

## Notes on Warren, Chapters 22-25

### Chapter 22: Use of aliphatic nitro compounds

Chapter 22 is a very straightforward introduction to the use of nitro compounds as nucleophiles, and as activated alkene systems, for the formation of C-C bonds. The chemistry is quite simple, once you understand that the  $\text{CHNO}_2$  group is homologous to the  $\text{CHCO}$  group in ketones, aldehydes and other carbonyl compounds.

### Page 180: Availability of nitro compounds

Warren notes that nitromethane and 2-nitropropane are the only readily available aliphatic nitro compounds. This is because, while it is easy to make aryl nitro compounds by electrophilic nitration, aliphatic nitro compounds are much less accessible. Notice that when we talk of aliphatic nitro compounds we are *not* referring to *nitrate esters*, which are easily made when alcohols are treated with nitric acid.

Alkyl nitro compounds can be made by  $\text{S}_{\text{N}}2$  displacement of some primary or secondary alkyl halides with silver nitrite. This is not a generally applicable method, however, and competing formation of *nitrite esters* is an important side reaction. This is reaction 10-64 in March.

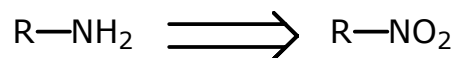
Alkanes are nitrated in the gas phase when heated with nitric acid to 400 °C. This reaction is used to make nitromethane industrially, and this is the only situation in which a pure product can be obtained. Nitration is unselective with any alkane more complex than methane. This is reaction 14-12 in March.

Primary alkylamines can be oxidized by a variety of oxygen-donating reagents. When the alkyl group is tertiary,  $\text{KMnO}_4$  may be used, but for other amines much milder reagents like dimethyldioxirane, peroxyacids or various peroxide/metal catalyst combinations must be used. This is reaction 19-24 in March.

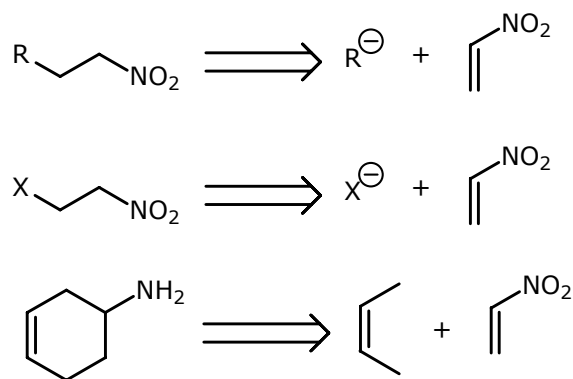
The best way of obtaining an alkyl nitro compound in general is to use nitromethane as a nucleophile towards an alkyl halide, as described in Warren.

### Other uses for nitro compounds

Nitro compounds are not only used as nucleophilic acyl anion equivalents. Since the nitro group is easily reduced, it is a good precursor for amines.



Nitro groups are strongly electron-withdrawing and so nitroalkenes are good Michael acceptors (towards relatively soft nucleophiles) and also act as dienophiles in Diels-Alder reactions.



### Page 183: Ketones from nitro compounds.

The conversion of nitro compounds to carbonyls is known generically as the *Nef Reaction*. Warren describes a mild version of this process using aqueous  $\text{TiCl}_3$ . This reagent should not be confused with the more commonly found  $\text{TiCl}_4$  (titanium tetrachloride), which is a powerful Lewis acid that would react violently with water to form  $\text{TiO}_2$ , an insoluble white solid. Warren *incorrectly* states (page 183) that the conversion of secondary nitro compounds to ketones is *catalyzed* by  $\text{TiCl}_3$ . The  $\text{TiCl}_3$  is in fact used stoichiometrically in the reaction, and it acts as a 1-electron reducing agent. You should consult the original publication (McMurry, J.E.; Melton, J. *J. Org. Chem.*, **1973**, 38, 4367-4373) for a very interesting account of how the reaction was discovered and developed, and how a basic mechanistic understanding was developed.

The important practical aspects of this reaction are:

- Acid-stable compounds are reduced simply by treating a THF or DME solution of the nitro compound with 4 equivalents of 20% aqueous  $\text{TiCl}_3$  solution at room temperature.
- Acid-labile compounds are best reacted under one of two sets of conditions:
  - Treatment with ammonium acetate-buffered  $\text{TiCl}_3$  (6:1) solution to afford a pH of 5 to 6.
  - Pre-treatment with  $\text{NaOCH}_3/\text{CH}_3\text{OH}$  to form the nitronate anion, followed by reaction with buffered aqueous  $\text{TiCl}_3$ .

The Nef reaction has been reviewed in detail in 2004 (Ballini, R.; Petrini, M. *Tetrahedron* **2004**, 60(5), 1017-1047). There are numerous other reagents that have been applied, and it can be performed oxidatively as well as reductively.

### Chapter 23: 1,2-Difunctional compounds - Acyl anion equivalents

In these chapters, Warren discusses the idea of “unnatural synthons” that was introduced a few chapters back. This refers to inverting the “normal” polarity of a functional group – in a purely retrosynthetic sense – and is commonly referred to by the German word *umpolung* meaning reversal or inversion. This concept is discussed in Smith section 8.6.B.

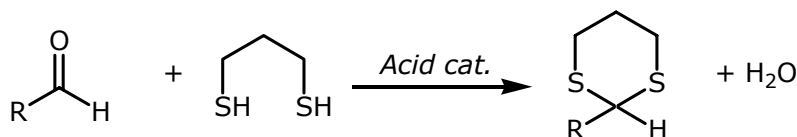
Warren mentions nitro compounds and terminal acetylenes as precursors for the acyl anion synthon, and also the use of cyanide ion as a carboxylate C-anion synthon. There are other structures which also serve as acyl anion equivalents that he neglects and which are probably more versatile.

## 1,3-Dithianes

The key features of an acyl anion synthon are:

1. Easy formation from a simple precursor, preferably a carbonyl.
2. A C-H pKa such that deprotonation by BuLi or LDA is quantitative.
3. High nucleophilicity towards carbonyls or other electrophiles.
4. Easy conversion of the product to a carbonyl.

The 1,3-dithiane, or dithioacetal, grouping is the most frequently used acyl anion equivalent (despite Warren's emphasis on nitro compounds). 1,3-Dithianes are the sulfur analogs of acetals, and they are formed in an analogous fashion by the acid-catalyzed reaction of propane-1,3-dithiol with an aldehyde. This chemistry is also used to *protect* carbonyl groups, and methods for installing and removing dithioacetal groups are covered in great detail in Greene's *Protective Groups* book (pages 329-344).

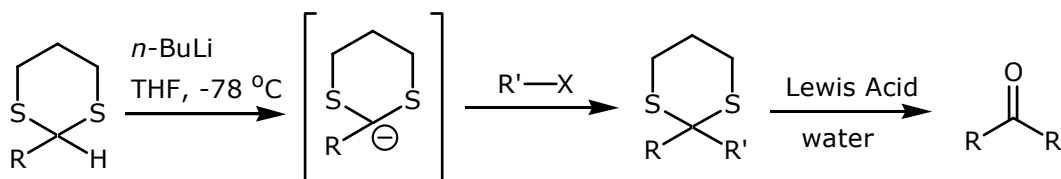


The pKa of the dithiane group depends on the nature of the R-group in a completely conventional way:

$$\text{R}-\text{C}(\text{S}-\text{CH}_2-\text{CH}_2-\text{S})-\text{H} \rightleftharpoons \text{R}-\text{C}(\text{S}-\text{CH}_2-\text{CH}_2-\text{S})-\text{C}^- + \text{H}^+$$

R Group	pKa
H	31.1
CH <sub>3</sub>	38.3
Ph	29.6

The typical reaction of a dithiane reagent involves deprotonation in THF at  $-78\text{ }^\circ\text{C}$  by *n*-BuLi, followed by addition of a primary or secondary alkyl halide (reaction is S<sub>N</sub>2), an acid chloride, a ketone or an aldehyde. Dithiane reagents will also react with epoxides. Reaction with conjugated ketones usually occurs in a 1,2-fashion.



As you can see, this chemistry gives access to a wide variety of unsymmetrical ketones. The one weak point in this scheme is the removal of the dithiane group. The cleavage of a dithiane is much more difficult than that of a ketal and so although it can be achieved using H<sub>3</sub>O<sup>+</sup>, this is not usually satisfactory. The Lewis acids that work best, however, are salts of heavy metal ions with high affinities for sulfur (i.e. they are *thiophilic*) such as Hg(II), Pb(IV) and Tl(III). These are all

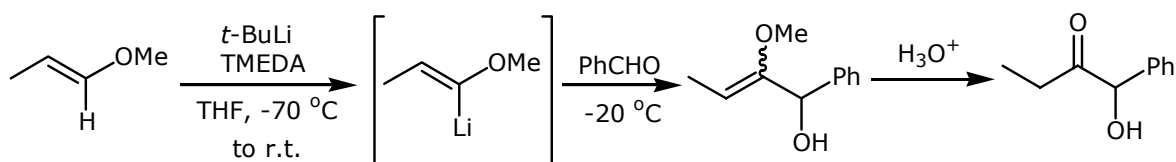
quite toxic and pose significant environmental problems. It is also possible to remove thioketals by oxidation with  $\text{Cl}_2$ ,  $\text{Br}_2$ ,  $t\text{BuOCl}$ , NBS, NIS or  $\text{Ce}(\text{NH}_3)_6(\text{NO}_3)_4$ , or by reaction with  $\text{MeI}$  in the presence of water. The choice of reagent will depend on the other functionality present in the molecule. Consult Greene for literally dozens of methods for removing dithioketals and dithianes.

Dithianes can also be reduced completely to  $\text{CH}_2$  groups by treatment with Raney Nickel, although these conditions will hydrogenate many other functional groups that might be present in the molecule as well. This application is not “acyl anion” chemistry, but provides an alternative to simple Grignard or alkyllithium reagents if the corresponding alkyl halides are unsuitable or unavailable.

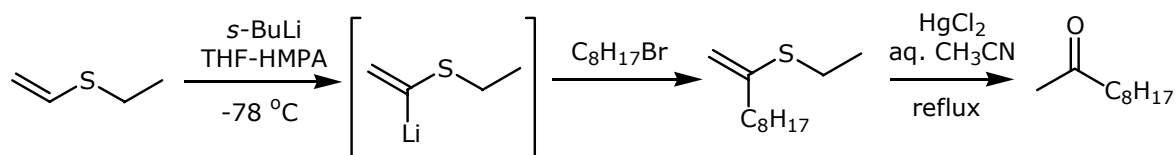
Smith discusses dithianes and other dithioacetal acyl anion equivalents in section 8.6.B.ii.

## Enol Ethers

Although not usually discussed in introductory organic classes, the deprotonation of activated alkenes is quite feasible with sufficiently strong bases. Thus, alkoxy-substituted alkenes (i.e. *enol ethers*) and alkylthio-substituted alkenes (i.e. *vinyl sulfides*) can form nucleophilic species on deprotonation with  $t\text{-BuLi}$  or  $s\text{-BuLi}$ . Note that  $n\text{-BuLi}$  is not sufficiently basic for this purpose. This chemistry was extensively reviewed by Friesen in 2001 (Friesen, R.W. *J. Chem. Soc. Perkin Trans. I*, **2001**, 1969-2001).



TMEDA = *N,N*-tetramethylethylenediamine

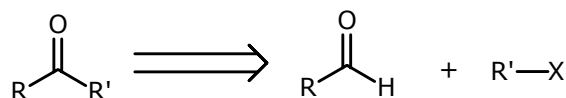


HMPA = hexamethylphosphoramide

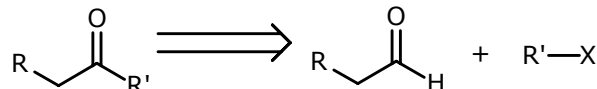
In these examples, strongly coordinating additives TMEDA and HMPA are used to facilitate the deprotonation and to increase the ionic character of the resulting vinyl lithium species. Note the use of  $\text{Hg}(\text{II})$  to facilitate hydrolysis of the vinylthioether in the second example.

When thinking about the use of acyl anion equivalents in synthesis, you should keep in mind the corresponding retrosynthetic transforms:

for dithianes



for enol ethers and vinyl sulfides



Notice that the transforms are slightly different. This is because you must have at least one  $\alpha$ -hydrogen in order to form an enol ether or vinyl sulfide reagent, whereas the dithiane has no such restriction.

### Page 189: Formation of 1,2-difunctional compounds from alkenes

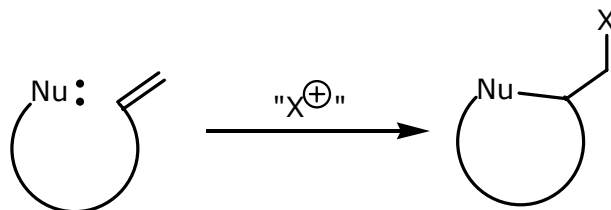
This should all be very familiar chemistry – epoxidation, vicinal bromination, and dihydroxylation ( $\text{OsO}_4$ ) are all part of introductory organic chemistry. Those of you who have taken 2.339 will also have encountered additional versions of these reactions (the Prévost and Woodward-Prévost dihydroxylations for example).

Some important additions to the material Warren discusses are summarized below, with references to further information. A recent review of this type of chemistry is found in Bonini, C.; Righi, G. *Tetrahedron* **2002**, 58(25), 4981-5021.

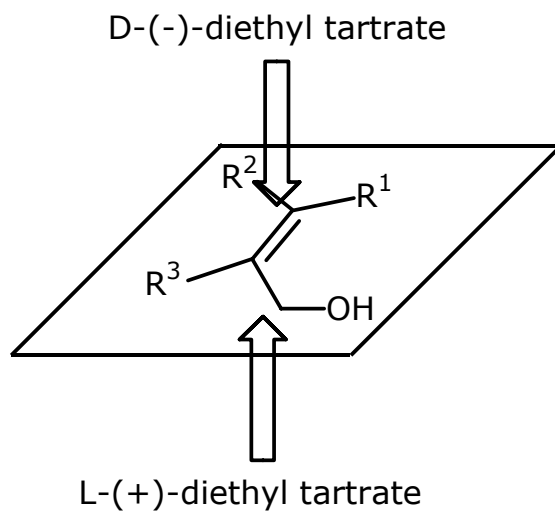
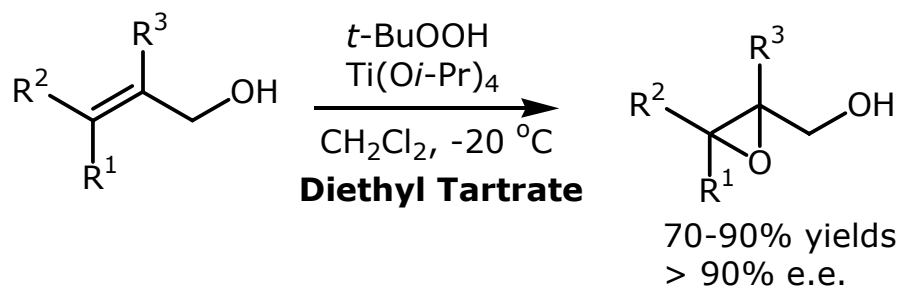
In the examples below, you will notice that one of the major developments from the chemistry discussed in Warren is the emphasis on *stereoselectivity*, particularly *enantioselectivity*. Also note that several of these reactions are in fact catalytic – reagents like  $\text{OsO}_4$  are too toxic and expensive to be used stoichiometrically, and so they are frequently packaged along with inorganic oxidizing agents that recycle the actual reagent. Both catalysis and enantioselectivity are major themes in modern organic chemistry. A complete issue of *Accounts of Chemical Research* Volume 37 Issue 8 (August 17, 2004) is dedicated to asymmetric catalysis.

#### Halocyclization

- Halolactonization
- Haloetherification
- Haloamination
- etc.

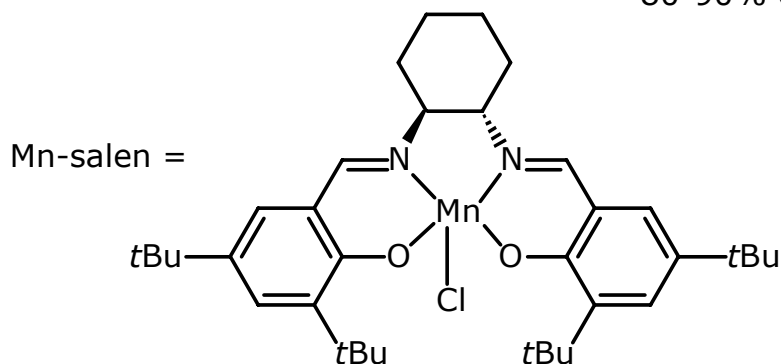
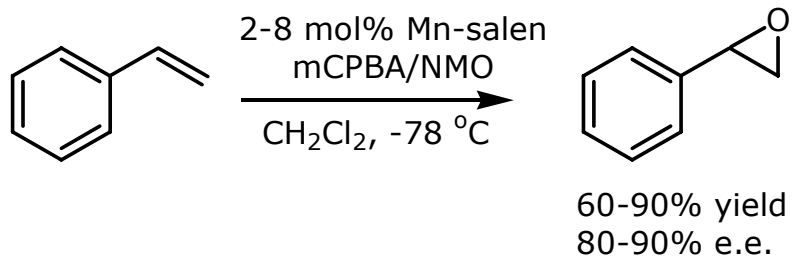


This is too large and diverse a family of processes to provide detailed examples for every case. The reaction is discussed in Carey and Sundberg Vol B, pages 181-185, with related chemistry in section 4.5 pages 185-190. It is reaction 15-38 in March, and it is found in Smith in section 2.10.C.

*The Sharpless Asymmetric Epoxidation*

See:

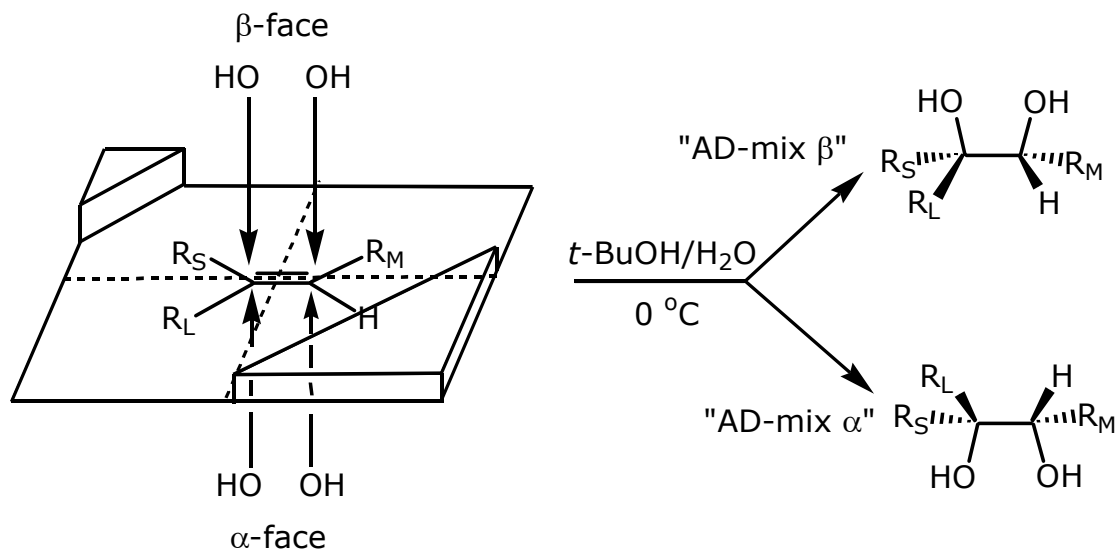
- 1) Nicolaou and Sorensen *Classics in Total Synthesis*, Chapter 19 and references therein.
- 2) March, reaction 15-48.
- 3) Smith, section 3.4.D.i.

*Jacobsen-Katsuki Epoxidation*

See:

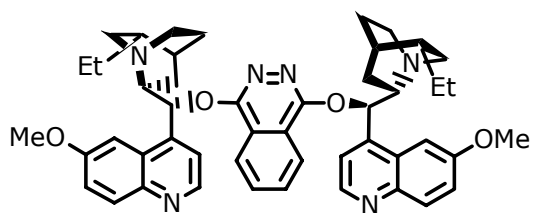
- 1) Smith section 3.4.D.ii.
- 2) Antoniotti, S.; Dunach, E. *Synthesis* **2003**, 2753-2762.
- 3) Katsuki, Tsutomu. *Synlett* **2003**, 281-297.

### Sharpless Asymmetric Dihydroxylation



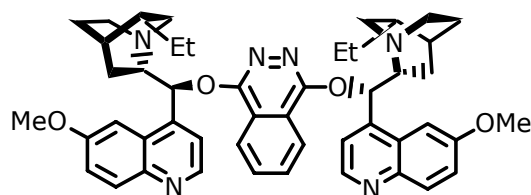
AD-mix  $\alpha$  = commercially available mixture of  $K_3Fe(CN)_6$ ,  $K_2CO_3$ , and  $K_2OsO_4$  hydrate, with chiral ligand  $(DHQ)_2PHAL$

AD-mix  $\beta$  = same mixture as AD-mix  $\alpha$ , but with chiral ligand  $(DHQD)_2PHAL$



$(DHQ)_2PHAL$

hydroquinine 1,4-phthalazinediyl diether



$(DHQD)_2PHAL$

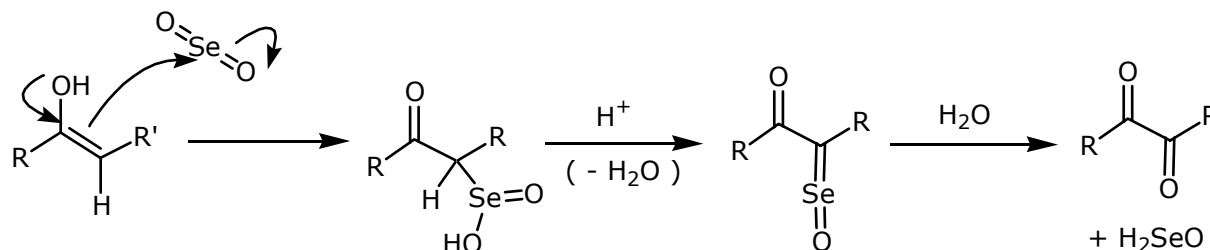
hydroquinidine 1,4-phthalazinediyl diether

See:

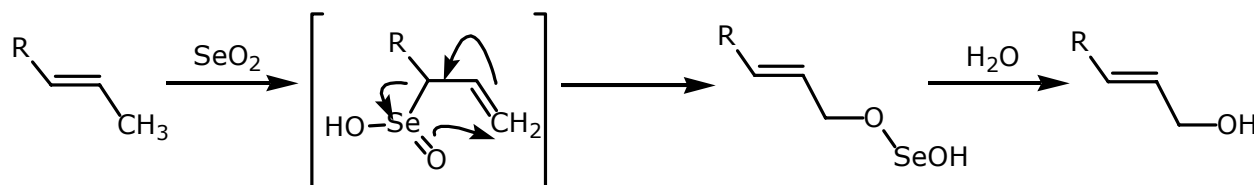
- 1) Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.*, **1994**, 94, 2483.
- 2) Berrisford, D.J.; Bolm, C.; Sharpless, K.B. *Angew. Chem. Int. Ed. Engl.*, **1995**, 34, 1059.
- 3) Smith section 3.5.B.ii.

### Page 191: $\alpha$ -Functionalization of Carbonyls

The reactions Warren discusses for installing a second carbonyl adjacent to another C=O group are all variations on the electrophilic bromination seen in the Hell-Vollhard-Zelinsky reaction. The use of  $\text{SeO}_2$  is probably new to you, however. The selenium atom is electrophilic, and it is attacked by the enol tautomer of the carbonyl:



This reagent is also very useful for allylic oxidations, to form either allylic alcohols or  $\alpha,\beta$ -unsaturated aldehydes and ketones. This application of  $\text{SeO}_2$  is discussed very briefly in Warren in Chapter 24 (page 200) but you can see more about it in Carey and Sundberg vol. B, section 12.6.2.



It is also possible to  $\alpha$ -functionalize carbonyls under basic conditions, via their enolates. While the halogenation of ketones in aqueous  $\text{NaOH}$  is not synthetically useful (recall the iodoform reaction), halogenation of the lithium enolate at  $-78\text{ }^\circ\text{C}$  using various sources of " $\text{X}^+$ " is very useful and selective. Consult March reactions 12-4 and 12-5 for further details.

### Page 194: Strategy of available starting materials

The compounds in Table 23.2 are all relatively cheap and readily obtained 1,2-difunctional materials. Whenever you can disconnect back to such a material, you probably have a viable approach to your target. As Warren notes, 1,2-difunctional skeletons may be awkward to construct, and so if Nature has done the work for you, or if you can easily modify a readily available skeleton, go for it!

## Chapter 24: Radical reactions in synthesis and Functional Group Addition

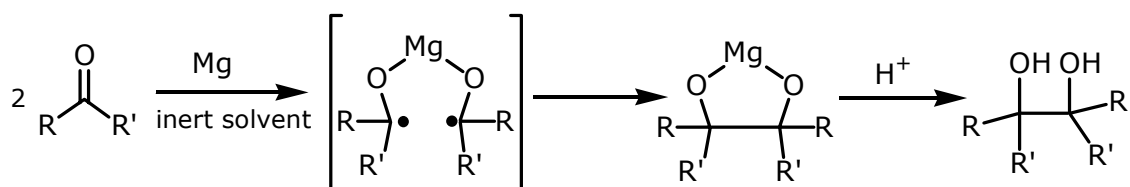
I don't really understand why Warren has grouped these two topics in one chapter. The first part of the chapter, on some radical reactions, has very little connection to the second part. I want to discuss some issues from each part, but I especially want you to recognize the importance of Functional Group Addition as a *retrosynthetic strategy*.

### Radical Reactions

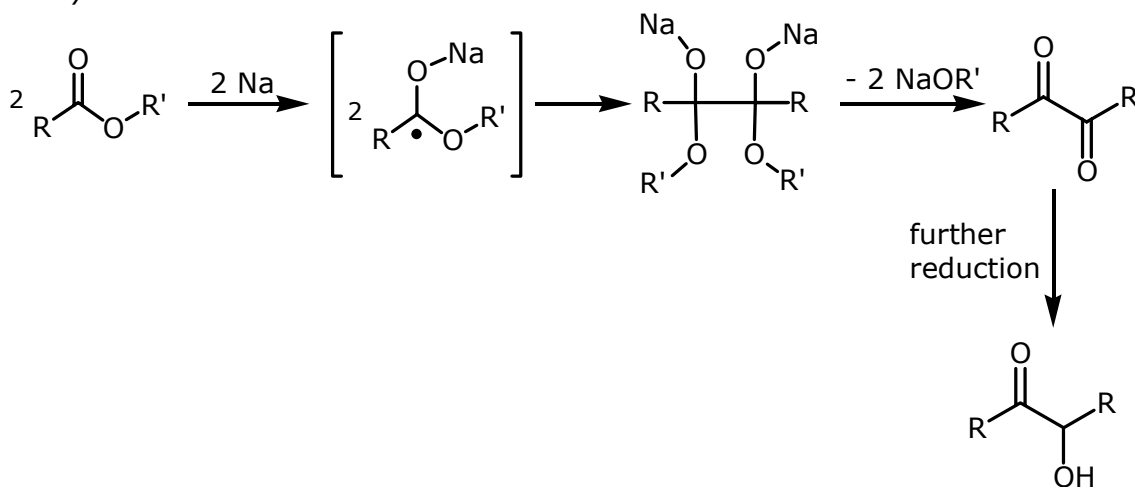
Warren really is only presenting a couple of radical reactions here: allylic/benzylic bromination, and symmetrical couplings or dimerizations. The latter category is represented by the *pinacol reduction* and the *acyloin reaction*. These both involve the reduction of a carbonyl to form a radical anion, or *ketyl radical*. This intermediate then couples to form a closed-shell dianion.

#### *Pinacol reduction*

(not to be confused with the *pinacol rearrangement*)



#### *Acyloin reaction*



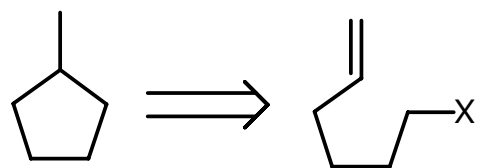
Although both of these reactions are depicted in Warren, I think it is useful to see them side-by-side as I have drawn them here. The fact that they are essentially identical processes should be clear on inspection.

Look closely at the various examples in the first part of this chapter because there is some interesting chemistry shown. Notice, however, that reactions like the pinacol reduction and the acyloin reaction are intrinsically limited to *symmetrical couplings*. This is by no means true of radical reactions in general.

Those of you who have taken 002.339 will recall that halides can be reduced to carbon-centred radicals using  $\text{Bu}_3\text{SnH}$ . If there is an alkene or other acceptor fragment available, and if the concentration of hydrogen atom donors is low, this radical will form a C-C bond.



The reaction is especially useful in intramolecular cases, as shown above, where it forms rings. Radical reactions of this type strongly favour 5-membered rings, although they will also form 6-membered rings under appropriate conditions. A retrosynthetic transform appropriate for radical C-C bond formation is:



You should all read Chapter 23 in Nicolaou and Sorensen *Classics in Total Synthesis*, which discusses D.P. Curran's radical-based syntheses of Hirsutene and  $\Delta^{9(12)}$ -Capnellene. In this chapter, reference 3 cites several overviews of radical chemistry that all appeared after Warren wrote our textbook, and the introduction to the chapter shows many different ways that this type of reaction can be applied. Curran's syntheses involve a radical "cascade" that forms two rings in a single reaction – this kind of cascade is one of the great strengths of radical C-C bond formation.

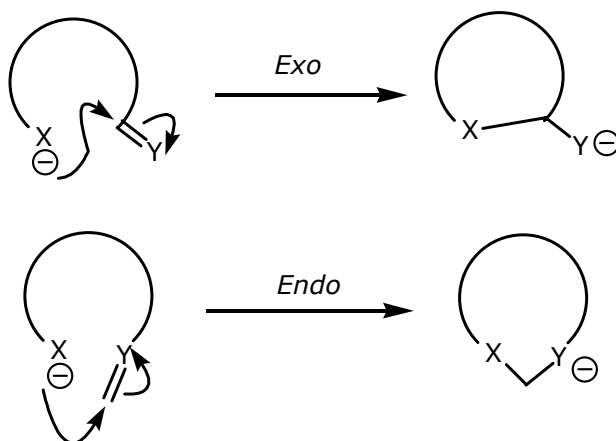
## A brief diversion: Baldwin's Rules for Ring Closure

Why are some kinds of rings easy to make, and others difficult? An even more interesting question is: why are some kinds of rings easy to make using a particular type of chemistry, but not using another kind of reaction? These questions are addressed by *Baldwin's Rules*.

You should all read section 6.6.A in Smith, where you will find a detailed discussion of Baldwin's Rules, with illustrations and examples. The topic is also discussed more briefly in March Chapter 6 (pages 282-284 in the 5<sup>th</sup> Ed.) I will provide a short précis of Baldwin's Rules here.

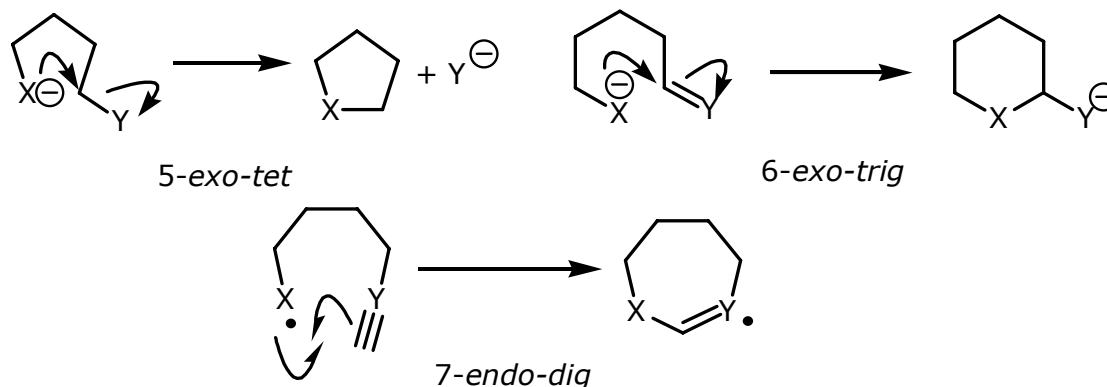
J.E. Baldwin developed his "rules" from an analysis of the outcomes of many reactions in his own laboratory and in the literature. The rules are generalizations of experimental observations and have no quantitative theoretical basis – except that they make sense in stereochemical terms when you look closely. They apply to nucleophilic, electrophilic (cationic) and radical ring-closing processes, and they describe the *kinetic* aspects of particular ring formation pathways. *They do not refer to the relative thermodynamic stability of the products.*

Baldwin noted that there were two basic situations in which ring-closure could occur, which he labeled *Exo* and *Endo*.



Notice that the flow of electrons moves outside the ring being formed in the *Exo* case, but moves within the ring in the *Endo* case. Although the illustration shows a nucleophilic reaction, the same idea applies to radical or electrophilic situations.

Baldwin also noted that the geometry of the acceptor atom was important, and he identified the possible situations as *tet*, *trig*, and *dig*, meaning *tetrahedral*, *trigonal*, and *digonal*. In the illustration above, the reactions are *Exo-trig* and *Endo-trig*. If the reaction was an  $S_N2$  displacement leading to ring closure, it would be *Exo-tet*. Finally, Baldwin added the size of the ring being formed, as a numerical prefix. The resulting terminology describes most ring-closing reactions quite compactly. In Smith you will find a chart showing the possibilities for forming 3-7 membered rings (Figure 6.2) – only a few are shown here.



With this nomenclature, Baldwin's Rules can be summarized very succinctly:

### 1. Tetrahedral (tet) systems

- a. Three to seven *exo-tet* are all favoured processes
- b. Five and six *endo-tet* are disfavoured processes

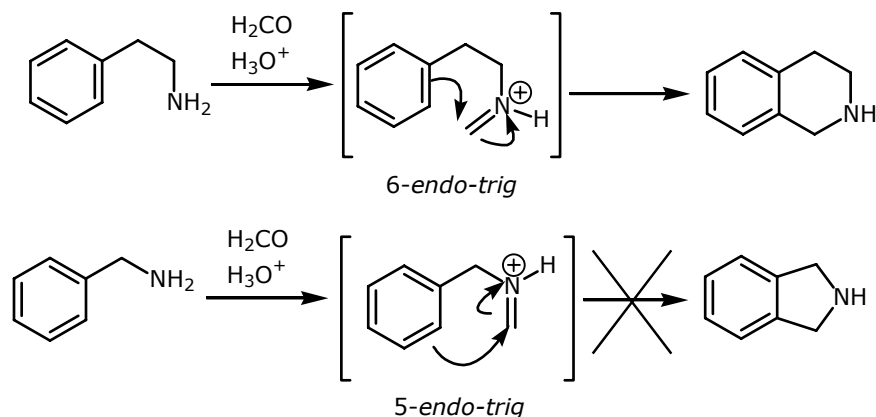
### 2. Trigonal (trig) systems

- a. Three to seven *exo-trig* are favoured
- b. Three to five *endo-trig* are disfavoured
- c. Six and seven *endo-trig* are favoured

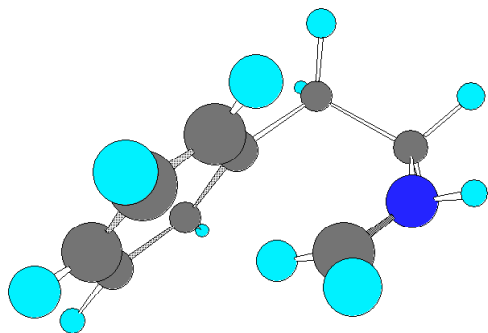
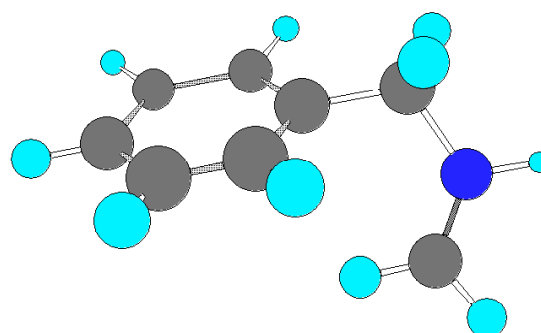
### 3. Digonal (dig) systems

- a. Three and four *exo-dig* are disfavoured
- b. Five to seven *exo-dig* are favoured
- c. Three to seven *endo-dig* are favoured

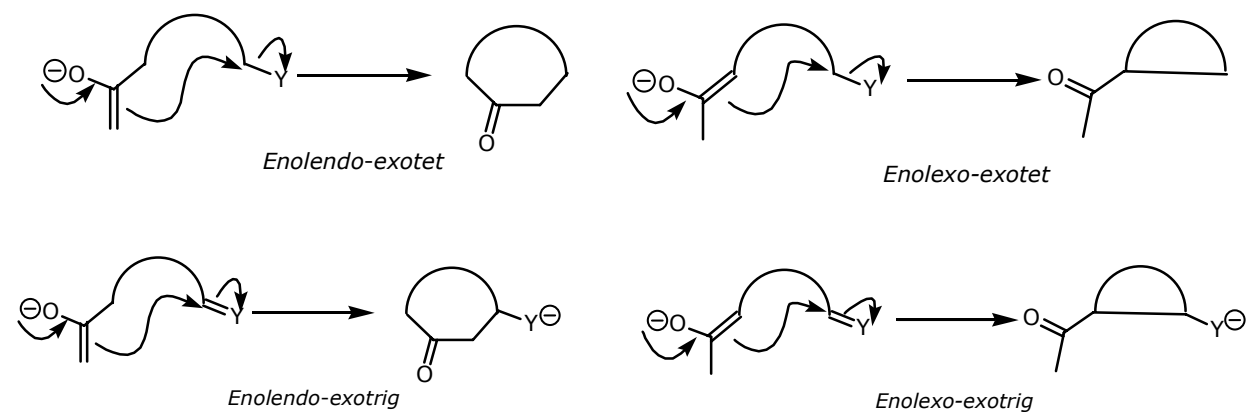
It is important to note that processes that are disfavoured are not necessarily impossible – but they are more difficult to achieve and usually proceed more slowly than favoured alternatives. The logical basis for these rules is found in considering the orbitals that would be involved in the reactions. We know that certain modes of approach give optimal orbital overlap, while other directions of approach may not permit any overlap at all. Since donor and acceptor fragments in a ring-closure are linked by a tether, their freedom to select their mode of interaction depends on the length of the chain between them. This can be seen in the following example, contrasting a favoured *6-endo-trig* cyclization with a disfavoured *5-endo-trig* analogue.



Since we know that approach to the electrophilic imminium ion will proceed best along the so-called Bürgi-Dunitz angle, perpendicular to the plane of the nuclei, it is not hard to understand why the smaller ring does not form easily by this route. A quick inspection of a molecular model will convince you that the aryl ring cannot use the Bürgi-Dunitz approach in the 5-endo-trig mode, but that the 6-endo-trig pathway is relatively easy to set up.

**6-Endo-Trig Cyclization - Favoured****5-Endo-Trig Cyclization - Disfavoured**

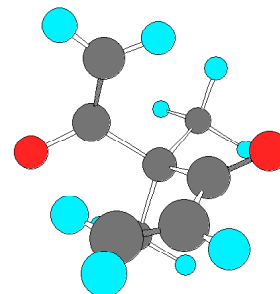
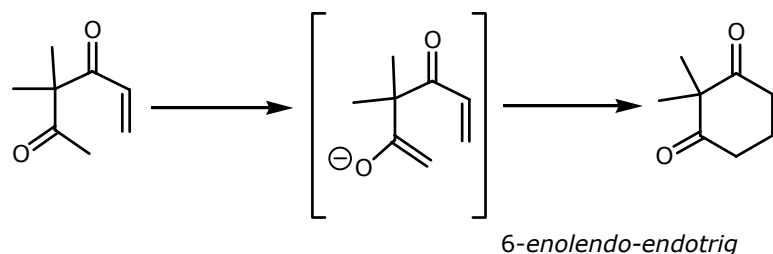
When enolate nucleophiles are the donors in ring-closure reactions, a modified set of Baldwin's Rules are employed, that take into account the more rigid geometry of the enolate and its own stereoelectronic preferences. The terminology is similar to that used for the standard set of rules, but it is additionally necessary to specify whether the enolate fragment becomes a part of the new ring (*enolendo*) or is an appendage to that ring (*enolexo*).



The additional rules for enolate ring closures of these types are:

1. Six and seven Enolendo-Exo-Tet reactions are favoured.
2. Three to five Enolendo-Exo-Tet are disfavoured.
3. Three to seven Enolexo-Exo-Tet are favoured.
4. Three to seven Enolexo-Exo-Trig reactions are favoured.
5. Six and seven Enolendo-Exo-Trig are favoured.
6. Three to five Enolendo-Exo-Trig are disfavoured.

Note that these rules do not address *endo-trig* situations, which could be imagined as viable ring-closure pathways on a purely mechanistic basis.



This particular example is not known in the literature. Note that in the “standard” Baldwin Rules, a *6-endo-trig* cyclization is favourable. Nevertheless, examination of molecular models suggests that this Michael cyclization is probably not favourable because the nucleophilic centre will have great difficulty approaching the  $\beta$ -carbon of the enone along the Bürgi-Dunitz angle. However, a larger system might well be able to cyclize by this pathway, so we could predict that perhaps a *7-* or *8-enolendo-endo-trig* closure might be a viable reaction.

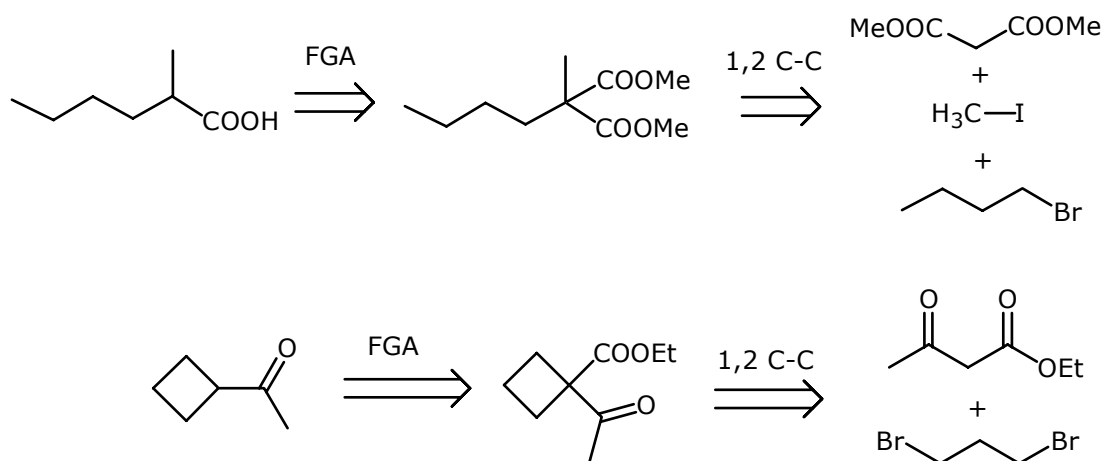
### Conclusion

What do Baldwin’s Rules mean for the design of a synthesis? If you are making rings in your synthesis, it would be wise to stick to “favoured” ring-closure reactions **unless** you have clear literature precedent suggesting that a “disfavoured” pathway is in fact accessible. Remember that these Rules are not absolute, and that “disfavoured” does not mean “forbidden”.

## Return to Chapter 24: Functional Group Addition

This is a very important idea, and one which is easy to miss. FGA refers to the conceptual installation of a functional group during the retrosynthetic analysis. This might at first seem counter-productive because instead of simplifying the molecular structure we are apparently making it more complicated. The goal here is to install a group whose presence creates the keying unit for a powerful simplifying retrosynthetic transform. In the forward (synthetic) direction the group is going to be removed, since it has no place in the target material, but it is necessary in a precursor to permit a key C-C bond forming reaction.

Note the examples in Warren, where target molecules that contain very little functionality are easily disconnected once a single additional functional group is added. The use of Friedel-Crafts acylation to install primary aliphatic chains on aryl rings should be a familiar idea from your introductory course. Viewed retrosynthetically this is an FGA-based strategy, as you can see from Warren's "Analysis 2" of target **47** (pages 205-207). The *malonic ester synthesis* and the *acetoacetic ester synthesis* are also implementations of FGA strategies.



## Chapter 25: 1,4-Difunctionalized Compounds

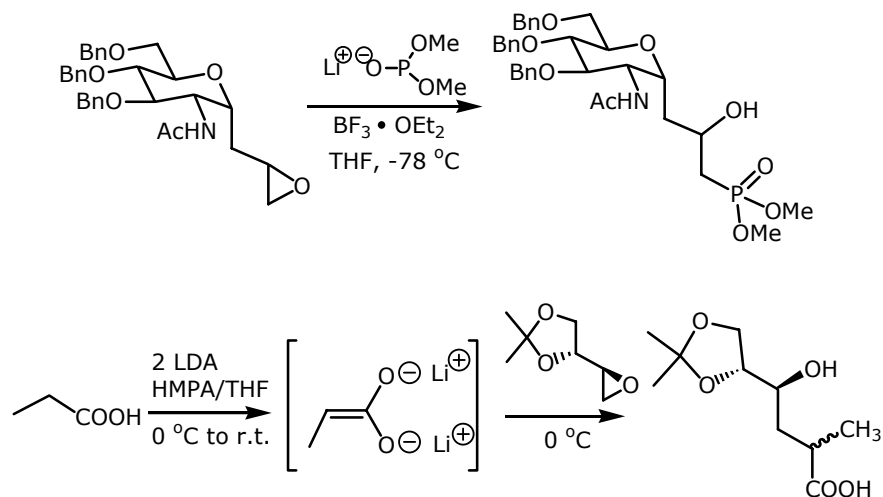
As functional groups get further apart, it becomes easier to overlook their relationships to one another. In the simple molecules that Warren presents, where there are only a couple of groups, the 1,4 relationship is pretty obvious, but in more complicated molecules you may have to look more closely. It helps to sit down with your target and make a table of all relationships for every functional group. Most of these relationships will have no significance for your retrosynthesis, but you will know that you have identified all your options by going through this process.

The chemistry in the first part of the chapter is quite straightforward. Note that there is an error in the top scheme on page 211, where structure **10** is one carbon too short.

### Page 211: Epoxide openings.

The example shown is a reasonable approach for the case at hand, but you might not want to stir some materials in alkaline solutions as suggested. If you need to open an epoxide under kinetic conditions at low temperatures, you may need a Lewis acid to help the reaction along. Two examples from my own research illustrate this type of reaction. Notice in the second case the use of a carboxylate *dianion*, rather than a conventional ester enolate. This was done because other

approaches failed to give the desired product, and addition of Lewis acids caused the epoxide to decompose.



### Page 212: Unnatural nucleophilic synthons

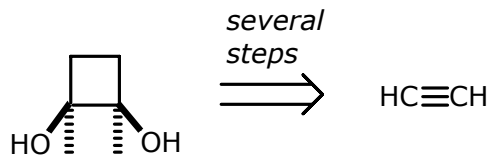
Note that the acyl anion equivalents we discussed earlier are also applicable in this situation. However, you should be aware that 1,3-dithiane anions generally do not add 1,4 to enones, favouring instead the 1,2 pathway.

### Page 214: Available starting materials

Think about the compounds shown in Table 25.1. This is by no means an exhaustive list of 1,4-difunctional compounds readily available, but these materials have all proven their value as synthetic starting compounds.

### Exercises:

1. Choose three compounds from Table 25.1. Starting with each of these, draw all the 3-step reaction sequences you can think of. Generic substructures are acceptable (e.g.  $\text{RMgX}$ ). How many different product structures can you come up with?
2. Suggest a route to prepare 1,2-dimethylcyclobutanediol from acetylene, using ideas from the last few chapters in Warren.



3. In Carey and Sundberg Vol. B, page 48, consult Problem #4. This problem asks you to disconnect complex polycyclic targets to precursors for an intramolecular enolate alkylation. Choose any two of these compounds. Identify the possible cyclizations of enolate precursors using the Baldwin nomenclature and choose the best option for a viable synthesis.