Prof Ben Davis

THIRD YEAR ORGANIC CHEMISTRY - REVISION COURSE Lecture 3

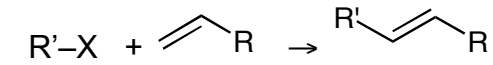
MOLECULAR REACTIVITY: TRANSITION METAL-MEDIATED PROCESSES

Books:**Tsuji *Palladium Reagents & Catalysts* Wiley 2004** and **van Leeuwen *Homogenous Catalysis* Kluwer 2004**

1. Pd(0)-Catalysed Reactions (X=OTf or Hal; Ar=aryl; Y=O or NH; L = leaving group)

These have common key steps that you should know Oxidative Addition (**O**), Insertion (**I**), β-elimination (**BE**), Reductive elimination (**RE**), Transmetallation (**T**) *See lecture notes for details*.

Heck *Pd(0) source plus base*



Mechanistic order: **O** then **I** then **internal rotation** then syn-**BE** then **RE**

Suzuki *Pd(0) source plus base*

$R'–X + R–B(OH)_2 \rightarrow R–R'$

Mechanistic order: **O** then **T** then **trans-cis isomerisation** then cis-**RE**

Stille *Pd(0) source*

$R'–X + R–SnR''_3 \rightarrow R–R'$

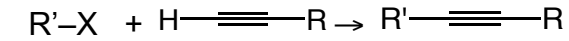
Mechanistic order: **O** then **T** then **trans-cis isomerisation** then cis-**RE**

Hiyama *Pd(0) source plus Bu_4NF*

$R'–X + R–SiF_3 \rightarrow R–R'$

Mechanistic order: **O** then **T** (of Si 'ate') then **trans-cis isomerisation** then cis-**RE**

Sonogashira *Pd(0) source plus Cu(I) source plus base (copper alkyne ensues)*



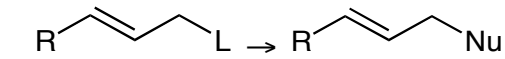
Mechanistic order: **O** then **T** (with Cu alkyne) then **trans-cis isomerisation** then cis-**RE**

Buchwald-Hartwig *Pd(0) source plus base*

$Ar–X + R–YH \rightarrow Ar–Y–R$

Mechanistic order: **O** then **ligand exchange** (cf **I**) the **RE**

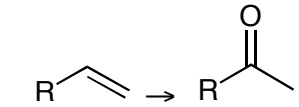
Tsuji-Trost Π-allyl substitutions *Pd(0) & Nu–H*



Mechanistic order: **Double displacement via η^3-Pd intermediate**

2. Pd(II)-mediated reactions

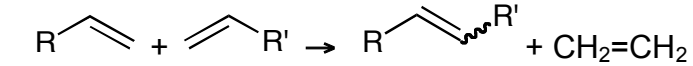
Wacker Pd(II) plus water



Mechanistic order: **I** with **concerted nucleophilic attack by water** then **BE** then **enol-keto tautomerism**

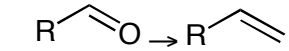
3. Metalloid Carbenes

Olefin Metathesis *L_nM=CH–R Grubbs catalysts (type 1,2) **Ru**; Grubbs-Hoveyda **Ru**; Schrock **Mo***



Mechanistic order: **[2+2]** then **retro[2+2]** then **[2+2]** then **retro[2+2]**

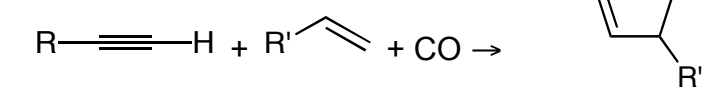
Tebbe $Cp_2Ti(CH_2)ClAlMe_2$



Mechanistic order: **retro[2+2]** then **[2+2]** then **retro[2+2]**

4. Co Mediated Reactions

Pauson-Khand *$Co(CO)_8$ + CO*



Mechanistic order: **Ligand exchange x 2 (alkyne coordination)** then **O** then **I** (alkene) then **I** (CO) then **migration** then **RE**

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MOLECULAR REACTIVITY 2: PROTECTING GROUPS IN ORGANIC SYNTHESIS

Books: J. Robertson OCP 95 - *top*

The need for protection.

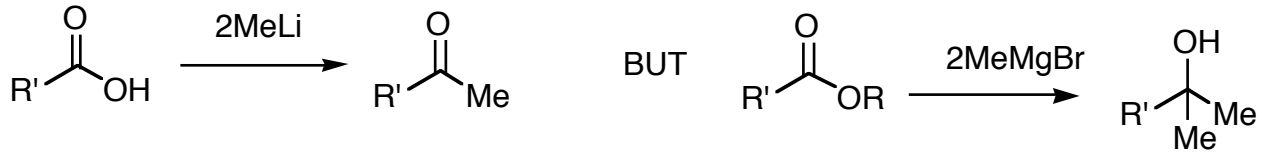
Modern synthetic chemistry is a beautiful craft. This is helped by

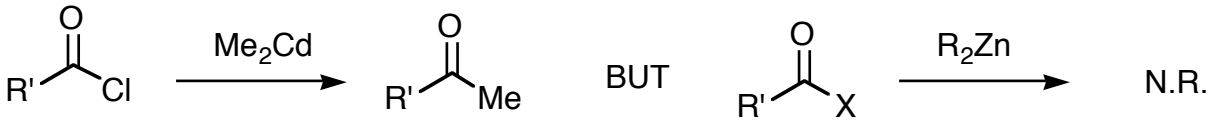
- existence of a wide range of synthetic methods
- availability of a wide range of reagents and starting materials
- usefulness of strategic planning ("retrosynthetic analysis") for the establishment of tactics to enable:
  - * the construction of the molecular skeleton
  - * the establishment of stereochemistry
  - * the introduction of the required functionality

But, chemoselectivity is a key problem with many reactions in synthetic chemistry. Reagent control is not perfect, and any given reagent will often attack a variety of functional groups, giving different products.

Useful examples of chemoselectivity:

A) *Organometallic Additions*

i) 

ii) 

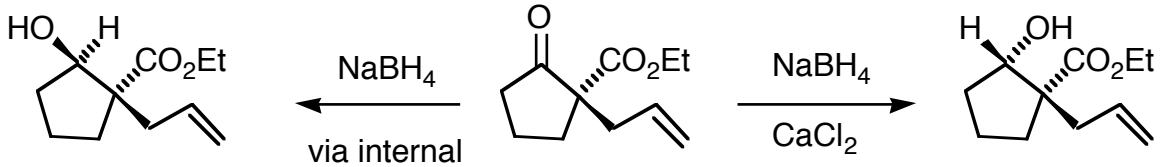
iii) RC(O)OLi ----------> RC(O)R' using $RLi/CeCl_3$

$CeCl_3$ suppresses enolisation of lithium carboxylate, and increases the rate of nucleophilic addition.

B*) Chemoselective Reductions*

$ZnBH_4$ selectively reduces aldehydes over ketones
ketones over enones
aliphatic esters over aromatic esters

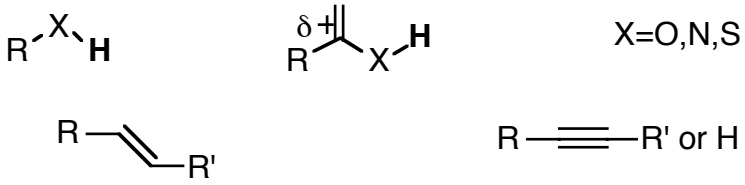
C) *Diastereoselective Reductions*



• The conflicting demands of the starting materials, reagents and the reaction to be performed often mean that recourse to the blocking of reactive functionality is required.
• Emil Fischer was the first to recognise that otherwise reactive groups could be temporarily rendered inert by suitable modification.
• We need to block reactivity at sites where reaction would be unwanted, and this is done with protecting groups, which are introduced temporarily and later removed (but this approach is unsatisfactory in so far as it adds 2 steps per protection to a synthetic scheme – *so the ON & OFF steps need to be efficient*).

Properties That Require Blocking

Groups typically require blocking if they are acidic, electrophilic or nucleophilic, or easily oxidised.



Properties of protecting groups.

An ideal protecting group has the following properties:

* It must be introduced selectively in the first instance in high yield, using reagents which are readily available, stable and easily handled;

* It must be stable to a wide range of reaction conditions;

* It must be readily removed by a specific, mild reagent, to regenerate the starting functional group;

* It must itself possess a minimum of functionality to avoid the possibility of side reactions;

* It must be achiral, in order to avoid the formation of diastereomers;

* It must confer solubility, and facilitate purification;

* It must stabilise the whole molecule (e.g. supress racemisation or epimerisation);

* Participation of the protecting group in any reaction should be either complete or absent.

Of course, few protecting groups meet all of these criteria, although it is not always necessary for them to do so, and generally a compromise must be found.

Strategies For Protection

1. *None* This could be achieved with selective reagents (so called **Reagent Control**), but is limited by the availability of such reagents. The next best thing is the use of transient protection.

2. *Substrate Control* - use of steric bulk to block reactivity;
   - use of chelation control;
   - use of negative electron density to repel reagents e.g. *via* dianions.

3. *Multiple protection*
   - Orthogonal Protection (a set of PG whose removal can be accomplished in any order with reagents and conditions which do not affect other PG);
   - Graded Protection (deprotection relies upon differences in relative rates of reaction of various PG under the same reaction conditions);
   - Uniform Protection (use of PG which are all removed under the same conditions)
   - Convert protecting groups to other functionality

4. Protecting groups which block more than one functional group.

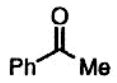
Types of protecting groups (by method of cleavage)

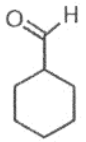
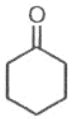
- acid labile
- base labile
- hydrogenolytically labile
  * H_2 and catalyst
  * catalytic transfer hydrogenation ($NH_4^+HCOO^-$) and catalyst;
- other conditions -
  * Reductive - Zn/HOAc;
  * S_N2-type cleavage - $PhSe^-$, Nu^-; F^-
  * Organometallic - Pd(0);
  * Lewis acid -$ZnCl_2$.
  * Oxidative
  * Photolytic

Protecting groups for a variety of functional groups

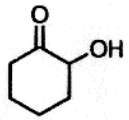
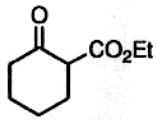
- heteroatom functional groups, i.e. ROH, carboxylic acid and derivatives, RNH_2 and RSH
- carbonyls
- unsaturated carbon-carbon bonds
- α-methylene groups of ketones
- phosphate.

3. Describe,with mechanisms, methods available for the direct synthesis of aldehydes and ketones which involve the formation of a new carbon-carbon bond at the carbonyl carbon atom. You may use some or all of the following to exemplify your answer **[20]**.

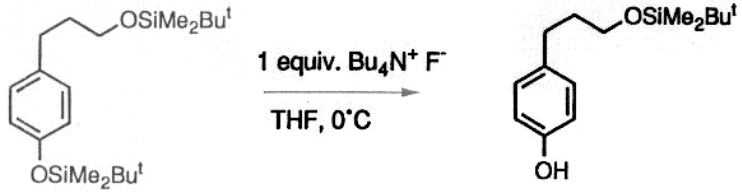
(a)  [from $PhCO_2H$, PhCOCl, PhCN, $PhCONMe_2$, PhNC, PhCON(Me)(OMe) and $PhCH_2NO_2$]

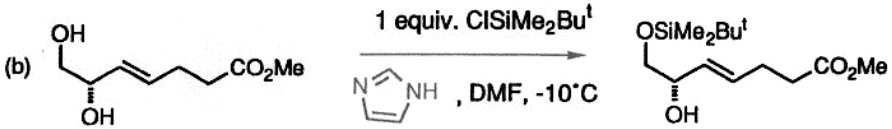
(b)  from 

(c) $PhCH_2CHO$ from $PhCH_2Br$

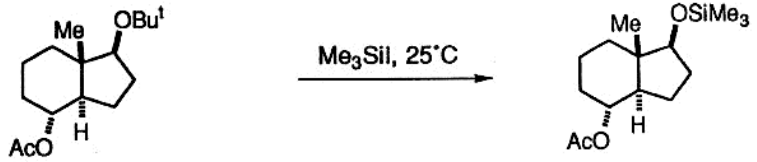
(d)  and  from acyclic precursors

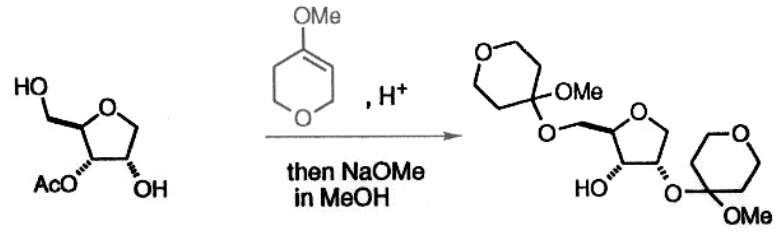
4. Show how functional groups containing oxygen may be selectively protected or deprotected, using **five** of the following to exemplify your answer **[5 x 4]**:

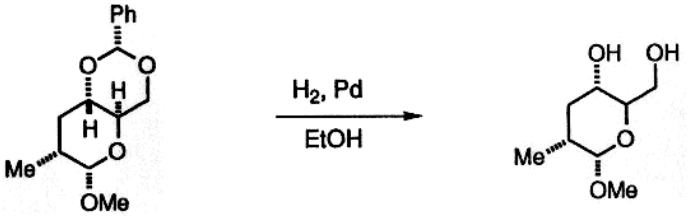
(a) 

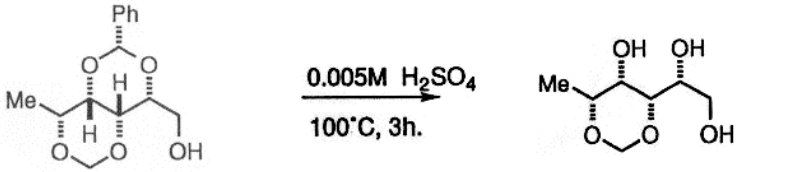
(b) 

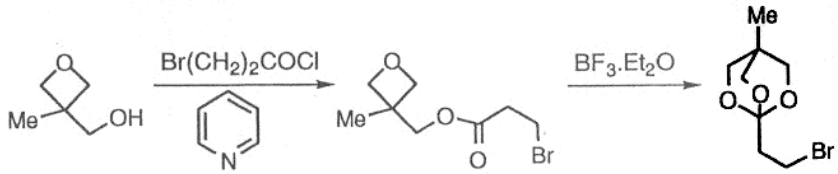
4. (continued)

(c) 

(d) 

(e) 

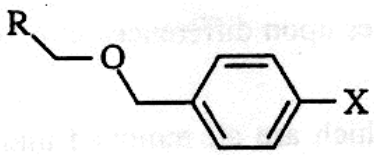
(f) 

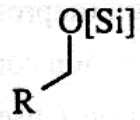
(g) 

2. Discuss critically the use of protecting groups in the chemistry of alcohols and amines. Your answer should include the following classes of protecting groups as well as examples of your own.

[20 marks]

(a)

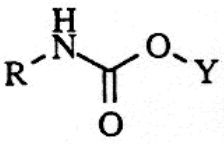




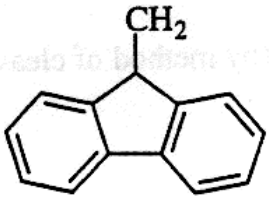
[Si] = Me_3Si
or t-$BuMe_2Si$
or t-$BuPh_2Si$

X = H or OMe

(b)



Y =



or $PhCH_2$
or CH_2=$CHCH_2$
or t-Bu