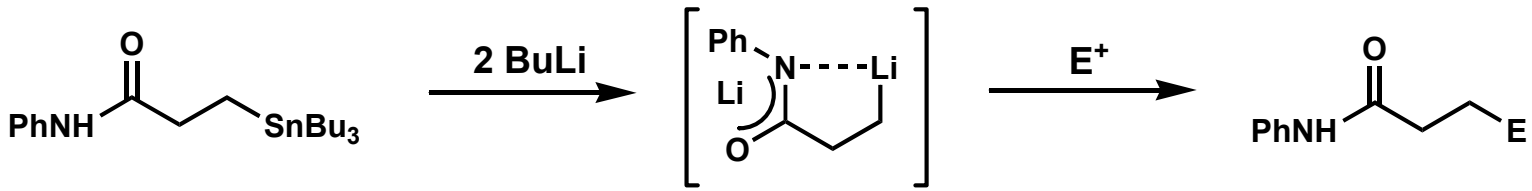


Kuwajima et al. Chem. Commun. 1979 708

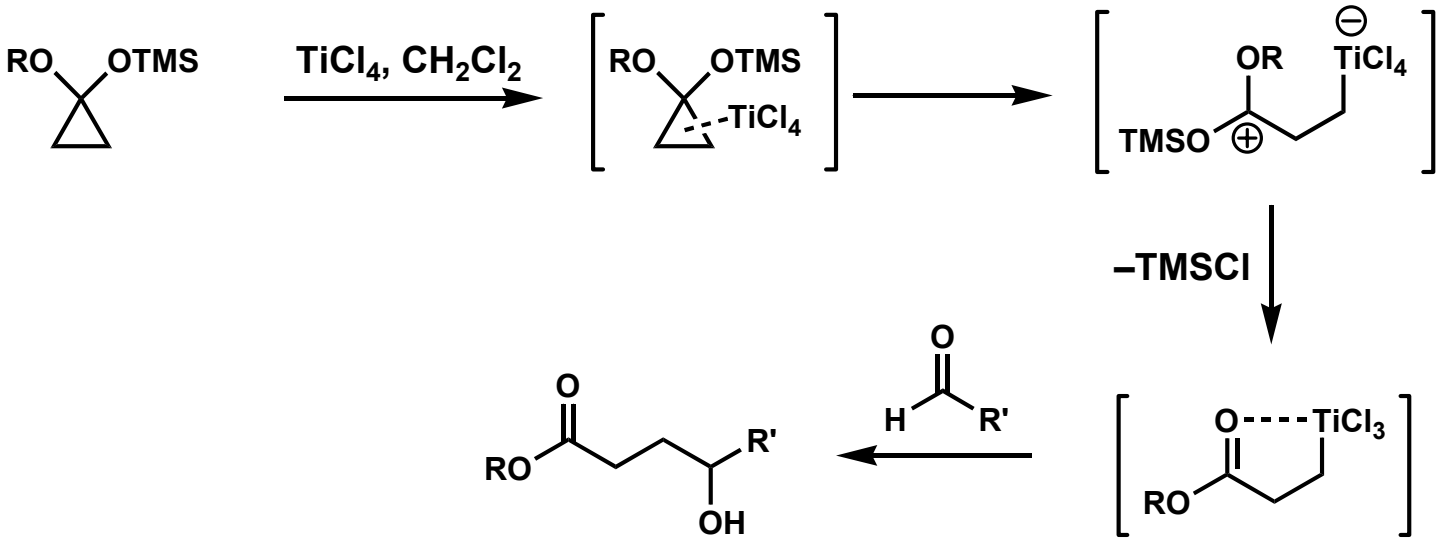


Corey et al. Org. Lett. 2002 2441

Homoenolates

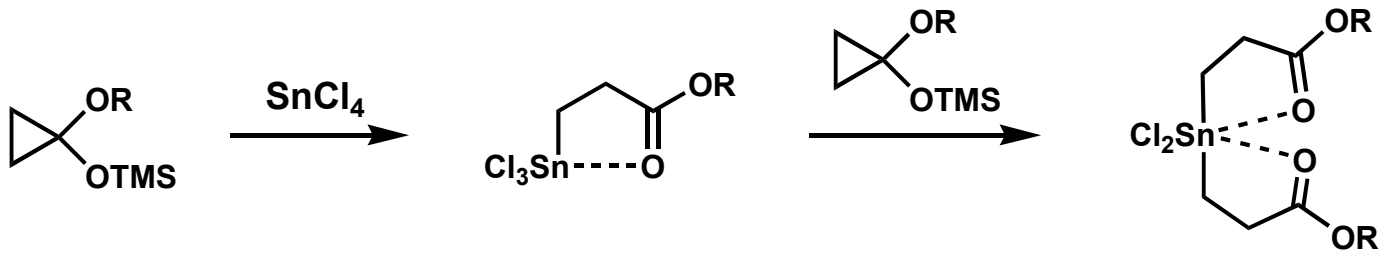


Goswami et al. JACS 1980 5973



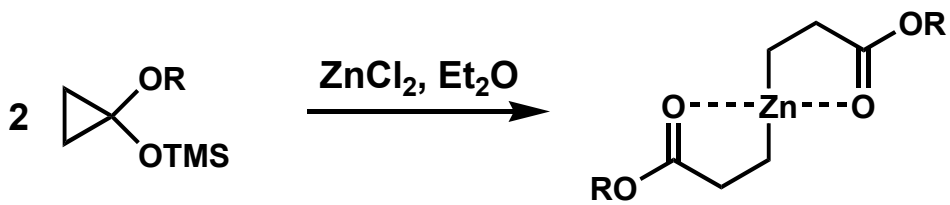
Kuwajima et al. JACS 1986 3745

Homoenolates



Kuwajima et al. Organometallics 1985 641

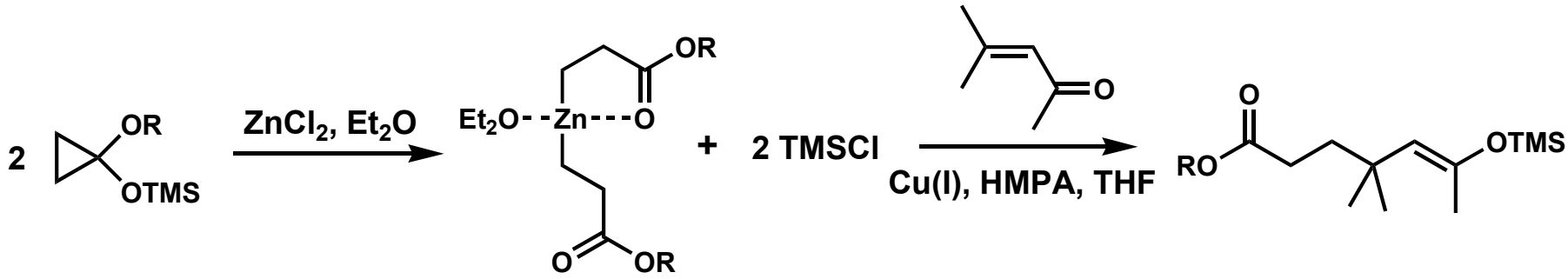
mercury, copper, silver, and gold homoenolates have also been synthesized



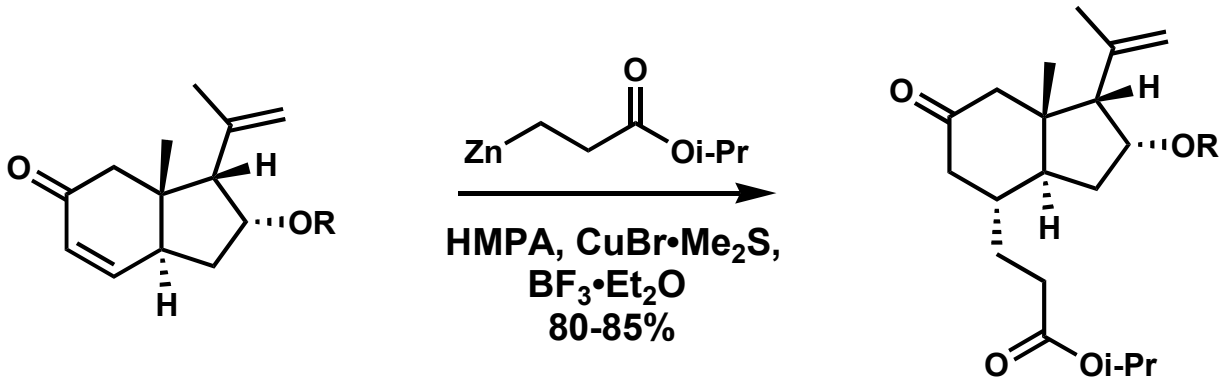
Nakamura, Kuwajima et al. JACS 1984 3368
Nakamura, Kuwajima et al. JACS 1987 8056

when the zinc reagent contains two homoenolates bound to each zinc atom, only one of the homoenolates can be transferred; the second is unreactive

Homoenolates



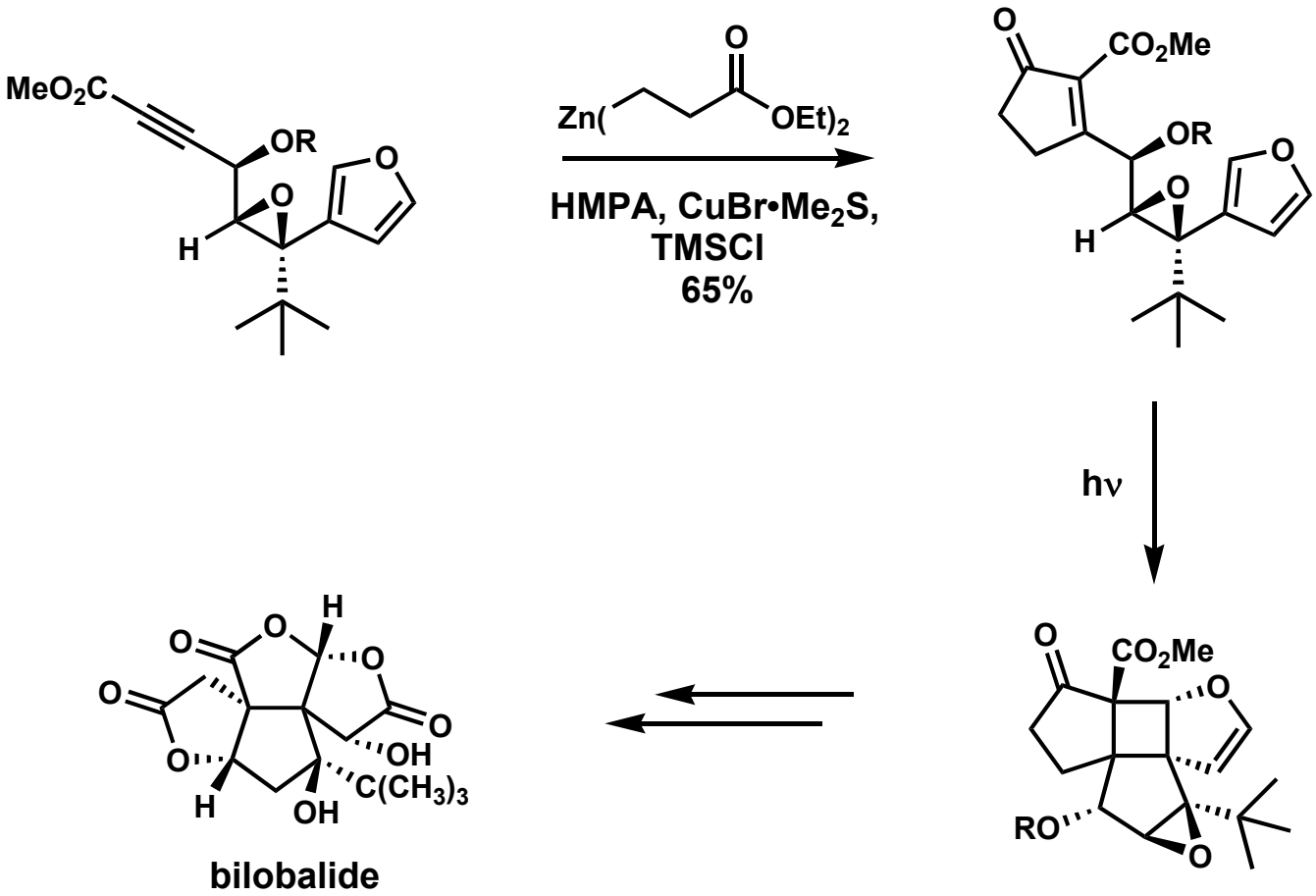
Kuwajima Pure and Applied Chem. 1988 115



Nakamura, Kuwajima et al. JOC 1986 4323
Nakamura, Kuwajima et al. JACS 1989 6257

> 97 : 3 diastereoselectivity
cortisone and adrenosterone
intermediate

Homoenolates

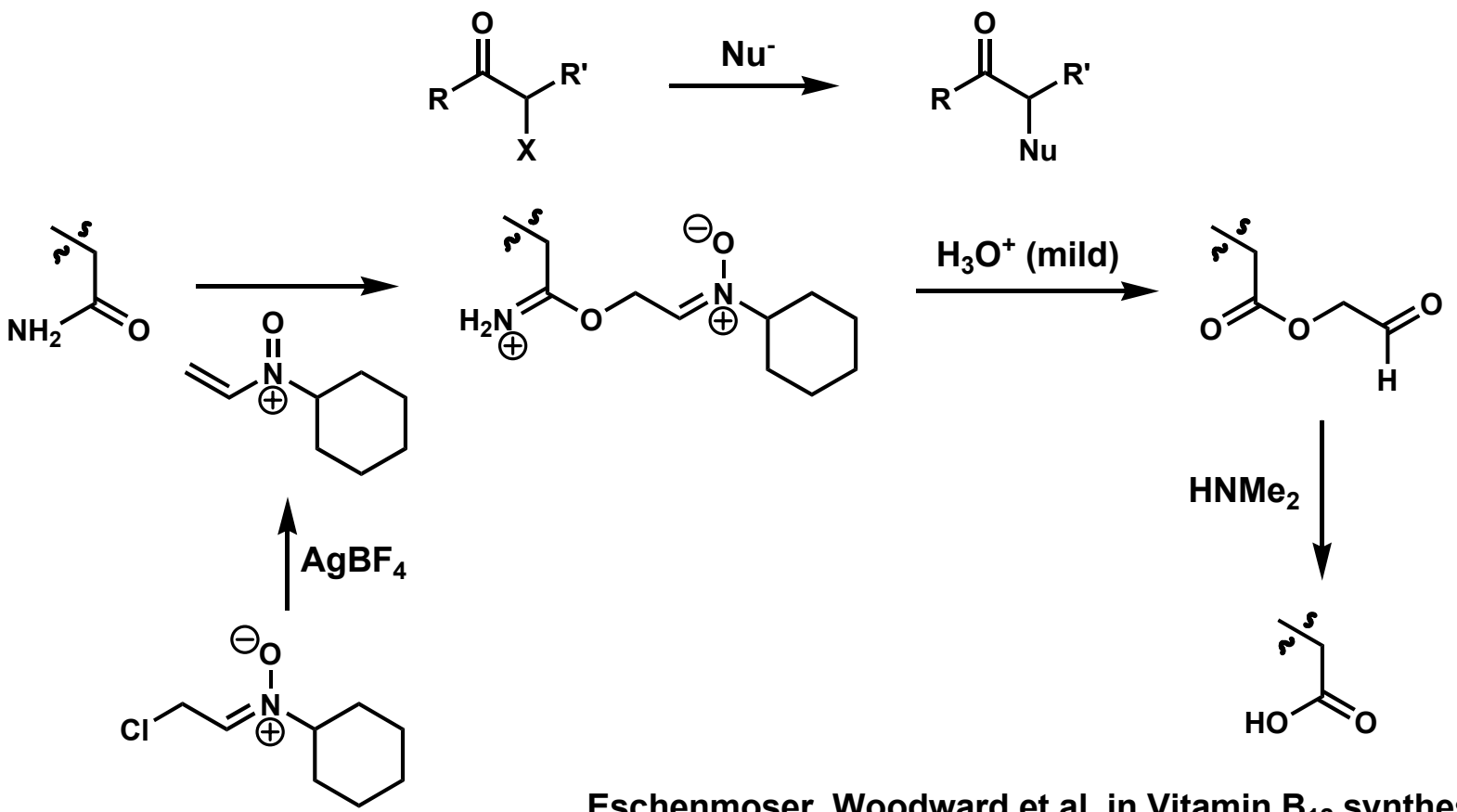


bilobalide

Crimmins et al. JACS 1993 3146

Reviews on Homoenolates:
Crimmins, Nantermet Org. Prep. and Proc. Int. 1993 41-81
Werstiuk Tetrahedron 1983 205

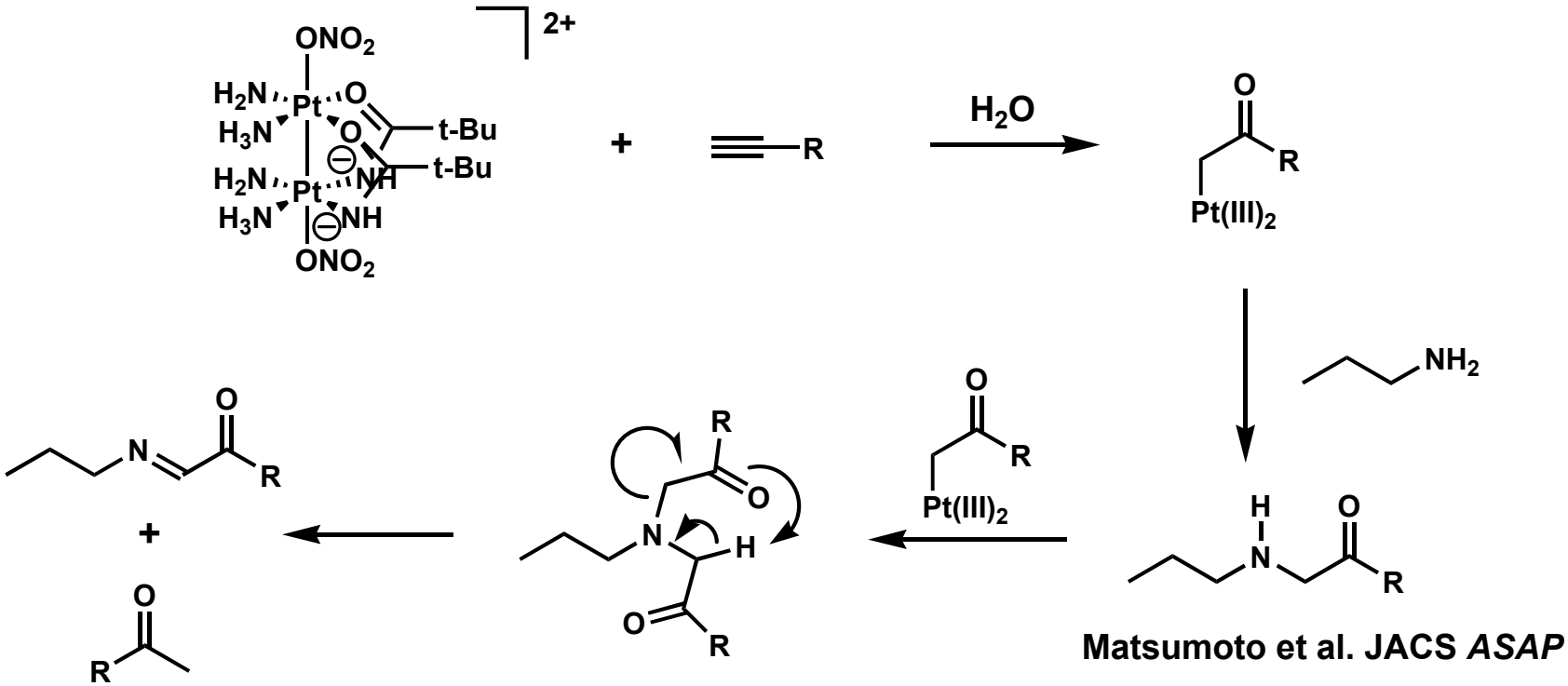
α-Electrophiles



Eschenmoser, Woodward et al. in Vitamin B_{12} synthesis
See *Classics In Total Synthesis*, p. 134

α-Electrophiles

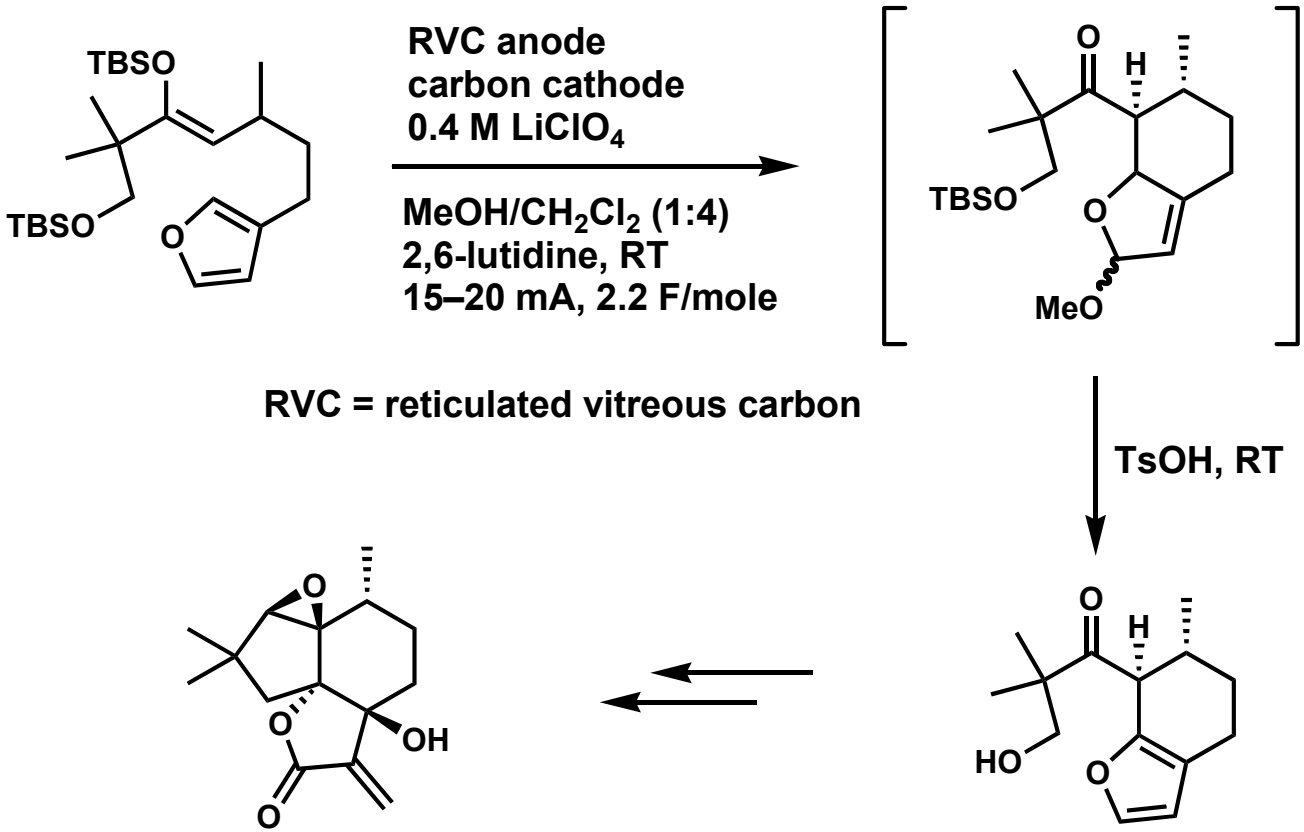
- π-coordination of triple bond to the Pt(III) atom
- nucleophilic attack of water
- ketonyl–Pt(III) complexes react with amines to give α-amino substituted ketone
- with 1° amines, further reaction occurs



Matsumoto et al. JACS *ASAP*

α-Electrophiles

Anodic Oxidative Cyclization:



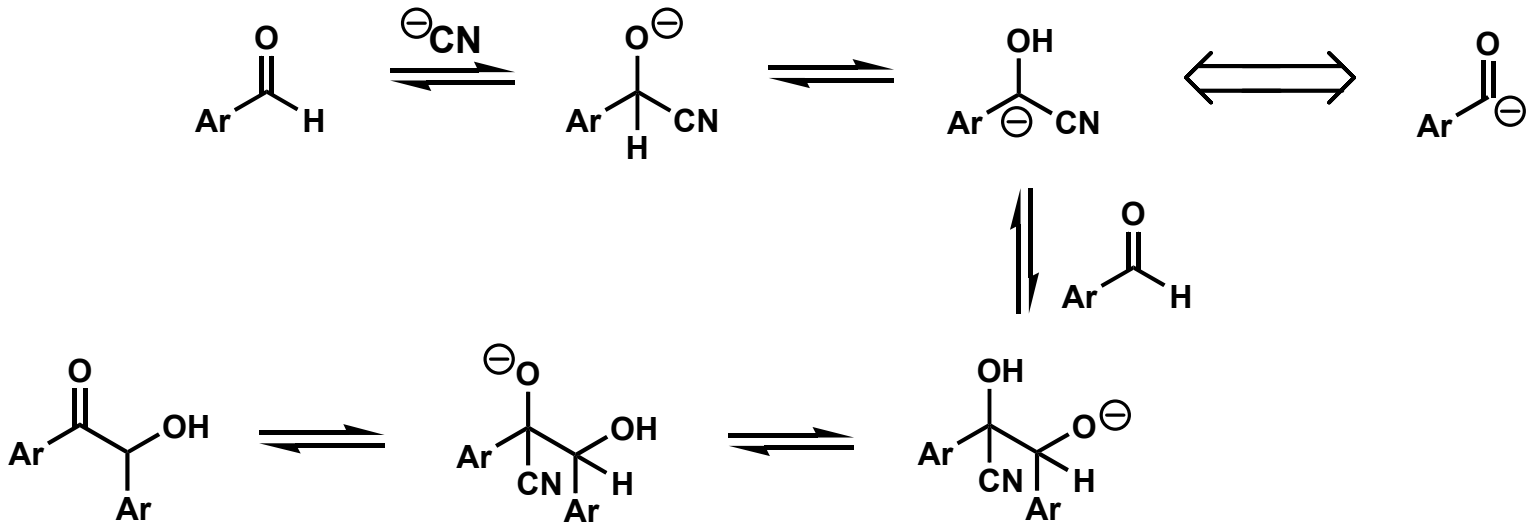
alliacol A

Moeller et al. JACS 2003 36

Acyl Anions

1a. Benzoin condensation: Cyanide ion catalyzed addition

- **cyanide ion catalyzed dimerization of aromatic and heterocyclic aldehydes to form α-ketols**
- **nitrile-stabilized anions can also add to α,β-unsaturated ketones, esters, and nitriles**
- **the reaction requires aprotic solvents (most preferably DMF)**
- **cyanide ion catalysis fails with aliphatic aldehydes because they undergo aldol condensations under the strongly basic conditions**



a benzoin

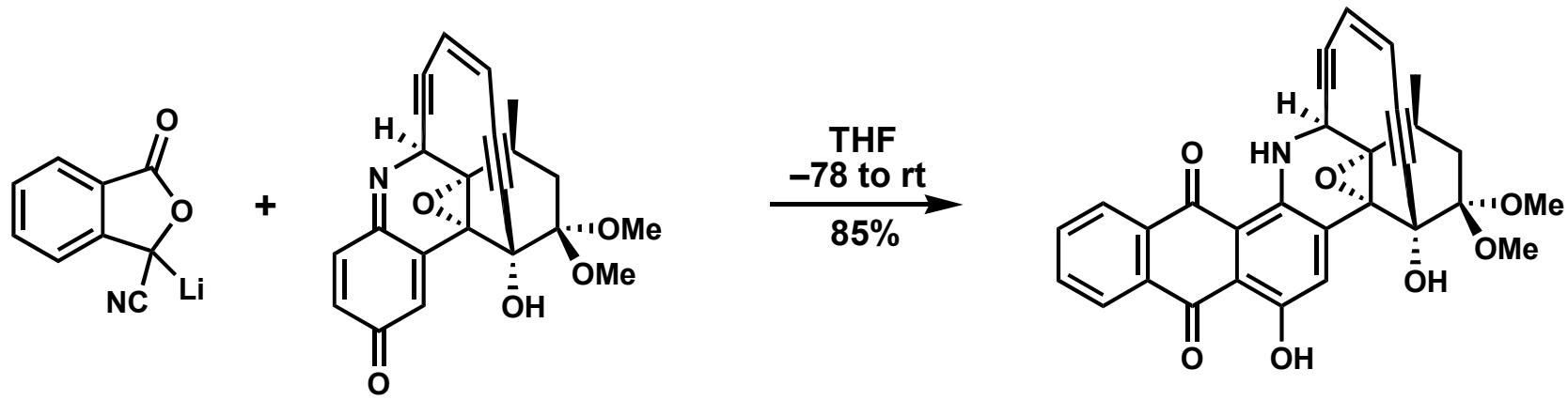
Lapworth J. Chem. Soc. 1903 995

Acyl Anions

1b. Protected cyanohydrins

- **can serve as reagents for annulation**

Stork et al. JACS 1974 5272
Kraus et al. Tet. Lett. 2000 21

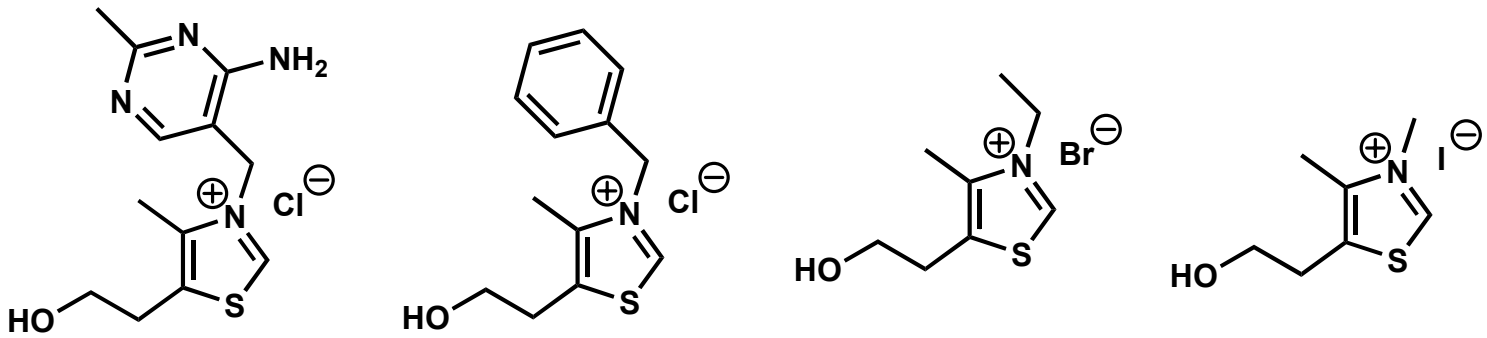


A. G. Myers et al. JACS 1997 6072

a dynemicin A intermediate

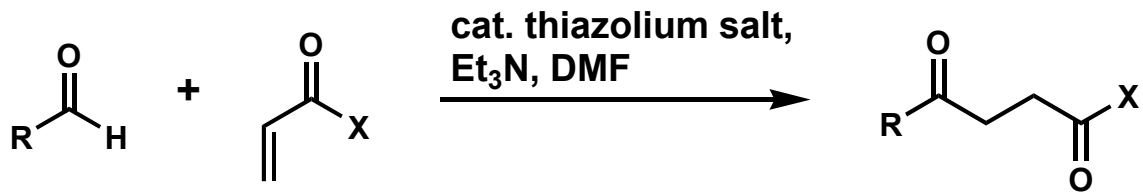
Acyl Anions

2. Thiazolium salt catalyzed addition



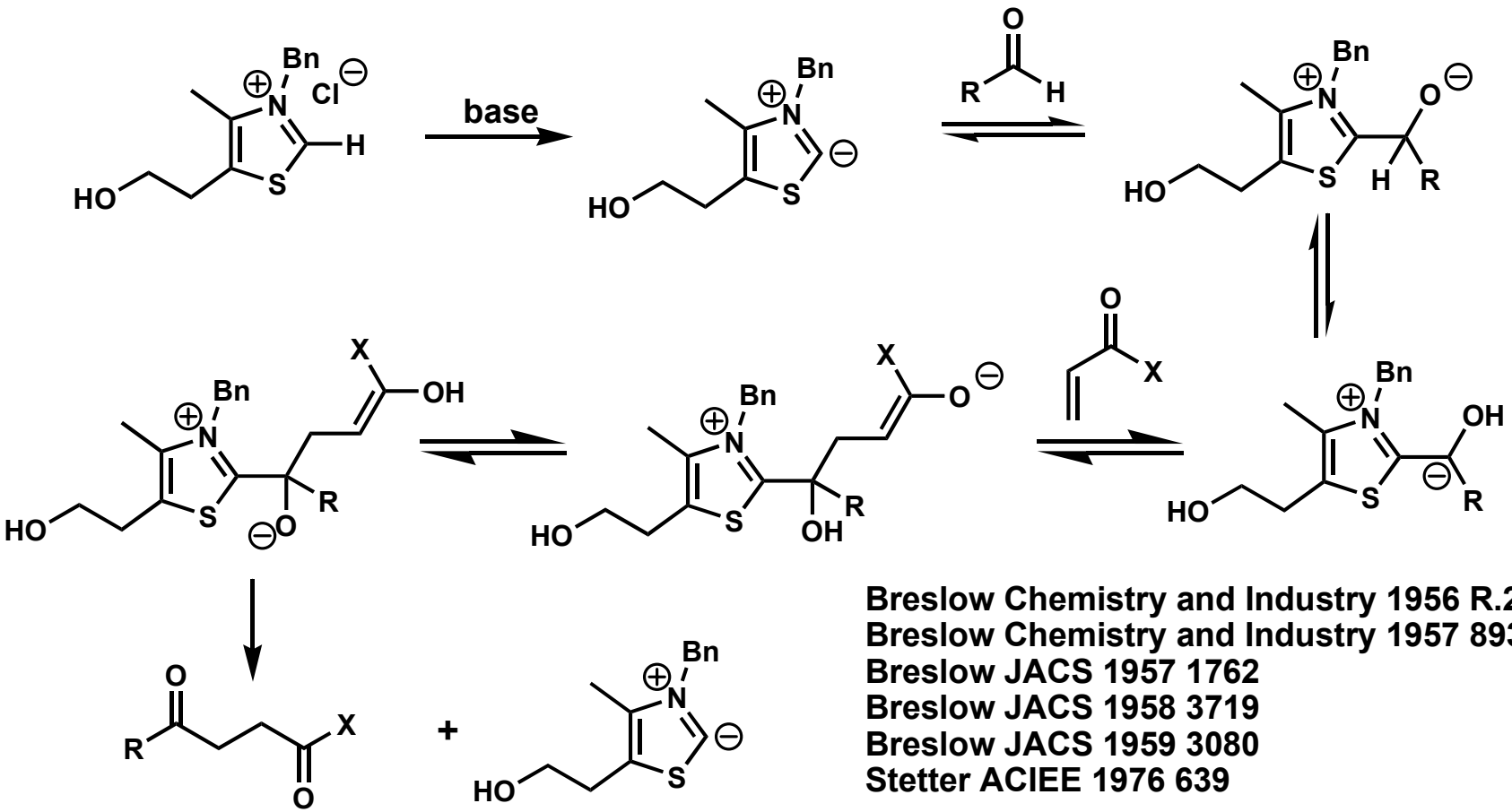
vitamin B_1 (thiamine)

- in the presence of base, quaternary thiazolium salts are converted to the ylide, which acts as catalyst (5-10 mol %)
- aliphatic, aromatic, and heterocyclic aldehydes add to α,β-unsaturated ketones, esters, and nitriles
- Et_3N or NaOAc are preferred bases
- DMF, dioxane, or even alcohols can function as solvent



Acyl Anions

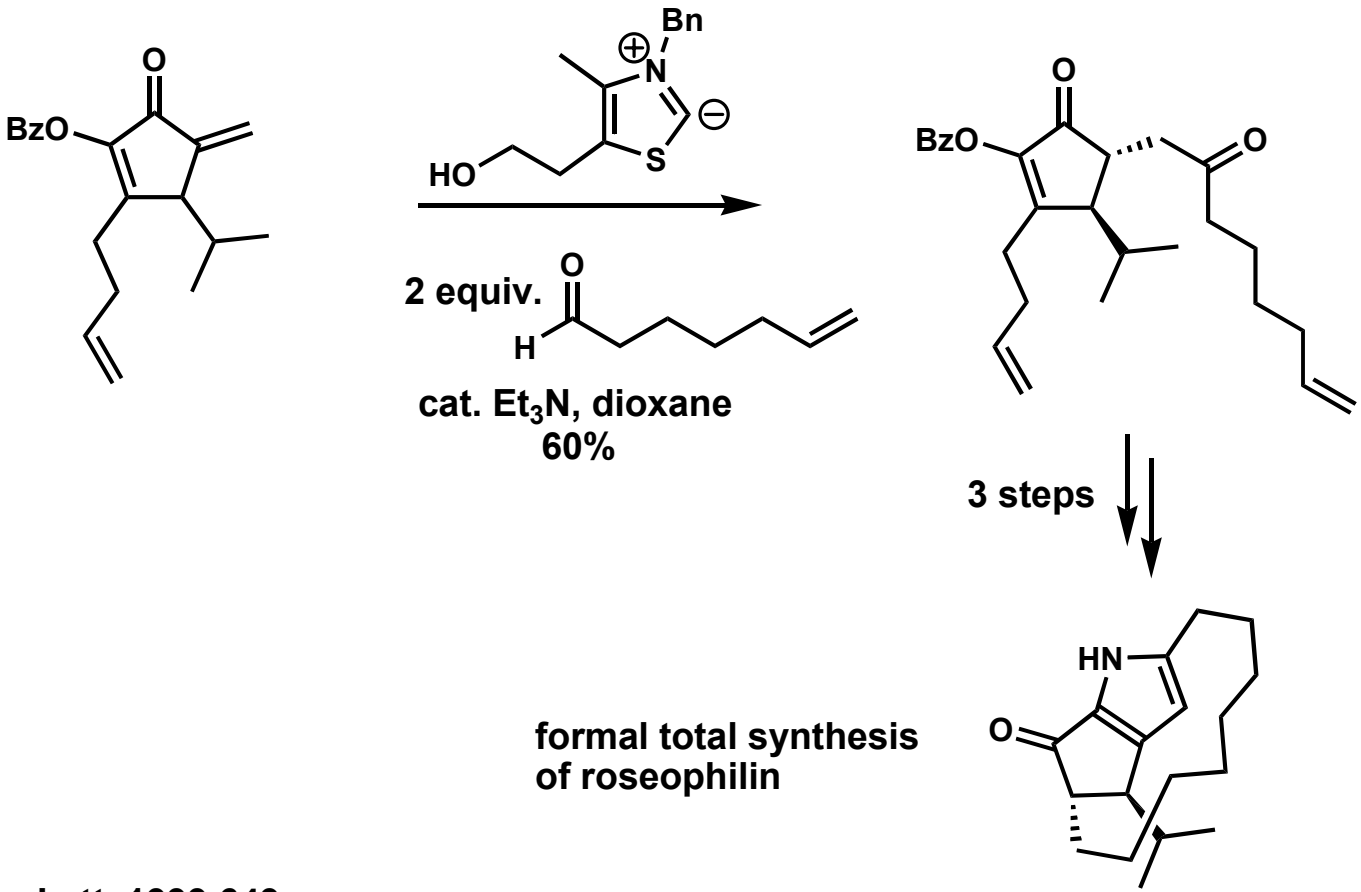
2. Thiazolium salt catalyzed addition (mechanism)



Breslow Chemistry and Industry 1956 R.28
Breslow Chemistry and Industry 1957 893
Breslow JACS 1957 1762
Breslow JACS 1958 3719
Breslow JACS 1959 3080
Stetter ACIEE 1976 639

Acyl Anions

2. Thiazolium salt catalyzed addition (example)

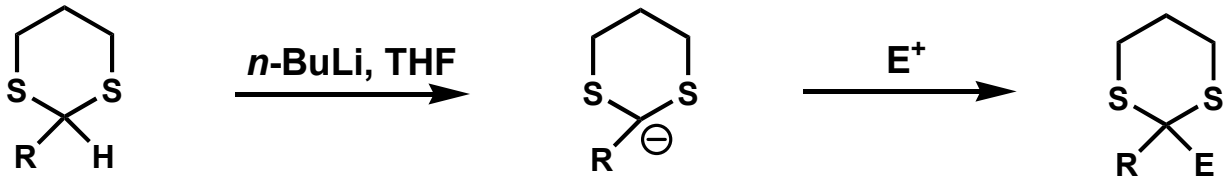


formal total synthesis
of roseophilin

Tius Org. Lett. 1999 649

Acyl Anions

3. Dithianes



- usually formed from corresponding aldehydes by thioacetalization
- R = primary, secondary, and tertiary alkyl, allyl, benzyl, aryl, and O-containing groups

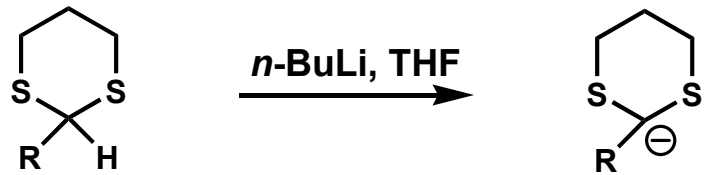
- with alkyl halides: 70-90% yield
  from protected formaldehyde, two alkylations can be done in a single reaction mixture without isolation of intermediates
- with epoxides: 70% yield to give mercaptals of β-hydroxy ketones or aldehydes
- with ketones and aldehydes: 70-90% yield to give mercaptals of α-hydroxy ketones or aldehydes
- with imines: 70% yield to give mercaptals of α-amino ketones or aldehydes
- with CO_2: 70-75% yield to give mercaptals of α-keto carboxylic acids

- biggest drawback: removal of dithiane
  1. hydrolysis 2. alkylative or oxidative hydrolysis 3. reductive desulfurization (Raney Ni)

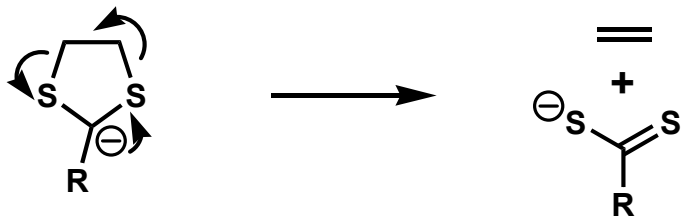
Corey, Seebach ACIEE 1965 1075
Corey, Seebach ACIEE 1965 1077
Seebach, Groebel Synthesis 1977 357
Page, Van Niel, Prodger Tetrahedron 1989 7643

Acyl Anions

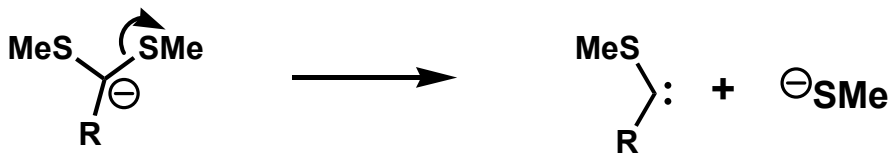
3. Dithianes



The 1,3-dithiane grouping was carefully chosen:



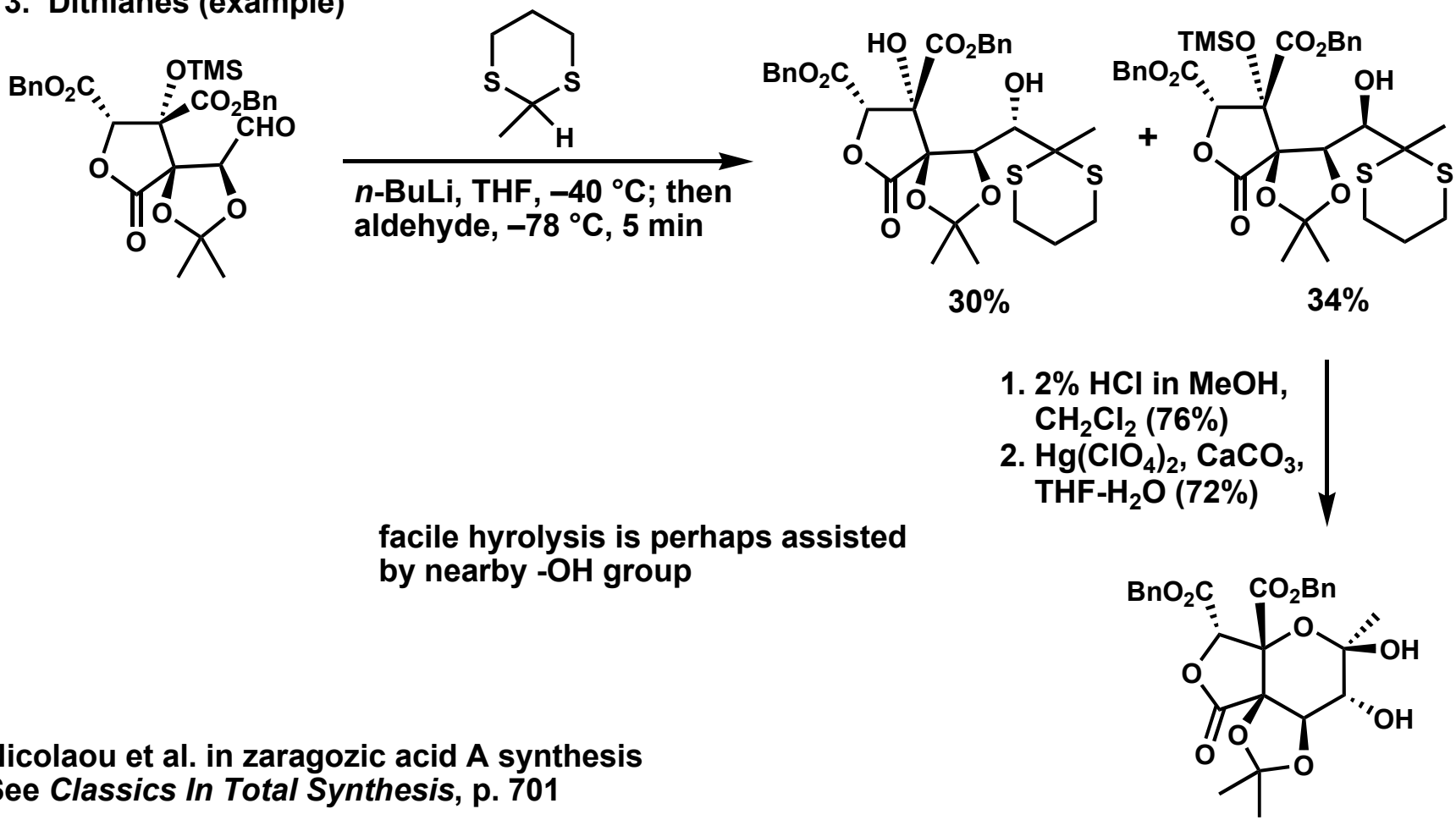
1,2-dithianes undergo a fragmentation reaction.



Dimethyl thioacetals are susceptible to carbene formation.

Acyl Anions

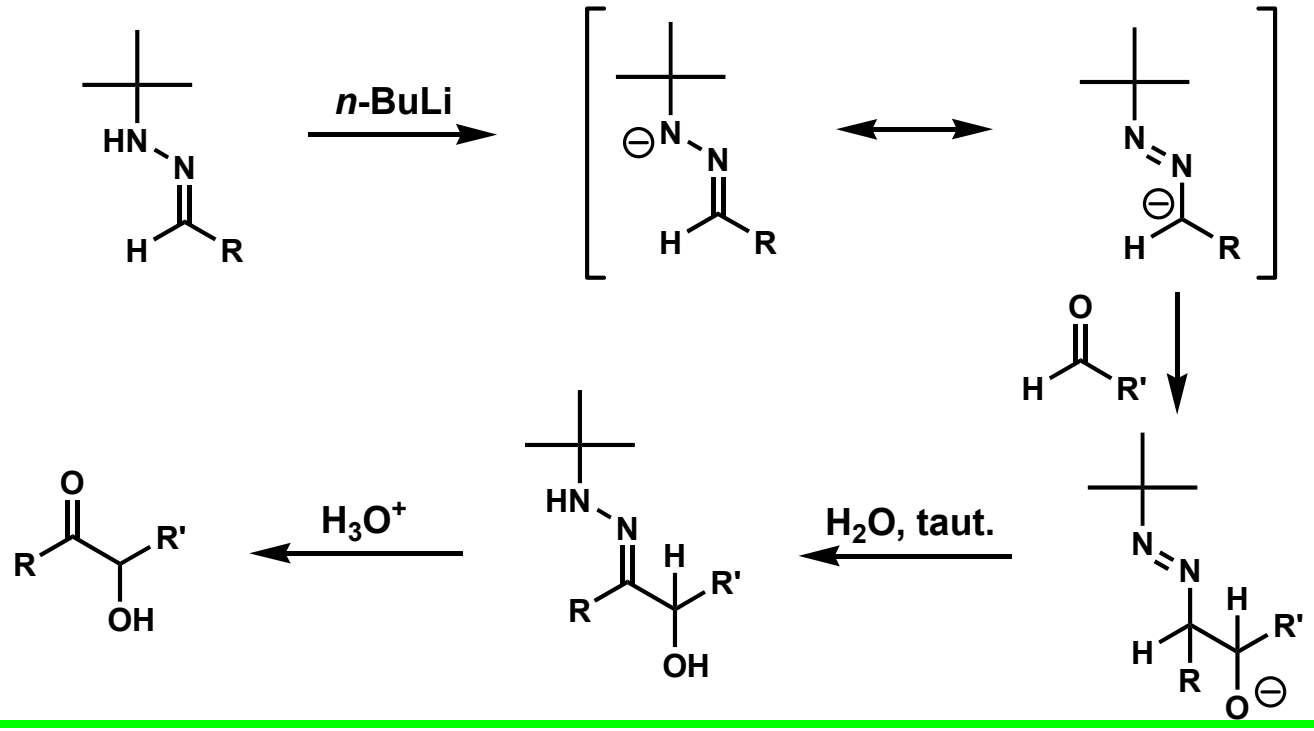
3. Dithianes (example)



Nicolaou et al. in zaragozic acid A synthesis
See *Classics In Total Synthesis*, p. 701

Acyl Anions

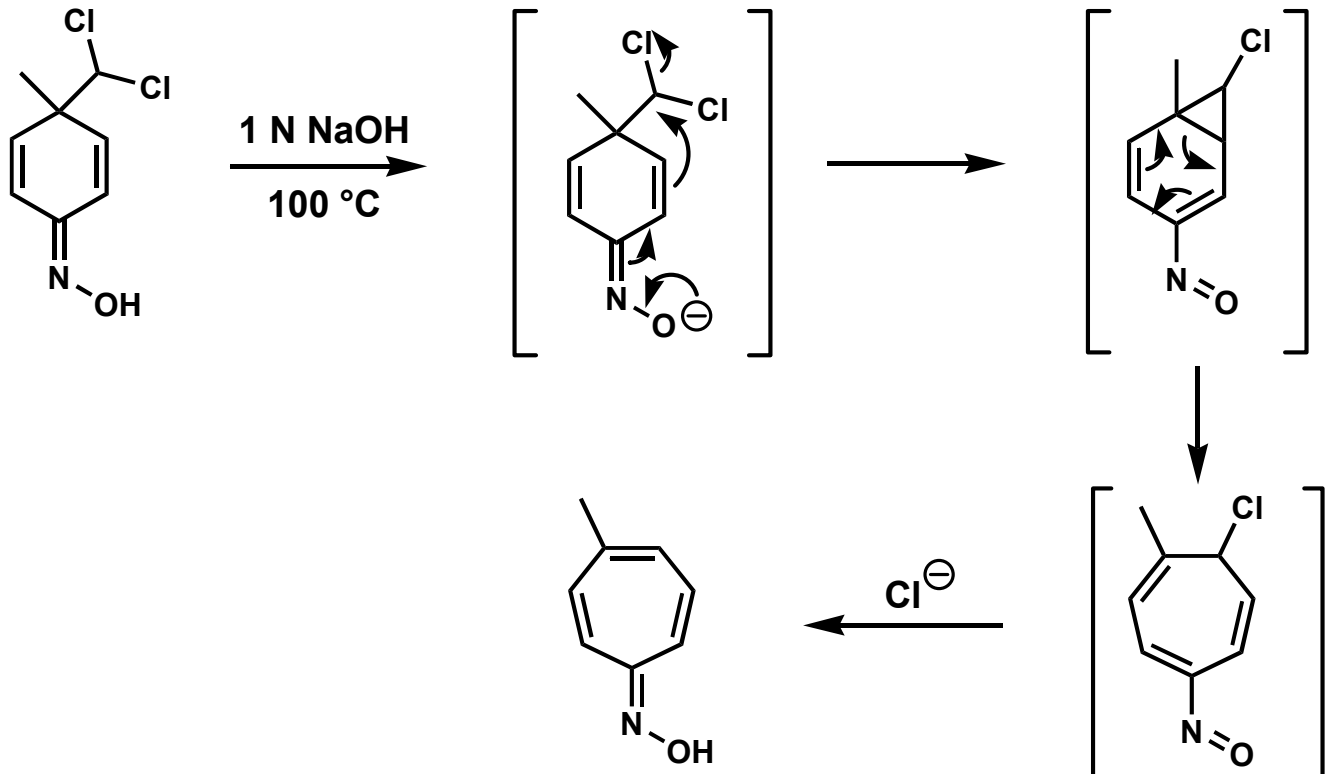
4. *t*-Butyl hydrazones
   - formed by condensation of *t*-butyl hydrazine with aldehydes or ketones
   - with methyl hydrazones, N-alkylation can be a problem; *t*-butyl group directs reaction along desired C-alkylation pathway
   - can add to:
     - aldehydes/ketones (40-95%)
     - alkyl halides (15-83%)
     - Michael acceptors (methyl crotonate, methyl acrylate, acrylonitrile)
   - acidic hydrolysis (oxalic acid) gives ketones



Baldwin et al. 1983 JCSCC 1040
Baldwin et al. 1984 JCSCC 1095

Acyl Anions

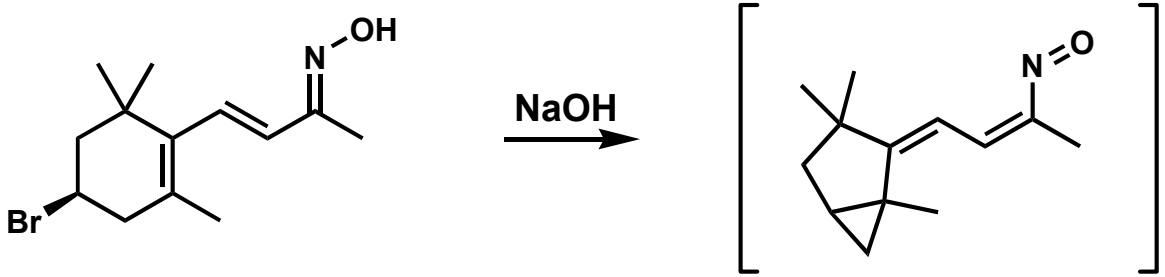
5. Oximes
   - formed by condensation of aldehydes or ketones with hydroxylamine
   - base causes an inversion of polarity by deprotonation of the N-hydroxyl
   - can be cleaved by oxidation, reduction, or hydrolysis



Eschenmoser et al. Helv. Chim. Acta 1958 2103

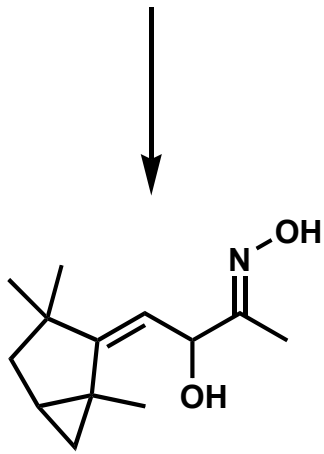
Acyl Anions

5. Oximes (example)



a β-ionone derivative

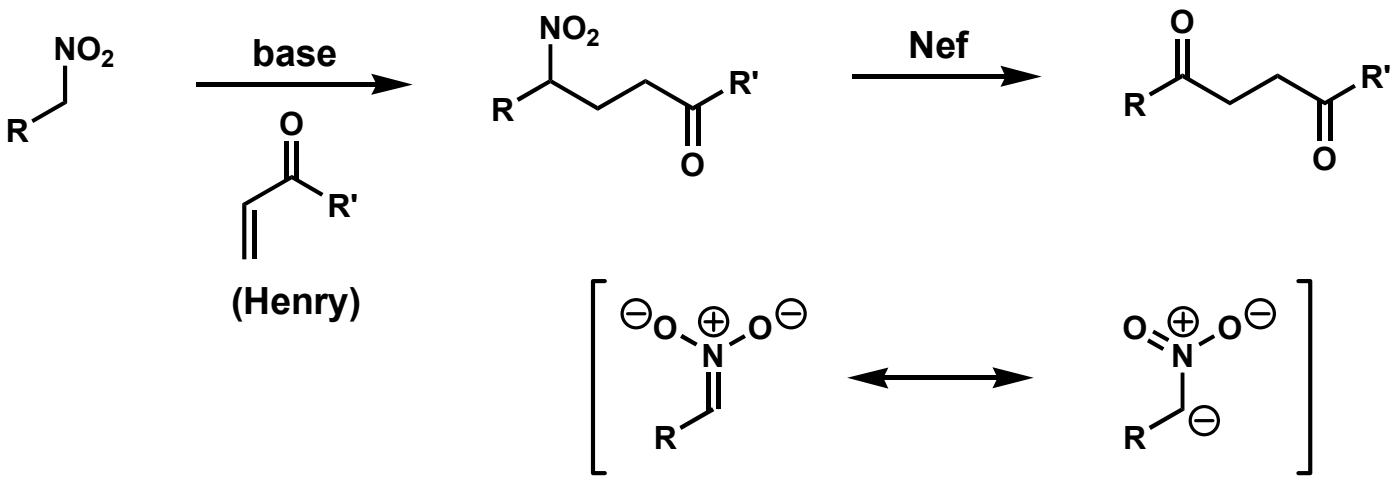
intense blue color



Eschenmoser et al. Chimia 1965 538

Acyl Anions

6. Nitronate anions (Henry reaction)

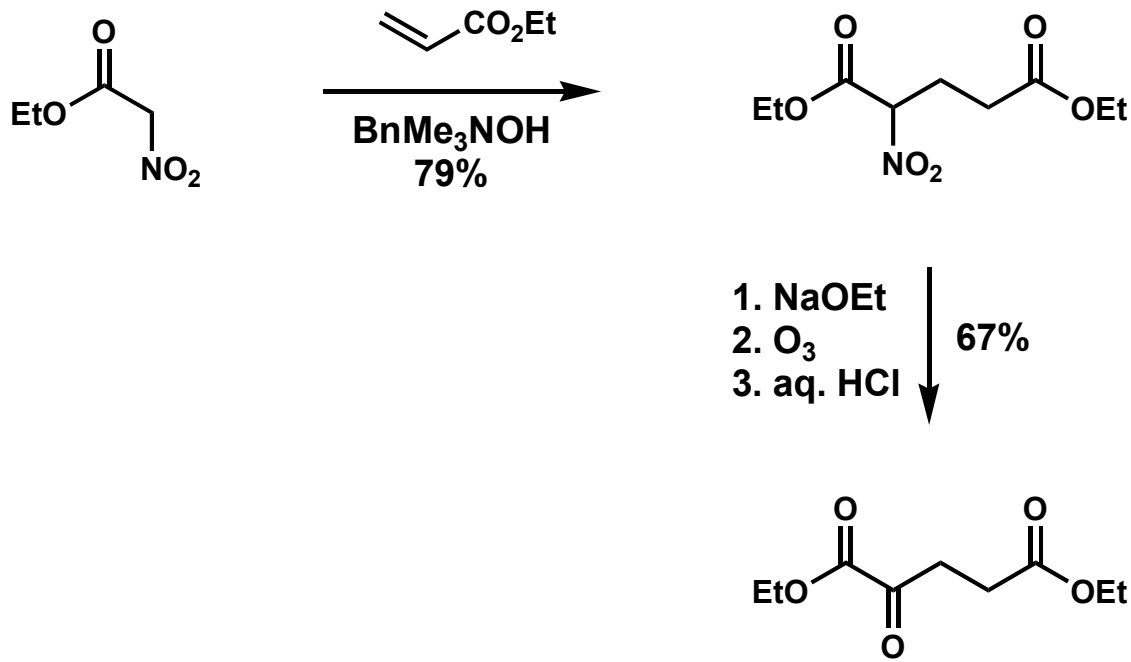


Henry reaction:
Henry Compt. Rend. 1895 1265
Rosini Comp. Org. Synth. 1991 321

Nef reaction:
Nef Liebigs Ann. Chem. 1894 263
Petrini Tetrahedron 2004 1017

Acyl Anions

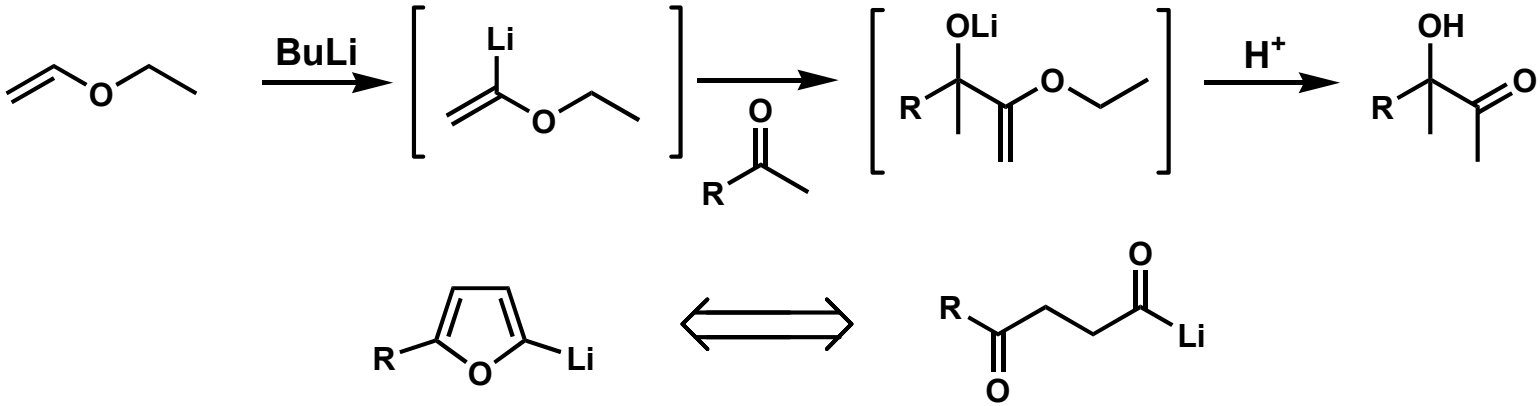
6. Nitronate anions (example)



Cappon et al. Recl. Trav. Chim. Pays-Bas 1991 158

Acyl Anions

7. **Metalated enol derivatives**
   - **metalation of a protected enol, followed by reaction with an electrophile**
   - **after hydrolysis, a net nucleophilic acylation has occurred**

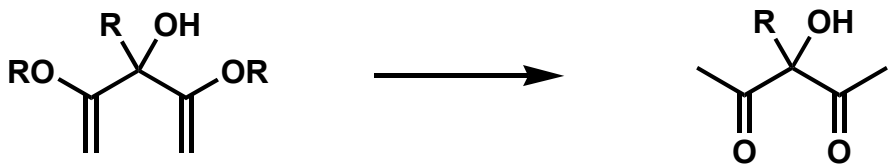


- **big advantage: enol ether products are hydrolyzed under very mildly acidic conditions**

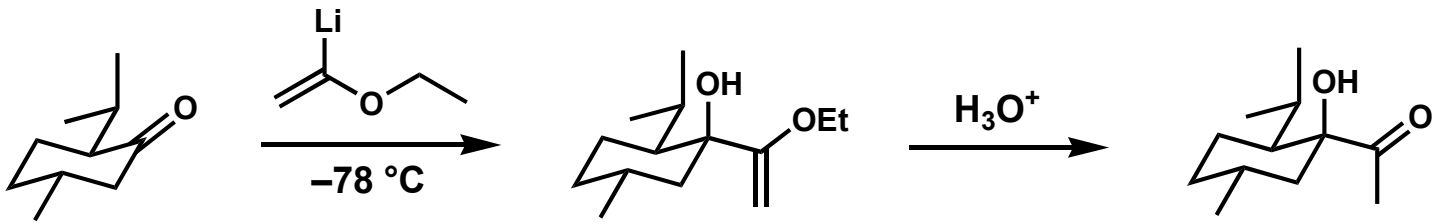
- **in addition to reactivity with ketones and aldehydes, lithio vinyl ethers are alkylated by primary iodides or allylic halides; acylated by aromatic acids (0.5 equiv.) or nitriles; silylated to give acylsilanes**

Acyl Anions

7. Metalated enol derivatives
   - aliphatic or aromatic esters add 2 equiv. of reagent to give bis-adducts
   - such products are difficult to access without nucleophilic acylation



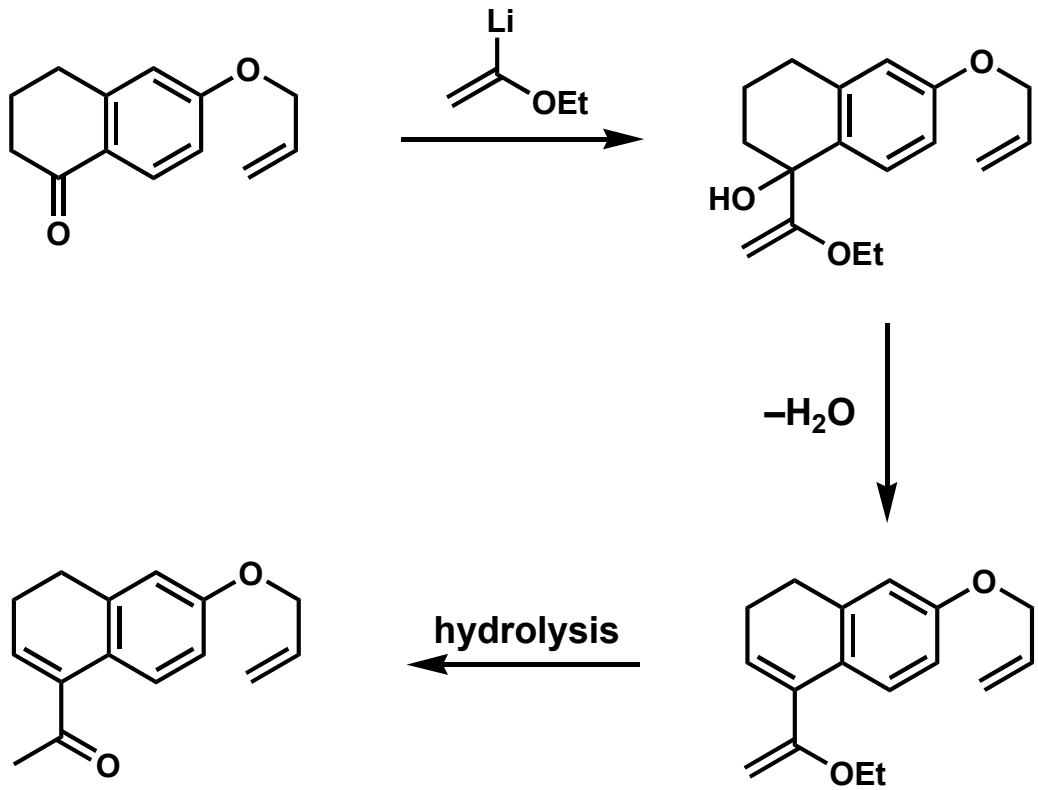
Review: Lever Tetrahedron 1976 1943



Funk, Shipe unpublished results

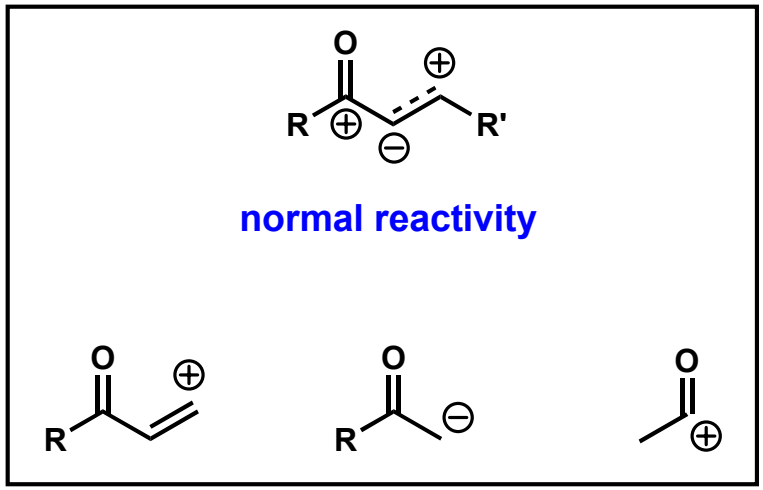
Acyl Anions

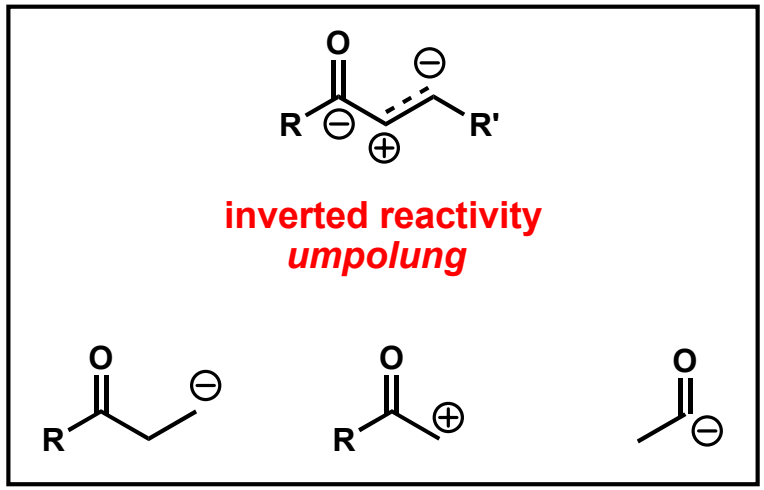
7. Metalated enol derivatives (example)



In total synthesis of nicandrenones:
Corey, Stoltz, Kano JACS 2000 9044

Umpolung - Carbonyl Synthons



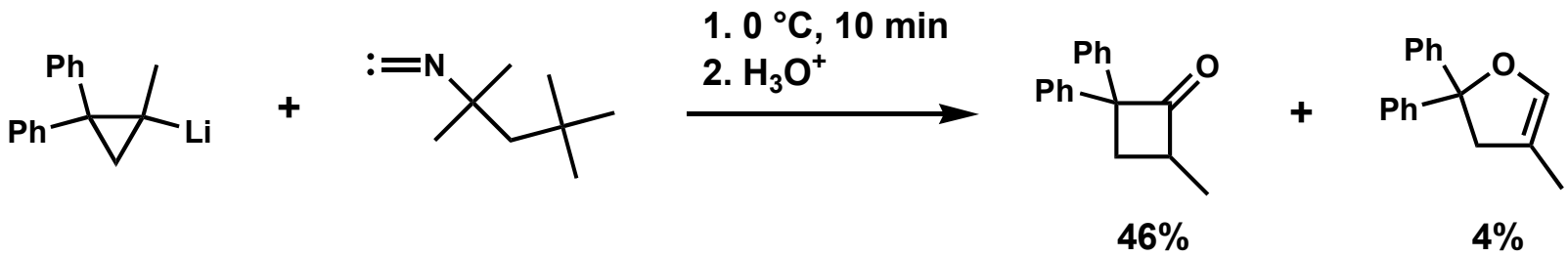


Umpolung **provides flexibility in synthetic planning:**

- **Michael acceptors vs. homoenolates**
- **enolates vs. α-electrophiles**
- **carbonyls vs. acyl anions**

Umpolung - Carbonyl Synthons

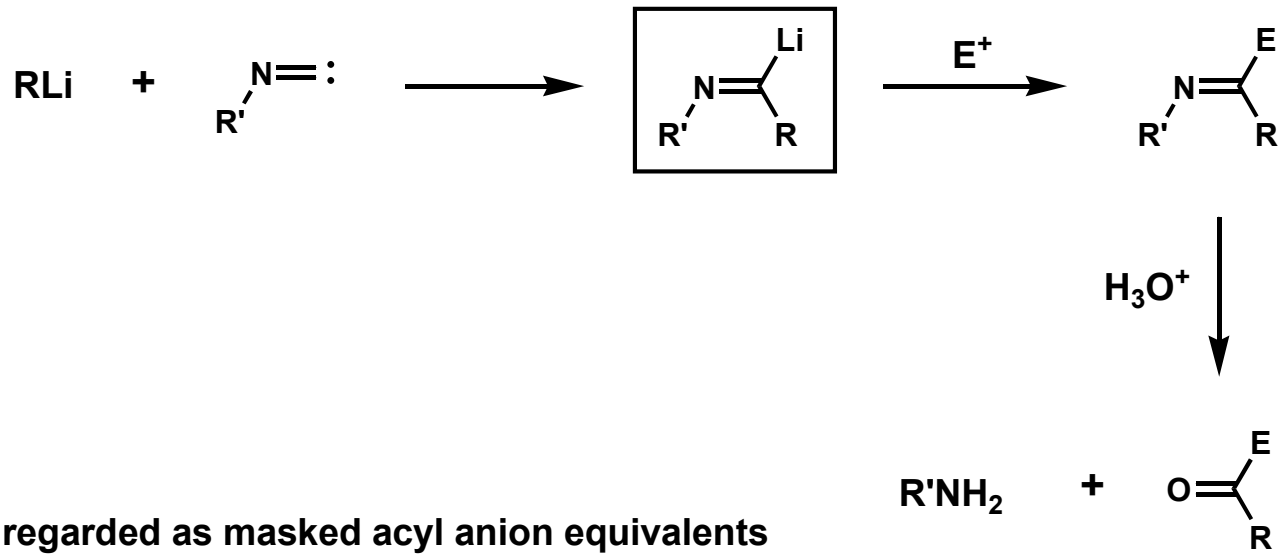
An interesting ring expansion was observed when a cyclopropyllithium reagent was treated with an isocyanide. Provide a plausible mechanism for the formation of the two products.



Walborsky JOC 1974 608

Acyl Anions

8. Metallo aldimines

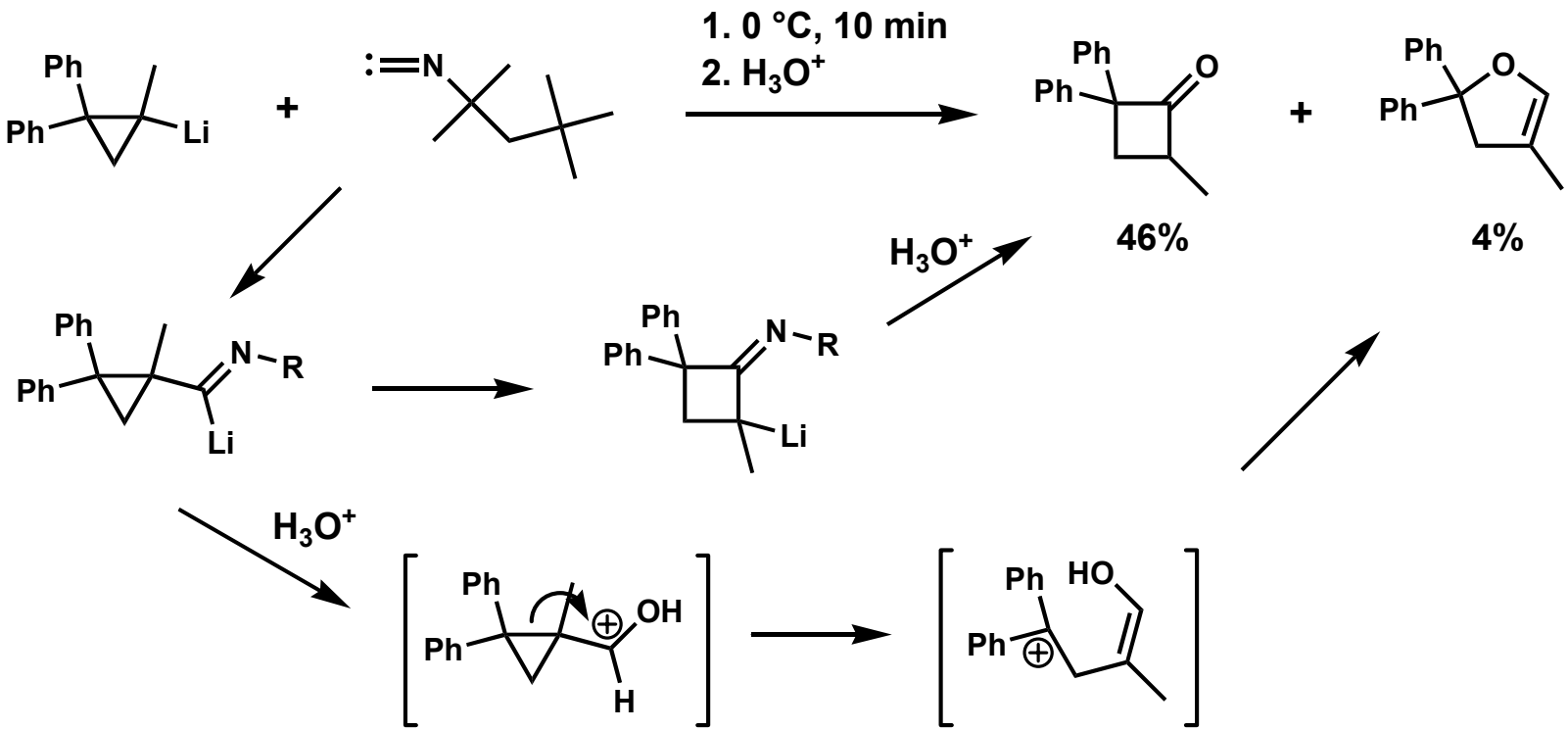


- can be regarded as masked acyl anion equivalents
- less efficient with Grignard reagents and aryllithiums
- fails with less basic anions like acetylides
- vinyl and propenyllithium undergo complicated side reactions

Walborsky et al. JOC 1974 600
Walborsky et al. JACS 1969 7778
Walborsky et al. JACS 1970 6675

Mechanism Problem

An interesting ring expansion was observed when a cyclopropyllithium reagent was treated with an isocyanide. Provide a plausible mechanism for the formation of the two products.



Walborsky JOC 1974 608