



# CHEMISTRY 4000

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Topic #5: The Basis for Planning  
Spring 2022  
Dr. Susan Findlay



# Bivalent Synthons

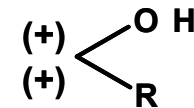
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- In addition to the monovalent synthons ( $a^1$ ,  $d^1$ ,  $a^2$ ,  $d^2$ ,  $a^3$ ,  $d^3$ , etc.), there is sometimes a need for bivalent synthons. In other words, a synthon may need to:
  - accept electrons at the same carbon twice,
  - donate electrons from the same carbon twice, or
  - accept one electron pair and donate one electron pair from the same carbon

We have already seen examples of the first two situations.

- In the textbook, Hoffmann uses two forms of notation when discussing these bivalent synthons.
  - For the synthons themselves, he writes species with two charges that clearly cannot actually exist.
  - He refers to the actual reagents corresponding to those synthons as bivalent conjunctive reagents.

# Bivalent Acceptor Synthons



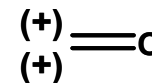
- As long as we want both nucleophiles to be the same, an ester or acid chloride is a conjunctive bivalent reagent corresponding to a bivalent  $a^1$  synthon when it is reacted with a Grignard or alkyllithium reagent.

- If  $R = H$ , the resulting alcohol can be oxidized to the corresponding ketone, if desired.



# Bivalent Acceptor Synthons

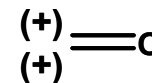
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- Alternatively, an aldehyde could be viewed as a bivalent conjunctive reagent allowing use of two different nucleophiles. The only catch is that it requires oxidation after addition of the first nucleophile.



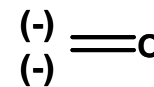
# Bivalent Acceptor Synthons



- Another method to add two different nucleophiles to a C=O is to use two different leaving groups with different reactivity.
- A chlorothioester corresponds to a bivalent a<sup>1</sup> synthon. In the paper referenced by the text, the first nucleophile (a Grignard) is coupled using a Ni<sup>2+</sup> catalyst and only displaces -Cl. The second nucleophile (also a Grignard) is coupled using a Fe<sup>3+</sup> catalyst, displacing -SPh.

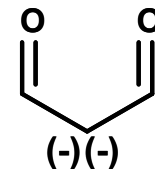


# Bivalent Donor Synthons



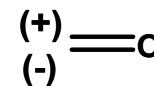
- 1,3-Dithiane can act as a bivalent d<sup>1</sup> synthon since it can be deprotonated, reacted with an electrophile, deprotonated again then reacted with another electrophile:
  
- 1,3-Dithiane can be prepared from a formaldehyde source and 1,3-propanedithiol (or it can be purchased directly):
  
- We saw two different ways to cleave dithiane in the last chapter. 6

# Bivalent Donor Synthons



- Any  $\beta$  dicarbonyl compound can act as a bivalent  $d^2$  synthon.
- Either (or both) carbonyl can be replaced by a nitrile since nitriles stabilize  $\alpha$  anions in much the same way as carbonyl groups do.
- If one of the two  $C=X$  groups is an ester or nitrile, it can be hydrolyzed to the carboxylic acid then removed by decarboxylation.

# Bivalent Donor-Acceptor Synthons



- Having the same reagent correspond to both a<sup>1</sup> and d<sup>1</sup> synthon presents a challenge. We cannot, for example, deprotonate the hydrogen of an aldehyde. We can, however, deprotonate HCN to give the cyanide anion (corresponds to d<sup>1</sup> synthon) then, after reaction with an electrophile, use the nitrile group as an electrophile (corresponds to a<sup>1</sup> synthon).

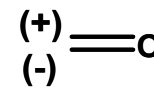
- Hydrolysis gives the ketone, if desired.





# Bivalent Donor-Acceptor Synthons

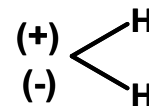
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- In fact, we could actually use the cyanide anion as a trivalent synthon – d<sup>1</sup> once then a<sup>1</sup> twice!



# Bivalent Donor-Acceptor Synthons



- Recall the juvenile moth hormone synthesis from the last chapter...





# Bivalent Donor-Acceptor Synthons

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