Drug synthesis

Ulf Ellervik
Organic Chemistry
Lund University
Lecturer: Martin Johansson 0708-678687
Martin.johansson@organic.lu.se
Organisk kemi, Sekretariat 046-2228210


• Molecular models are allowed during examination

Examination: • Written examination in two parts
  Part 1: no literature allowed
  Part 2: one advanced and one basic organic chemistry textbook allowed

Repetition: • the exam in the basic organic chemistry course can be found at:

  http://www.organic.lu.se/Education/Kemiteknik/OrganAK/OrganAK.html

  • do the exam and repeat any weak topics

Directions
The course is defined by the textbook. Some name reactions (see list below) are important and will be examined during the first part of the examination (name to mechanism and mechanism to name).

Name reactions:
Baeyer-Villiger oxidation*                         Knoevenagel condensation
Beckmann rearrangement                           Kolbe reaction*
Birch reduction*                                 Mannich reaction
Claisen condensation*                            Michael reaction*
Claisen rearrangement                            Mitsunobu reaction
Claisen-Schmidt reaction*                        Mukaiyama reaction
Clemmensen reduction                            Peterson reaction
Cope rearrangement                              Pummerer reaction
Curtius rearrangement                            Reformatsky reaction*
Dieckmann condensation*                         Robinson annulation*
Diels-Alder reaction*                           Sandmeyer reaction*
Favorski rearrangement                          Sharpless epoxidation
Fisher esterification*                          Stille reaction
Friedel-Crafts acylation*                        Swern oxidation
Friedel-Crafts alkylation*                       Williamson’s ether synthesis*
Grignard reaction*                              Wittig reaction*
Heck reaction                                  Wolf-Kishner reduction
Horner-Wittig reaction

(* basic organic chemistry)
Schedule:
Mondays: 8-10
Wednesdays: 10-12
Thursdays: 8-10
Fridays: 10-12

Mon 22/10 8-10 L1 K:R Introduction, Chap 4 Molecular orbital theory
Wed 24/10 10-12 L2 K:N Chap 5, 7, 13, 16. Basic concepts
Thu 25/10 8-10 L3 K:N Chap 6, 12, 14. Addition to carbonyl
Fri 26/10 10-12 L4 K:K1, K:K2 Chap 6, 12, 14. Addition to carbonyl

Tue 30/10 (Obs) 8-10 E1 K:G Exercise 1. Carbonylgroup

Ons 31/10 10-12 L5 K:N Chap 21, 26, 27, 28, 29. Enolate chemistry
Thu 2/11 8-10 L6 K:N Chap 21, 26, 27, 28, 29. Enolate chemistry
Fri 2/11 10-12 L7 K:B Chap 21, 26, 27, 28, 29. Enolate chemistry

Mon 5/11 8-10 E2 K:F Exercise 2. Enolate chemistry
Thu 8/11 8-10 L9 K:N Chap 23. Addition to double bonds

Mon 12/11 8-10 E3 K:F Exercise 3. Addition to doublebonds, reduction.
Thu 15/11 8-10 L12 K:N Chap 35, 36. Pericyclic reactions
Fri 16/11 10-12 L13 K:B Chap 35, 36. Pericyclic reactions

Mon 19/11 8-10 E4 K:F Exercise 4. Pericyclic reactions
Wed 21/11 10-12 L14 K:N Chap 9. Organometallic chemistry I: Mg, Li, etc
Thu 22/11 8-10 L15 K:N Chap 48. Organometallic chemistry II: Cu, Ni, Pd etc
Fri 23/11 10-12 L16 Cancelled due to dissertation

Mon 26/11 8-10 L17 K:F Chap 47. Borane, silicon and tin chemistry
Wed 28/11 10-12 E5 K:N Exercise 5. Organometallic chemistry incl borane, silicon and tin
Thu 29/12 8-10 L18 K:N Chap 39, 40. Reactive intermediates (radicals and carbenes)
Fri 30/11 10-12 L19 K:B Chap 22, 43, 44. Aromatic substitution and heterocyclic chemistry

Mon 3/12 8-10 L20 K:F Chap 24. Oxidation
Thu 6/12 8-10 L21 K:N Review of exam 2006-12-13
Fri 7/12 10-12 K:B Conclusion, total synthesis

Wed 17/12 8-13 Examination. K:K1, K:K2
Exercise 1 (Wednesday, Oct 31), The carbonyl group Chapters 6, 12, 14 and 34

**Goals:** You should be able to
- find suitable reagents for reactions with the carbonyl group and nucleophilic substitutions
- predict the stereochemical outcome of carbonyladdition reactions
- use retrosynthetic transformations including the carbonyl group

Problems:

1.1 Clayden: Chapter 14. Problem 4

2.2 Clayden: Chapter 14. Problem 8

2.3 Show the products of the following reductions

\[
\begin{align*}
\text{a)} & \quad \text{NaBH}_4 \\
\text{b)} & \quad \text{1) } \text{HNEt}_2 \\
& \quad \text{2) pH 5, NaCNBH}_3 \\
\text{c)} & \quad \text{BH}_3
\end{align*}
\]

2.4 Predict the stereochemical outcome of the following reductions

\[
\begin{align*}
\text{a)} & \quad \text{LiAlH}_4 \\
\text{b)} & \quad \text{Zn(BH}_4)_2 \\
\text{c)} & \quad \text{NaBH}_4 \\
\text{d)} & \quad \text{Zn(BH}_4)_2
\end{align*}
\]

2.5 Clayden: Chapter 34. Problem 8
Exercise 2 (Monday, Nov 5), Enolates Chapters 21, 26, 27, 28 and 29

Goals: You should be able to
• determine the most acidic proton in a compound
• determine the kinetic and thermodynamic enolate
• give suitable reagents to direct a reaction towards any enolate
• use enolates to build new compounds by nucleophilic substitutions
• use retrosynthetic analysis for enolates

2.1 Arrange these compounds in order of decreasing acidity:

2.2 Clayden: Chapter 21. Problem 9

2.3 Draw the possible enolates of these compounds and indicate which one will be favored in a kinetically controlled deprotonation.

2.4 Clayden: Chapter 26. Problem 5

2.4 Give reaction conditions for the following transformation (more than one step is necessary).

2.5 Compound A can be condensed with benzaldehyde to give compound B. Give reaction conditions that will ensure that compound B is formed in excess. Discuss all aspects of regioselectivity and stereoselectivity.

2.6 Clayden: Chapter 27. Problem 4

2.7 Clayden: Chapter 28. Problem 10

2.8 Clayden: Chapter 29. Problem 7
Goals: You should be able to
• use reductions (including electrophilic and nucleophilic hydride reagents as well as hydrogenations) in your synthetic planning
• predict the stereo- and regiochemical outcome of reductions
• use retrosynthetic transformations including reductions

3.1 Clayden: Chapter 31. Problem 2

3.2 Clayden: Chapter 31. Problem 6

3.3 The compound below was treated with BH$_3$ in THF and then lactonized using acid. Does the name of the product start with (R) or (S)? Explain.

3.4 Propose a synthetic pathway for the molecule shown below using starting material containing maximum six carbon atoms. Show your synthetic planning.

3.5 Clayden: Chapter 23. Problem 7

3.6 Clayden: Chapter 24. Problem 1

3.7 Clayden: Chapter 30. Problem 10
Exercise 4 (Monday, Nov 19), Pericyclic reactions

Goals: You should be able to
- identify different pericyclic reactions
- predict the outcome of pericyclic reactions
- plan syntheses using pericyclic reactions

4.1 Classify the following pericyclic reactions as cycloadditions, electrocyclic reactions, sigmatropic rearrangements or ene-reactions.

a) ![Image of reaction a)](attachment:image1.png)

b) ![Image of reaction b)](attachment:image2.png)

c) ![Image of reaction c)](attachment:image3.png)

d) ![Image of reaction d)](attachment:image4.png)

e) ![Image of reaction e)](attachment:image5.png)

f) ![Image of reaction f)](attachment:image6.png)

g) ![Image of reaction g)](attachment:image7.png)

h) ![Image of reaction h)](attachment:image8.png)

i) ![Image of reaction i)](attachment:image9.png)

j) ![Image of reaction j)](attachment:image10.png)
4.2 Endiandric acids are natural products isolated from an Australian plant (cf. figure below). The endiandric acids are supposed to be formed from the common precursor A.

![Diagram of precursor reactions]

a) Endiandric acids D and E are both formed from precursor A via precursor B in two consecutive electrocyclic reactions. Show these two reactions and give a detailed explanation to the stereochemical outcome.

b) Endiandric acid A is then formed from endiandric acid E in another pericyclic reaction. Which reaction? Show the stereochemistry of the four new stereocenters in endiandric acid.

4.3 Citral is a key intermediate in the synthesis of vitamin A. BASF manufacture citral by the remarkable three-step synthesis shown below. Show the structure of compounds A and B and the mechanisms of the pericyclic reactions.

![Diagram of citral synthesis]

4.4 The body needs sunlight to produce vitamin D. The reason is actually the electrocyclic reaction shown below. Show the reaction mechanism and clearly indicate the stereochemistry of the carbon atom marked with a bullet.

![Diagram of vitamin D synthesis]

4.5 The reaction shown below was presented at a dissertation at Lund University. Present a reasonable mechanism for this reaction.
4.6 A marine brown algae uses a pheromone to attract males. The active pheromone (shown below) is deactivated, with a half-life of a few minutes, to ectocarpene. Show the mechanism for this deactivation. What is the driving force for this reaction?

![Active Pheromone to Ectocarpene](image)

4.7 Compound A below was synthesized in order to be used in an intramolecular Diels-Alder reaction. However, the expected compound B was not formed. Instead compound C was formed. The reason was a [1,5]-sigmatropic shift of the starting material and then a Diels-Alder reaction. Show the mechanisms for the synthesis of C.

![Synthesis of Compound C](image)

4.8 Show how you synthesize the compound below from phenol using at least one pericyclic reaction.

![Synthesis of Compound](image)

4.9 Propose a synthetic pathway for each of the two molecules shown below using the powerful Diels-Alder disconnection. Show your synthetic planning.

![Synthetic Planning](image)
Exercise 5 (Monday, Nov 26), Metals, boron, silicon and tin. Chapters 9, 47, 48

**Goals:** You should be able to
- use organometallic reagents
- use boron and silicon reagents
- predict the stereo- and regiochemical outcome of reactions involving Grignard and lithiumorganic reagents

5.1 Show the products of the following reactions

a) \[ \text{LiCu(CH=CH}_2\text{)}_2 \rightarrow \text{Cu(I)} \]

b) \[ \text{MgBr} \rightarrow 1) \text{tBuLi, -120°C} \]

2) benzaldehyde

i) \[ \text{EtMgBr} \rightarrow \text{Pd(PPPh}_3\text{)}_4 \]

j) \[ \text{(tBuCuCN)Li} \]

k) \[ \text{Pd(OAc)_2} \rightarrow \text{Ph}_3\text{P, Et}_3\text{N} \]

l) \[ \text{Pd(PPPh}_3\text{)}_4 \rightarrow \text{Ph}_3\text{P, Et}_3\text{N} \]

5.2 Show how you perform the following reactions using boron chemistry

a)  

b)  

c)  

d)  
5.3 Reduction of compound A (*cf.* figure below) using LiAlH$_4$ gives a 3:1 mixture of compounds B and C. Show the structure of compound B and explain why this compound is formed in excess.

\[
\begin{align*}
\text{A} &\xrightarrow{\text{LiAlH}_4} \text{B} + \text{C} \\
\text{D} &\xrightarrow{\text{EtMgBr}} \text{B} + \text{C}
\end{align*}
\]

Reaction of the aldehyde D with EtMgBr gives a 1:3 mixture of B and C. Explain why.

How would the stereochemical outcome of the Grignard reaction be changed if the methyl group in D was exchanged for a methoxy group?

5.4 Clayden Chapter 47, Problem 14

5.5 Clayden Chapter 47, Problem 11

5.6 Explain the role of TMSCl in the following reaction

\[
\begin{align*}
\text{H} &\xrightarrow{1) \text{BuLi}} \text{O} \\
\text{H} &\xrightarrow{2) \text{TMSCl}} \text{O} \\
\text{H} &\xrightarrow{3) \text{acetyl chloride, AlCl}_3}
\end{align*}
\]

5.7 Clayden Chapter 48, Problem 6

5.8 Clayden Chapter 48, Problem 14
Exercise 6 (Wednesday, Dec 5), Intermediates, aromatic substitution, oxidation. Chapters 23, 24, 39, 40, 43, 44,

Goals: You should be able to
• use reactive intermediates such as carbocations, carbenes and radicals for synthetic purposes
• use a large variety of reagents for oxidations
• plan multistep synthesis of aromatic structures
• design the synthesis of advanced organic structures

6.1 Clayden Chapter 23, Problem 7
6.2 Clayden Chapter 43, Problem 2
6.3 Clayden Chapter 43, Problem 13
6.4 Clayden Chapter 44, Problem 1
6.5 Clayden Chapter 44, Problem 6
6.6 Clayden Chapter 39, Problem 10
6.7 Clayden Chapter 40, Problem 3
6.8 Clayden Chapter 40, Problem 11
6.9 Show the products in the following oxidations

\[
\begin{align*}
&a) \quad \text{CH}_3\text{COOH} \\
&b) \quad (+)-\text{diisopropyl tartrate} \\
&c) \quad \text{mCPBA} \\
&d) \quad 1) \text{OsO}_4, 2) \text{NaIO}_4 \\
&e) \quad \text{SeO}_2, \text{HOAc} \\
&f) \quad \text{mCPBA} \\
&g) \quad \text{NaIO}_4 \\
&h) \quad 1) \text{O}_3, -70^\circ\text{C}, 2) \text{H}_2\text{O}_2, \text{AcOH}
\end{align*}
\]
Summary

Retrosynthetic analysis

Transforms
- disconnection
- connection
- functional group interconversion (FGI)
- functional group removal (FGR)
- functional group transposition (FGT)
- functional group addition (FGA)
- rearrangement

Tactics
- α-hydroxycarbonyl compounds
- 1,3-dicarbonyl compounds
- 1,4-dicarbonyl compounds
- 1,5-dicarbonyl compounds
- 1,6-dicarbonyl compounds
- 4-ring system
- 5-ring system
- 6-ring system
- large ring system
- polycyclic system
HSAB - hard-soft acid-base

<table>
<thead>
<tr>
<th>acid</th>
<th>base</th>
</tr>
</thead>
<tbody>
<tr>
<td>hard</td>
<td>NH₃, H₂O, HO⁻, RNH₂</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>ROH, RO², R₂O</td>
</tr>
<tr>
<td>BF₃, AlCl₃, AlH₃</td>
<td>AcO⁻, F⁻</td>
</tr>
<tr>
<td>CO₂</td>
<td></td>
</tr>
<tr>
<td>borderline</td>
<td>Fe²⁺, Ni²⁺, Co²⁺</td>
</tr>
<tr>
<td>Cu²⁺</td>
<td>Cl⁻, Br⁻, N₃⁻</td>
</tr>
<tr>
<td>soft</td>
<td>H²⁺, R₂⁻, CN⁻, CO</td>
</tr>
<tr>
<td>Pd²⁺, Cu⁺, Ag⁺</td>
<td>R₃P, RSH, RS⁻</td>
</tr>
<tr>
<td>Hg²⁺, Hg⁺</td>
<td>I⁻</td>
</tr>
<tr>
<td>Br⁺, I⁻</td>
<td>metal atoms</td>
</tr>
</tbody>
</table>

Stereo- and regioselectivity in aldol reactions

1) Formation of the enolate

kinetic control gives the least hindered enolate
• use strong base (LDA)
• use a hindered base
• use aprotic solvent
• use lithium as counter ion
• use excess base
• low temperature (−78°C)

thermodynamic control gives the more substituted enolate
• use weak base (Et₃N)
• use a less hindered base
• use excess ketone
• room temperature

2) The aldol reaction

use kinetic control:
• the Z-enolate is usually formed
• the stereoselectivity is directed by a chair-like transition state
• the aldehyde prefers a pseudoequatorial orientation

• Z usually gives syn
• E usually gives anti
• Z usually gives better selectivity
• bulky substituents give better selectivity
• boron-enolates give better selectivity
Stereoselectivity in nucleophilic attack on the carbonyl group

- Use a Felkin-Anh model:
  - Order the three different groups in the chiral α-position after size: small (S), medium (M) and large (L)
  - View the Newman projection
  - Arrange the three groups so that the large group is perpendicular to the carbonyl group
  - The attack will come from the least hindered position

- Cram's rule: old rule that usually gives the right result but sometimes not. Avoid!

- Bürgi-Dunitz angle: the angle of attack, 107° from the carbonyl group
Pericyclic reactions

1) Cycloadditions ($\Delta\sigma = \pm 2$)
• Two new $\sigma$-bonds are formed or broken

\[ \begin{array}{c}
\text{Diels-Alder [4+2]} \\
\text{1,3-dipolar cycloadditions}
\end{array} \]

- X should be EDG (-alkyl, -aryl, -O-alkyl)
- Z should be EWG (-CHO, -COOH, -CN)
- It usually gives "ortho" and "para" products
- EWG on dienophile usually results in endo-product
- Catalyzed by Lewis acids

2) Sigmatropic rearrangements ($\Delta\sigma = 0$)
• One new $\sigma$-bond is formed while another is broken

\[ \begin{array}{c}
\text{Cope [3,3]} \\
\text{Oxy-Cope [3,3]} \\
\text{Claisen [3,3]}
\end{array} \]

- $i, j$ - number of atoms that migrates,
  - $j$ - number of atoms in the $\pi$-system

3) Electrocyclic reactions ($\Delta\sigma = \pm 1$)
• One new $\sigma$-bond is formed or broken

- All electrocyclic reactions are allowed

4) Ene-reactions
• One new $\sigma$-bond is formed while a hydrogen migrates
  • Similar to the Diels-Alder reaction
Organometallic chemistry

Transition metals want 18 (or 16) electrons in the outer shell

<table>
<thead>
<tr>
<th>ligands</th>
<th>formal charge</th>
<th>electrons donated</th>
</tr>
</thead>
<tbody>
<tr>
<td>anionic ligands</td>
<td>-1</td>
<td>2</td>
</tr>
<tr>
<td>(Cl(^{2-}), Br(^{2-}), CN(^{-}), RO(^{2-})alkyl(^{2-}))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neutral (\sigma)-donor ligands</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>(PH(_3), R(_2)N, R(_2)O, R(_2)S, CO, RCN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aryl, (\alpha)-allyl</td>
<td>-1</td>
<td>2</td>
</tr>
<tr>
<td>olefins</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>(\alpha)-allyl cation</td>
<td>+1</td>
<td>2</td>
</tr>
<tr>
<td>conjugated dienes</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>cyclopentadienyl</td>
<td>-1</td>
<td>6</td>
</tr>
<tr>
<td>arenes</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>cyclooctatetraene</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

number of valence electrons

<table>
<thead>
<tr>
<th>number of valence electrons</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transition metals</th>
</tr>
</thead>
<tbody>
<tr>
<td>3d</td>
</tr>
<tr>
<td>Ti</td>
</tr>
<tr>
<td>Cr</td>
</tr>
<tr>
<td>Mn</td>
</tr>
<tr>
<td>Fe</td>
</tr>
<tr>
<td>Co</td>
</tr>
<tr>
<td>Ni</td>
</tr>
<tr>
<td>Cu</td>
</tr>
<tr>
<td>4d</td>
</tr>
<tr>
<td>Zr</td>
</tr>
<tr>
<td>Mo</td>
</tr>
<tr>
<td>Ru</td>
</tr>
<tr>
<td>Rh</td>
</tr>
<tr>
<td>Pd</td>
</tr>
<tr>
<td>5d</td>
</tr>
<tr>
<td>W</td>
</tr>
<tr>
<td>Os</td>
</tr>
<tr>
<td>Pt</td>
</tr>
</tbody>
</table>

\[ R^1: \text{M} \Rightarrow \text{M} = \text{Na}, \text{K} \]
\[ R^1: \text{M} \Rightarrow \text{M} = \text{Mg}, \text{Li}, \text{Zn}, \text{Cu} \]
\[ R^1: \text{M} \Rightarrow \text{M} = \text{Pb}, \text{Hg}, \text{Sn} \]

**Reactions:**
- **Oxidative addition**
  - \(M(0) + X-Y \xrightarrow{\text{oxid. add.}} X-M(II) \xrightarrow{Y} XM-Y \)
- **Reductive elimination**
  - \(X-M(II) \xrightarrow{\text{red. elim.}} M(0) + X-Y \)
- **Migratory insertion**
  - \(X-M \xrightarrow{\text{mig. ins.}} L = R_3P, CO X-M \)
- **\(\beta\)-Hydride elimination**
  - \(L \xrightarrow{\text{L-M-H \rightarrow R}} L \)

**Heck reaction**
- \(R_1-X + H \xrightarrow{\text{Pd(II), base}} R_1-R_2 \)
- \(R_1 = \text{vinyl, aryl} \)
- \(X = \text{I, Br, sulfonates} \)

**Stille coupling** (M = Sn)
- \(R_1-M + R_2-X \xrightarrow{\text{Pd(PPh\(_3\))}_4} R_1-R_2 \)
- \(M = \text{Mg, Zn, Sn, B} \)

**Suzuki coupling**
- \(R_1=\text{alkyne}, R_2 \rightarrow R_1 \)
- \(R_1=\text{alkyne}, R_2 \rightarrow R_1 \)
- \(Pd(PPh\(_3\))_4 \rightarrow \text{Ar-R, base} \)
Silicon in organic synthesis

1) Nucleophilic substitution is easier on silicon compared to carbon.
2) Double bonds to silicon are weak due to bad overlap of 3sp² and 2sp².
3) Single bonds between Si and O, F, Cl are very strong.

<table>
<thead>
<tr>
<th>Compound</th>
<th>ΔH₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₃Si-H</td>
<td>370 kJ/mol</td>
</tr>
<tr>
<td>Me₃Si-Me</td>
<td>360 kJ/mol</td>
</tr>
<tr>
<td>Me₃Si-OME</td>
<td>530 kJ/mol</td>
</tr>
<tr>
<td>Me₃Si-Cl</td>
<td>530 kJ/mol</td>
</tr>
<tr>
<td>Me₃Si-F</td>
<td>810kJ/mol</td>
</tr>
</tbody>
</table>

4) Me₃Si⁻ is similar to H⁻.
5) Silicon stabilizes positive charges in β-position.
6) Silicon stabilizes C-metal bonds.
7) Me₃SiH add to double bonds.
8) The steric effect of Me₃Si is small.

Boron in organic synthesis

1) Synthesis of boranes
   a) from alkenes

   ![Diagram of borane synthesis from alkenes]

   ![Diagram of borane synthesis by organometallic reagents]

   ![Diagram of borane synthesis by alkyne addition]

2) Reactions

   ![Diagram of borane reactions]

- cis-addition to the least hindered position
- by heating the borane, the boron migrates to the least hindered position
# Common protective groups

<table>
<thead>
<tr>
<th>group</th>
<th>on</th>
<th>off</th>
<th>other information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>protection of alcohols</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acetate, OAc</td>
<td>Ac₂O/pyridine, 1–12 h</td>
<td>NaOMe/MeOH, 0.05 M, 10 min or</td>
<td>+versatile</td>
</tr>
<tr>
<td></td>
<td>or AcCl/pyridine, 1–12h</td>
<td>HCl/MeOH, o.n.</td>
<td>+cheap</td>
</tr>
<tr>
<td></td>
<td>*faster with DMAP</td>
<td></td>
<td>+some selectivity</td>
</tr>
<tr>
<td>benzoate, OBz</td>
<td>BzCl/pyridine, 1–12 h</td>
<td>NaOMe/MeOH, 0.05 M, 1 h</td>
<td>+often very good selectivity</td>
</tr>
<tr>
<td></td>
<td>or H₂/Pd-C, 1 h</td>
<td></td>
<td>+UV-active</td>
</tr>
<tr>
<td></td>
<td>or Na/NH₃</td>
<td></td>
<td>+less sensitive compared to</td>
</tr>
<tr>
<td>benzyl, OBn</td>
<td>BnCl, NaH, DMF, 12 h</td>
<td>H₂/Pd-C, 1 h</td>
<td>acetate</td>
</tr>
<tr>
<td>tetrahydropyranyl, OTHP</td>
<td>R–OH</td>
<td>AcOH, THF, H₂O, 50°C, 3–12 h</td>
<td>+orthogonal</td>
</tr>
<tr>
<td></td>
<td>pTSA, 1h</td>
<td></td>
<td>-gives new stereocenter</td>
</tr>
<tr>
<td>t-butyldimethylsilyl,</td>
<td>TBDMS/pTSA, 2–12h</td>
<td>tetrabutylammonium fluoride</td>
<td>+orthogonal</td>
</tr>
<tr>
<td>OtBDMS</td>
<td>or BocCl, TEA, DMF, 12 h</td>
<td>(TBAF or QF), THF, 1 h</td>
<td>±bulky</td>
</tr>
<tr>
<td></td>
<td>or AcOH (80%), reflux, 3–12 h</td>
<td></td>
<td>+selective</td>
</tr>
<tr>
<td></td>
<td>or Me₂CO</td>
<td></td>
<td>-can change conformation</td>
</tr>
<tr>
<td></td>
<td>pTSA, 3–12 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>protection of diols</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>isopropyliden</td>
<td>acetone, pTSA, 3–12 h</td>
<td>AcOH (80%), reflux, 3–12 h</td>
<td>+high selectivity</td>
</tr>
<tr>
<td></td>
<td>or Me₂CO, pTSA, 3–12 h</td>
<td></td>
<td>+no stereocenter</td>
</tr>
<tr>
<td></td>
<td>*gives 1,2-acetals on triols</td>
<td></td>
<td>+cheap</td>
</tr>
<tr>
<td>benzylidene</td>
<td>PhCHO, ZnCl₂, 4 h</td>
<td>H₂/Pd-C, AcOH</td>
<td>+high selectivity</td>
</tr>
<tr>
<td></td>
<td>or PhCH(OH)₂₂₃, or PhCH(OMe)₂₂₃</td>
<td>or Na/NH₃ or H₂OAc (80%), reflux,</td>
<td>-stereocenter</td>
</tr>
<tr>
<td></td>
<td>or pTSA, MeCN, 2–12h</td>
<td>3–12 h</td>
<td>+cheap</td>
</tr>
<tr>
<td>*gives 1,3-acetals on</td>
<td></td>
<td></td>
<td>+can be regioselectively</td>
</tr>
<tr>
<td>triols</td>
<td></td>
<td></td>
<td>opened</td>
</tr>
<tr>
<td>protection of amines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amides</td>
<td>Ac₂O/pyridine 20°C, 1h or</td>
<td>HCl (1M), 100°C, 12 h or</td>
<td>±very stable</td>
</tr>
<tr>
<td></td>
<td>Ac₂O/MeOH/H₂O (selective for</td>
<td>hydrazin (85%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>–NH₂ in the presence of –OH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>car bamates</td>
<td>TrocCl/pyridine</td>
<td>Zn/H₂OAc (Troc)</td>
<td>+easy to remove</td>
</tr>
<tr>
<td></td>
<td>Boc₂O,TEA, DMF</td>
<td>TFA, DCM, anisol (Boc)</td>
<td>-sensitive to nucleophiles</td>
</tr>
<tr>
<td></td>
<td>R' = –CH₂CCl₃ (Troc)</td>
<td></td>
<td>+orthogonal deprotection</td>
</tr>
<tr>
<td></td>
<td>R' = –Bu (Boc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R' = FmocCl/NaHCO₃, dioxane</td>
<td>piperidine (Fmoc)</td>
<td></td>
</tr>
<tr>
<td>protection of carboxylic acids (use esters; see alcohols)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>