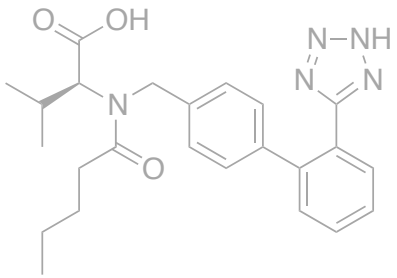
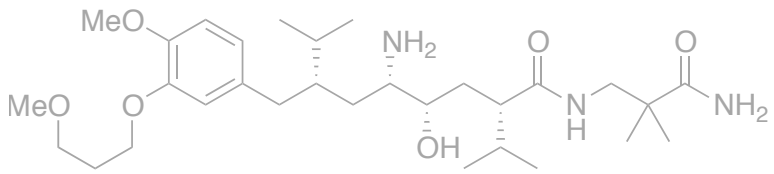
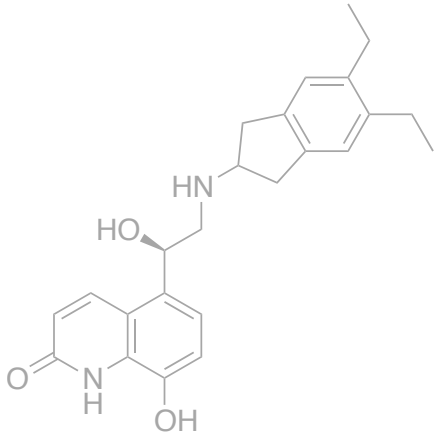
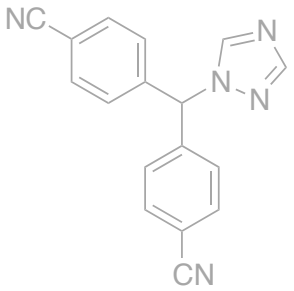




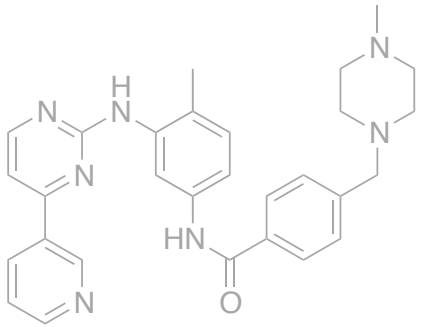
Pharma Disconnections

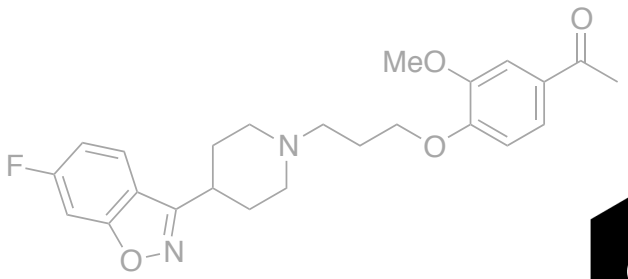


Prof Edward A. Anderson



Synthesis for Biology and Medicine CDT
October 26th-27th 2016





Aims of the Course

UNIVERSITY OF OXFORD

- Cover ‘classical’ ways to disconnect molecules, which are fundamental to organic synthesis

- Develop an understanding of how these disconnections link to heterocycle synthesis

- Recognize how multiple solutions are available for given target molecules, and how to critically assess retrosynthetic options

- ***Interactive Problem session***: Extended practice with ‘classical’ disconnection problems through teamwork

Retrosynthesis: Course Outline

UNIVERSITY OF OXFORD

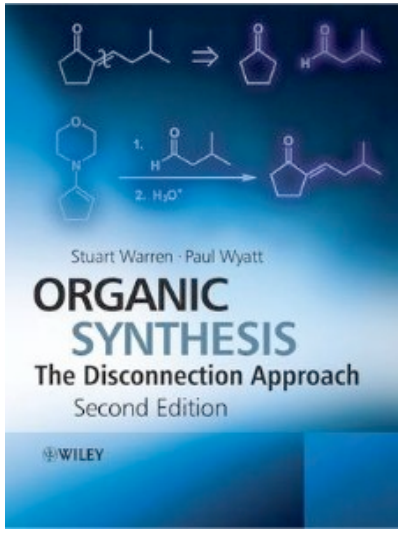
The principles of retrosynthesis

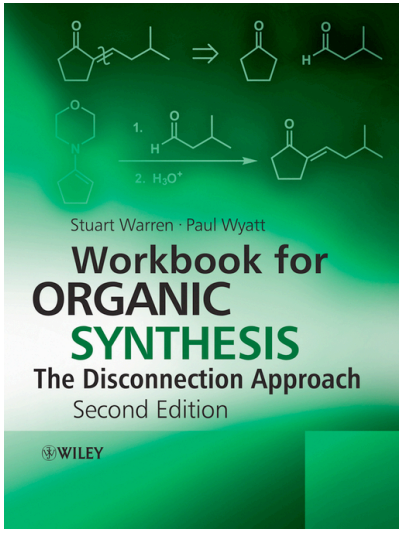
- **Introduction to retrosynthesis:** The origins of the subject, nomenclature, how we go about breaking up molecules
- **Key strategic considerations:** Functional group interconversions, selectivity, protecting groups
- **Synthons and Reagents**: Acceptor and Donor synthons – how to recognise these disconnections and the importance of (di)oxygenation relationships
- Focus on specific reaction types and methods to install functionality (e.g. amines, alkenes, cycloadditions, cross-coupling)
- Worked examples throughout these topics
- ***Interactive Problem session***: Extended practice with 'classical' disconnection problems

Retrosynthesis in medicinal chemistry

- Coverage of 5- and 6-membered aromatic heterocycle disconnections with worked examples
- Advanced disconnections of arenes
- Asymmetric synthesis including worked examples
- Case studies to illustrate principles
- ***Interactive Problem session***: Extended practice with a range of pharmaceuticals

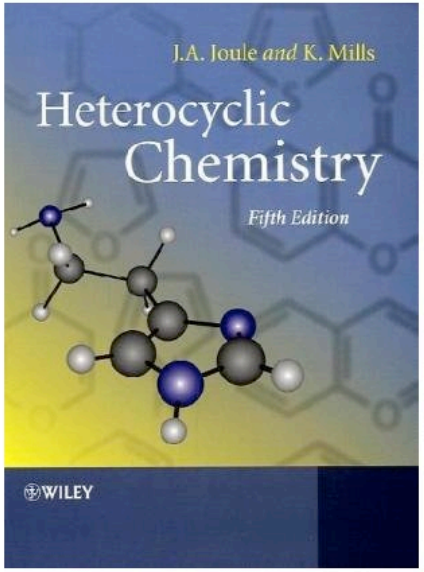
Retrosynthesis: Supporting Material





Stuart Warren's 'Disconnection approach' is the classic text on this subject, and highly recommended!

Joule and Mills' classic Heterocyclic Chemistry textbook also provides a useful introduction

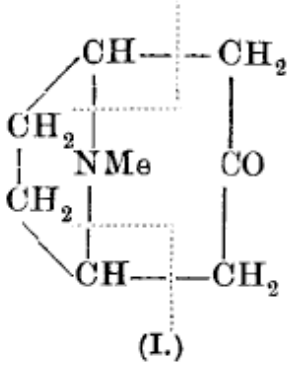


Introduction: The history of retrosynthesis

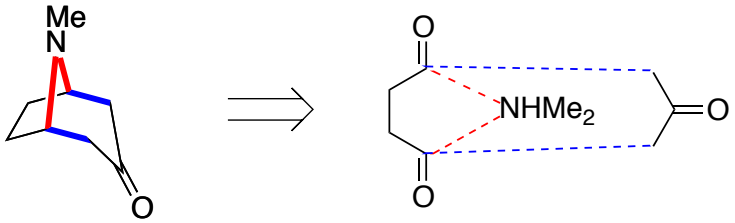
• The birth of retrosynthesis can be traced to Sir Robert Robinson's landmark synthesis of the alkaloid **tropinone** in 1917.

Nevertheless, an inspection of the formula of tropinone (I) discloses a degree of symmetry and an architecture which justify the hope that the base may ultimately be obtained in good yield as the product of some simple reaction and from accessible materials. By imaginary hydrolysis at the points indicated by the dotted lines, the substance may be resolved into succindialdehyde, methylamine, and acetone, and this observation suggested a line of attack of the problem which has resulted in a direct synthesis.

Recognition of available starting materials!



(I.)

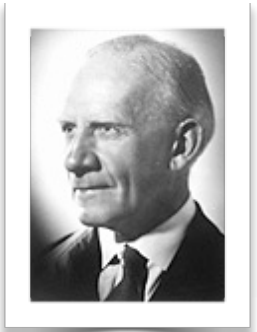


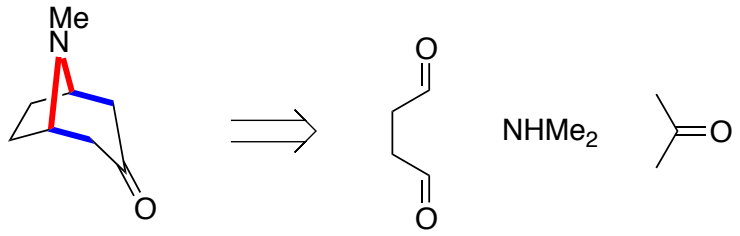
The possibility that tropinone might result from the condensation of succindialdehyde or a derivative with acetone or a derivative and methylamine or by the addition of methylamine to a *cyclo*heptadienone occurred simultaneously to Professor A. Lapworth and the author, and a joint research was contemplated, but Dr. Lapworth's preoccupation with more urgent investigations did not allow him to undertake this fresh experimental work.

R. Robinson, *J. Chem. Soc., Trans.*, **1917**, *111*, 762

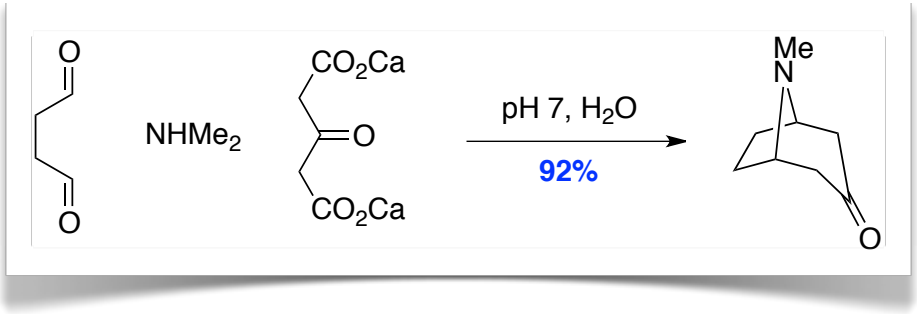
Introduction: The history of retrosynthesis

• The birth of retrosynthesis can be traced to Sir Robert Robinson's landmark synthesis of the alkaloid **tropinone** in 1917.





In the event, use of the calcium salt of acetone dicarboxylic acid at neutral pH facilitates the Mannich reactions:



R. Robinson, *J. Chem. Soc., Trans.*, **1917**, *111*, 762; C. Schöpf, G. Lehmann, *Leibigs Annalen*, **1935**, *518*, 1.

Introduction: Getting started!

• ***Retrosynthesis arrows:***

Forward reaction (Synthetic connection)

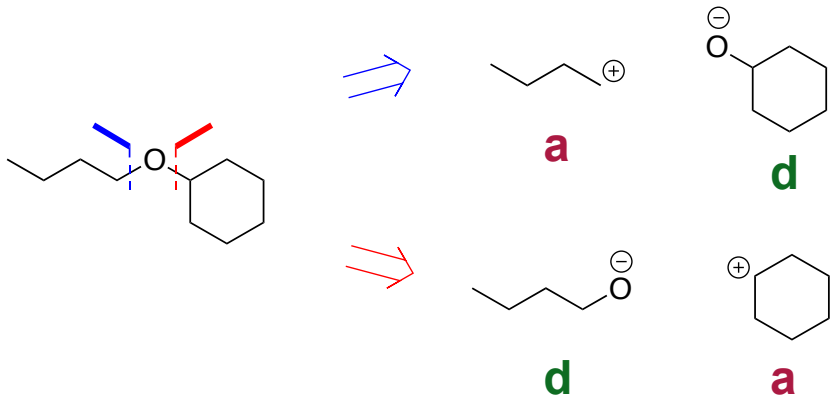
Retrosynthetic disconnection

• A **disconnection** is the reverse of a known reaction (*known by YOU!*)

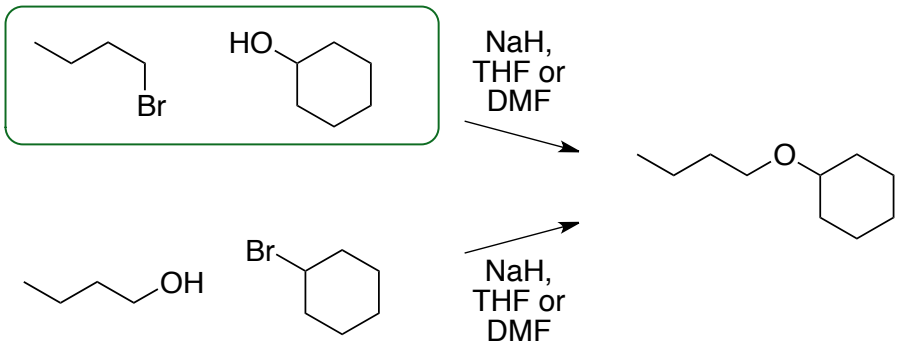
• ***WHERE* should we start to disconnect molecules?**

Example 1:

Synthons



Reagents



Risk of E2; S_N2 on 2° halide not great!

Key principle: Disconnect at a bond that is *EASY TO MAKE*; it may be a strong bond!

• A **synthon** is an imaginary (charged) species formed by the conceptual process of breaking a bond in a molecule (retrosynthetically). Our job is to identify real-life **reagents** that correspond to these synthons.

• Synthons are assigned **labels** (**a (acceptor)**, **d (donor)**) so we can talk about what type of disconnection we are using.

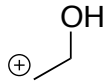
Introduction: Synthons

• A **synthon** is an imaginary (charged) species formed by the conceptual process of breaking a bond in a molecule (retrosynthetically). Synthons are assigned **labels** (**a (acceptor)**, **d (donor)**) so we can talk about what type of disconnection we are using. The subscript number refers to the position of the charge relative to a heteroatom that forms part of the functional group.

Acceptor Synthons:

a

a¹



a²

Donor Synthons:

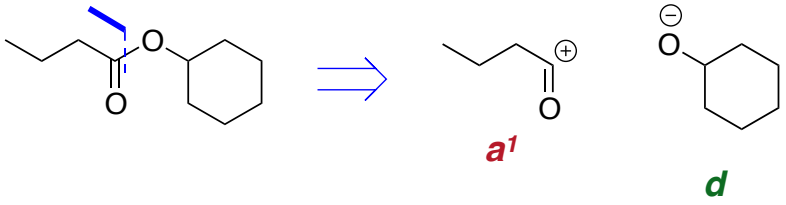
d

d¹

d²

Example 2:

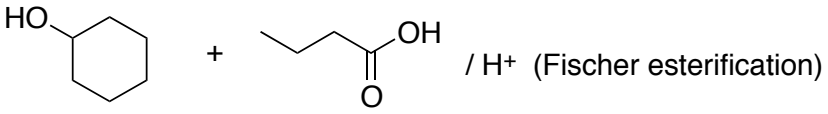
Synthons:



a¹

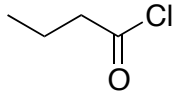
d

Reagents (e.g.):



/ H^+ (Fischer esterification)

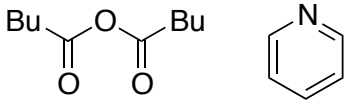
or



/ Et_3N;

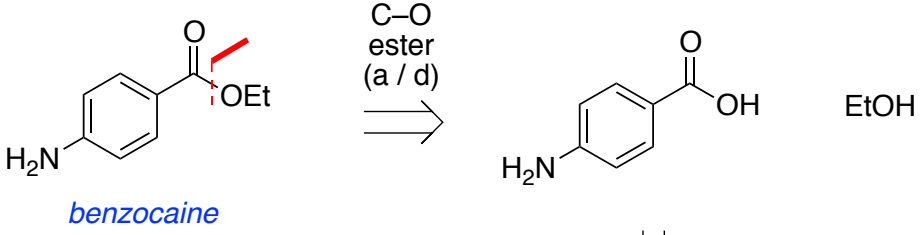
or $NaHCO_3$ aq. / Et_2O
"Schotten-Baumann conditions"

or



Introductions: Functional group interconversions

• In addition to disconnections that break / make bonds, we can carry out **functional group interconversions** that change either the nature, or number, of functional groups present in a molecule.

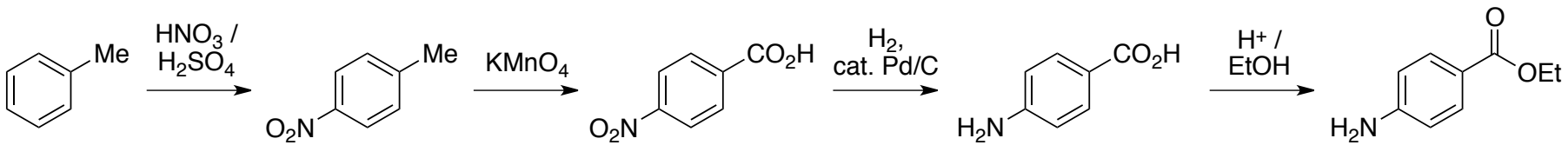


benzocaine

Problem:
• We cannot directly introduce either of these functionalities
• The acid group is *meta*-directing in S_EAr

Solution: Interconvert functional groups to enable ring functionalization (**FGI**)

Synthesis:



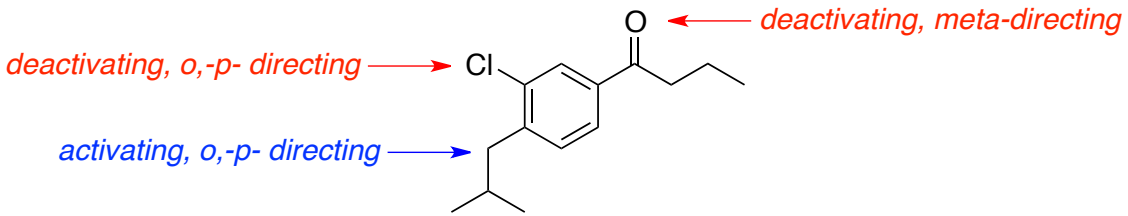
benzocaine

• Me is *o,p*-directing; *p*-nitration favoured by sterics
• Mono-nitration as product less reactive than sm

• Amine does not react as it is protonated (protected!) under the reaction conditions

Order of events

One of the crucial considerations in planning a synthesis is to consider the order of events of the planned reactions. This is particularly important in the manipulation of aromatic rings where regioselectivity is paramount; directing effects rule!

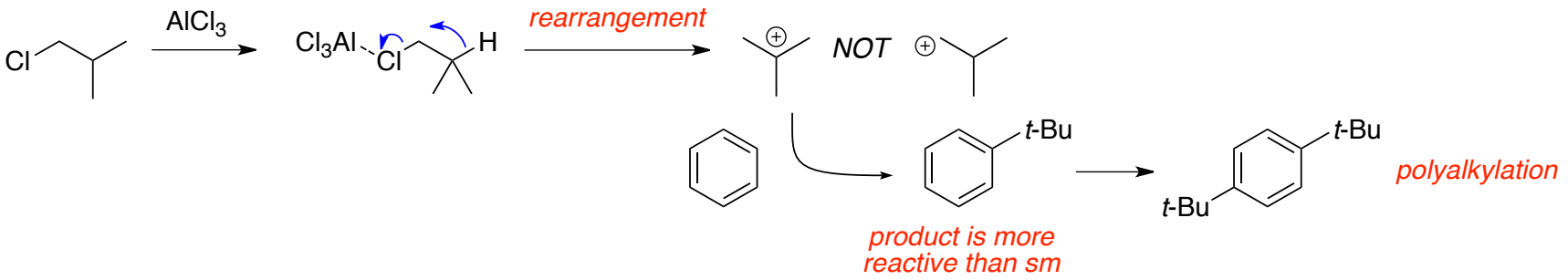


see Appendix for aromatic chem recap

The **best electron donating group** (activator) is the one that 'wins' – stabilisation is more important than 'lack of destabilisation'

***Q**: Should we acylate or chlorinate first?*
***A**:* Sterics suggest we should acylate *then* chlorinate; the alkyl group favours *p*-substitution so chlorination first would give poor selectivity.

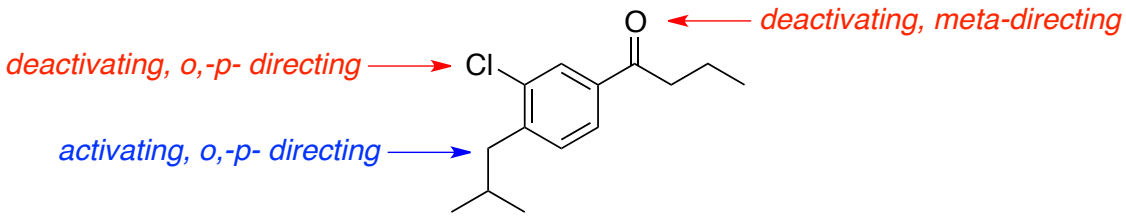
***Q**: How do we introduce the alkyl group?*
A: NOT Friedel-Crafts *alkylation*...



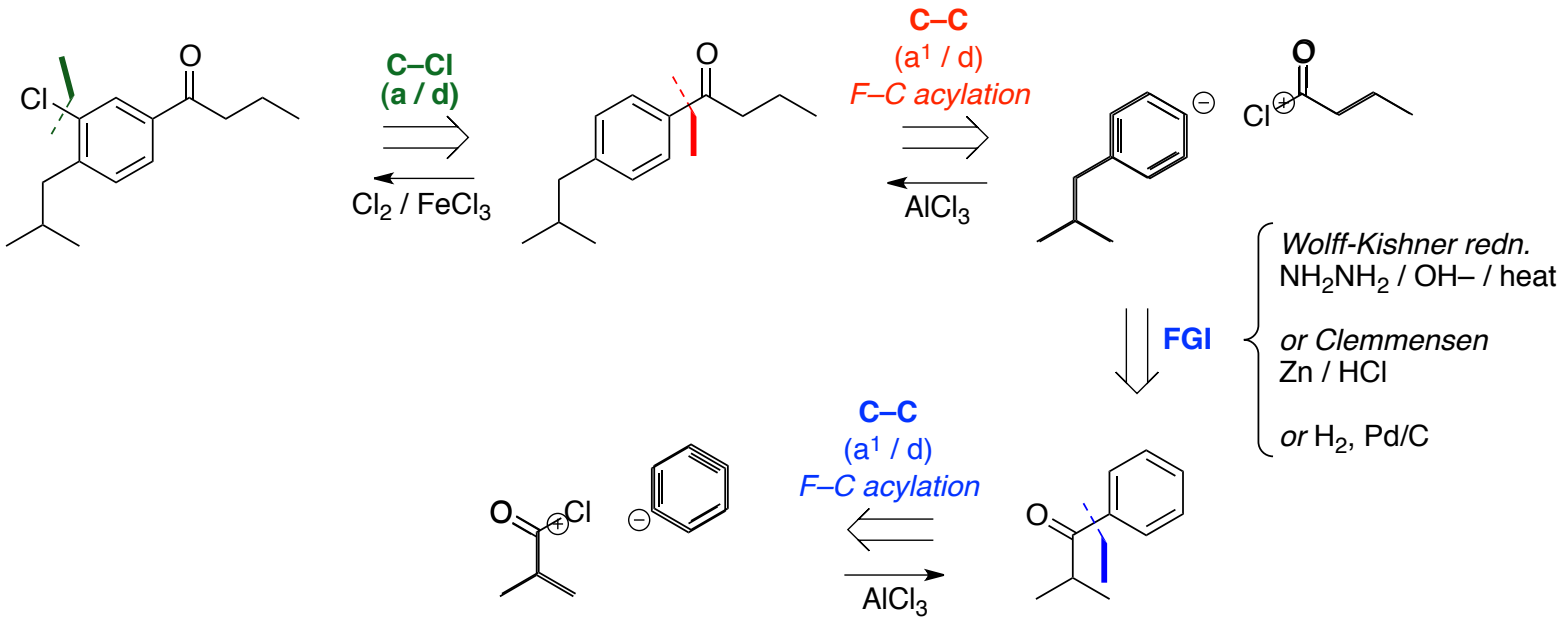
Key principle: To achieve / guarantee mono-substitution, the product must be less reactive than the starting material...

Order of events

One of the crucial considerations in planning a synthesis is to consider the order of events of the planned reactions. This is particularly important in the manipulation of aromatic rings where regioselectivity is paramount; directing effects rule!

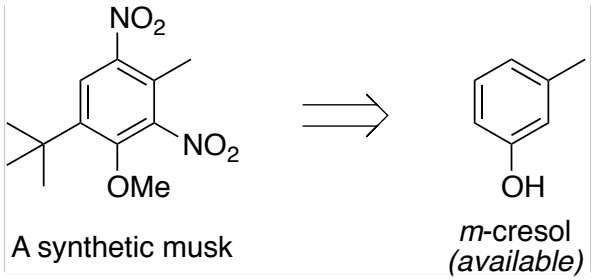


• **Solution**: Use Friedel-Crafts *Acylation* then remove carbonyl group. This again uses the important concept of FGI to *reintroduce* functionality into the molecule to *enable control*.

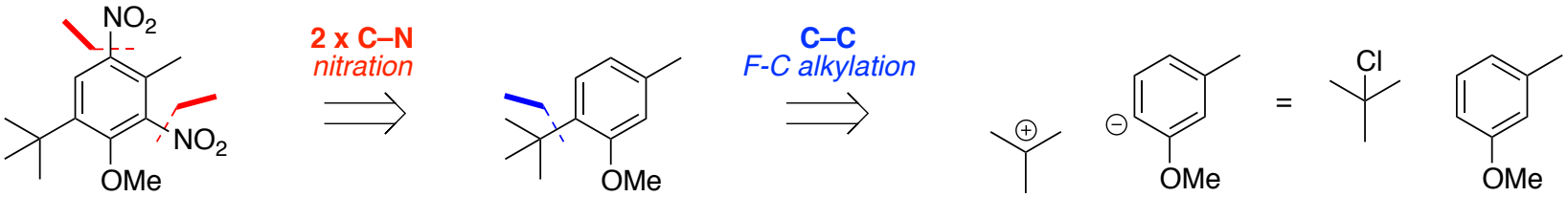


Exercise

Plan a synthesis of the following molecule from *m*-cresol:

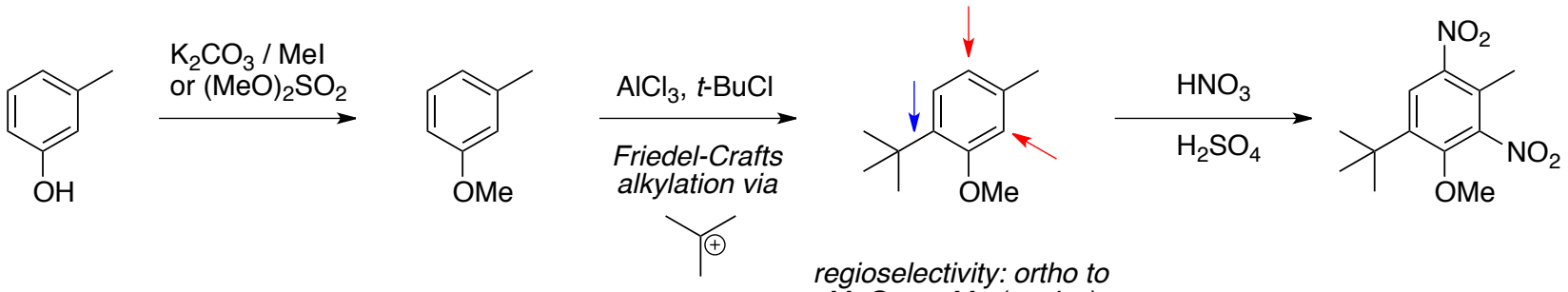


Retrosynthesis:



Note: this is a 'good' F-C disconnection as cation rearrangement is unlikely

Synthesis:



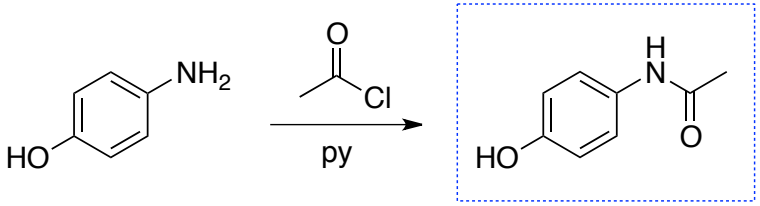
regioselectivity: ortho to MeO, not Me (sterics)

Selectivity

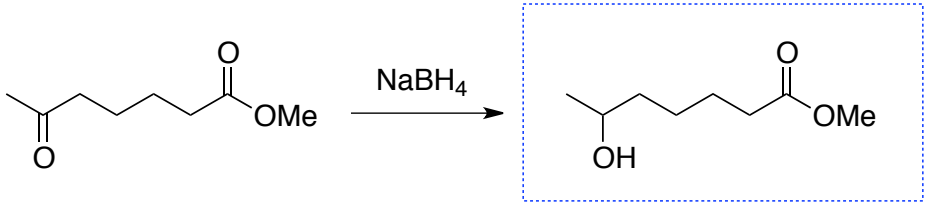
Control / selectivity is paramount in planning a synthesis. There are three main considerations we need to think about:

1a. Chemoselectivity. WHICH group will react?

a) Differentiating between different functional groups:

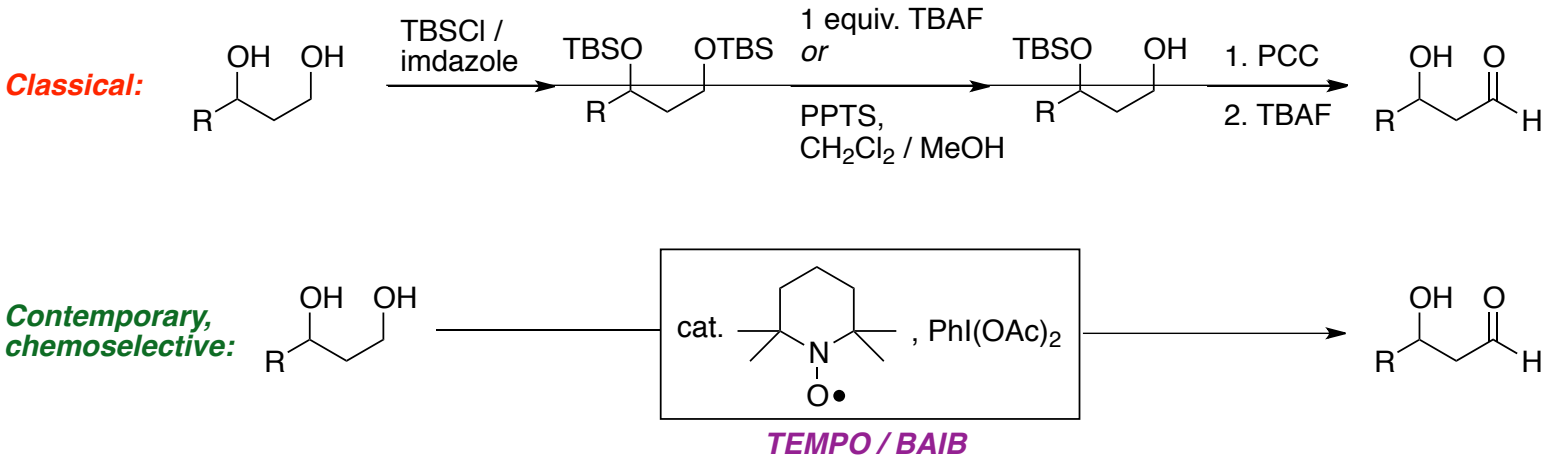


The amine is more nucleophilic than the alcohol...
(see Appendix for stereoelectronic discussion)



The ketone is more electrophilic than the ester...
(see Appendix for stereoelectronic discussion)

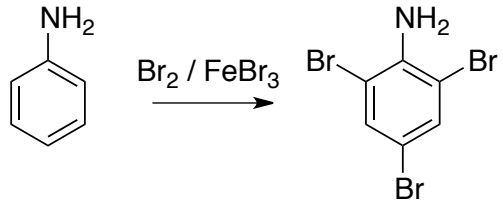
b) Differentiating between the same functional group in different environments:



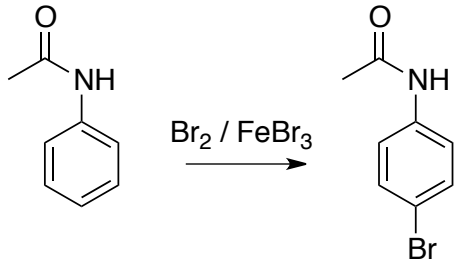
TEMPO / BAIB mech: e.g., *Eur. J. Org. Chem.*, **2006**, 4323

Selectivity

1b. Chemoselectivity: over-reaction.



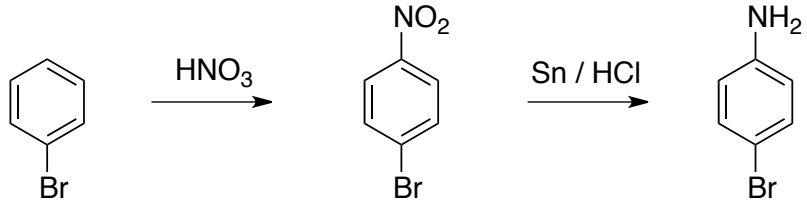
The aniline nitrogen atom is such a powerful activating group that it is difficult to prevent over-bromination, despite the lower reactivity of the product.



The acetamide nitrogen atom is now a weaker activating group due to conjugation. Mono-bromination can now be achieved.

Key principle: Modifying functional groups (by FGI) can help us to control / influence selectivity

... or an alternative disconnection?

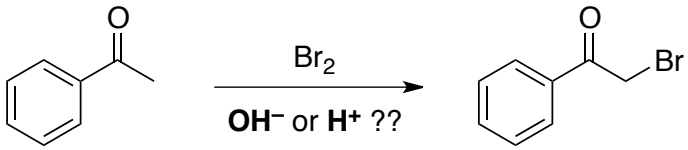


Mono-nitration occurs as product is less reactive than sm. Reduction reveals the powerful amine activating group

Key principle: To achieve / guarantee mono-substitution, the product must be less reactive than the starting material...

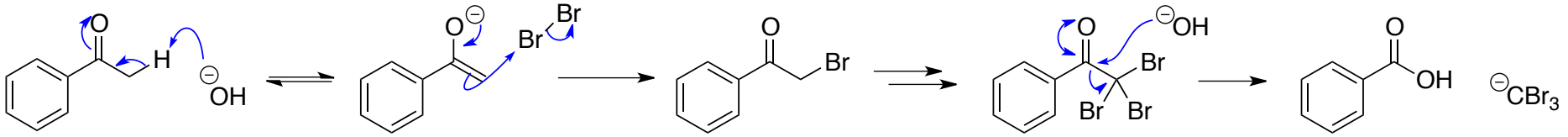
Selectivity

1b. Chemoselectivity: over-reaction.



The haloform reaction can be quite a useful route to carboxylic acids!

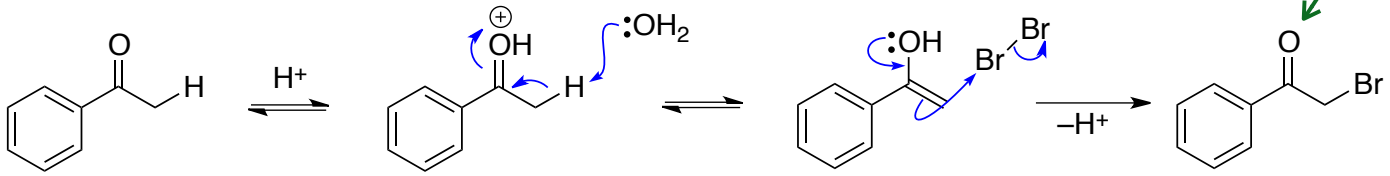
• *Under basic conditions:*



pKa = 25 *pKa = 21*

• *Under acidic conditions:*

Carbonyl less basic due to inductive EWG from Br!



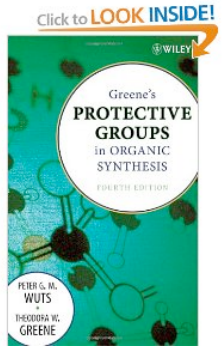
Key principle: To achieve / guarantee mono-substitution, the product must be less reactive than the starting material...

Key principle: Thinking about mechanism can also help us to control selectivity

Protecting groups

Protecting groups provide an obvious way to protect reactive functionality and achieve chemoselectivity. The cost is at least one additional step in a synthesis, usually two.

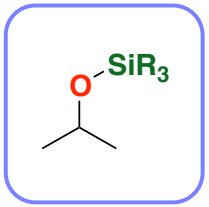
- Sometimes the deprotection of protecting groups can be the most challenging step in a synthesis!
- Protecting group-free synthesis preferred – and may be achieved using a careful ordering of steps...



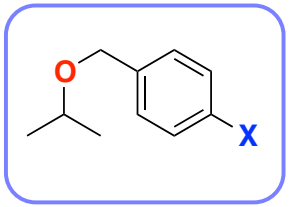
See Appendix for a short summary of PG methods

1. Protection for alcohols

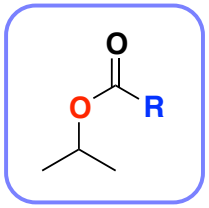
- **Silyl ethers**



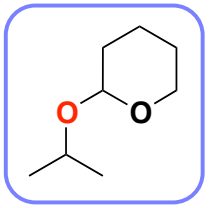
- **Benzyl ethers**



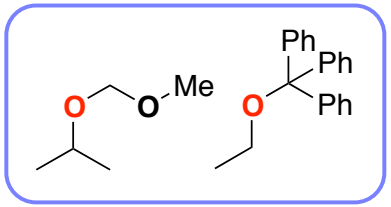
- **Esters / carbonates**



- **Acetals**

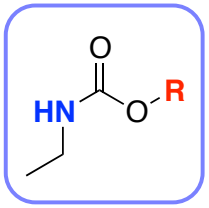


- **Other ethers**

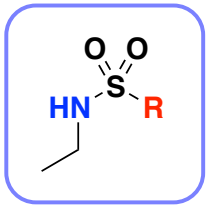


2. Protection for amines

- **Carbamates**

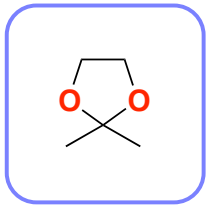


- **Sulfonamides**



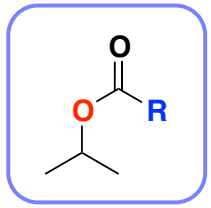
3. Protection for carbonyls (and diols!)

- **Acetals**



4. Protection for carboxyls

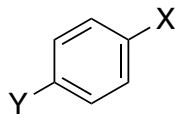
- **Esters / carbonates**



Introduction: Selectivity

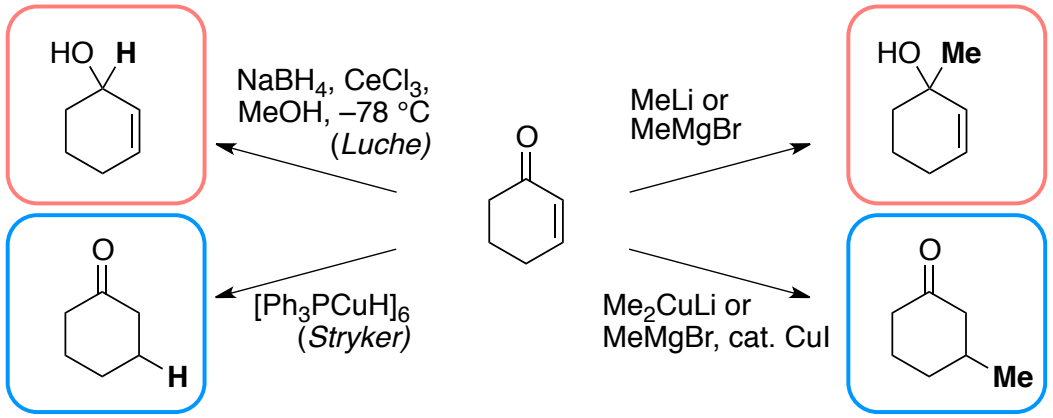
2. Regioselectivity. WHERE will the molecule or functional group react?

a) Aromatic compounds: Directing effects



• We have already looked at this. The best cation stabilising group wins!

b) Hard vs Soft



• 1,2-Addition = '**hard**': These reactions are ***charge controlled*** and depend on electrostatic attraction of nucleophile and electrophile. Highly charged / charge dense reagents.

• 1,4-Addition = '**soft**': These reactions are ***orbital controlled*** and depend on the overlap and energies of the HOMO and LUMO. Neutral / polarisable reagents.

Many other examples such as: ***Enolisation*** (see d^2): Control over the site of enolisation for non-symmetrical carbonyls; ***Elimination*** (e.g. Hofmann vs Saytzeff elimination), etc.

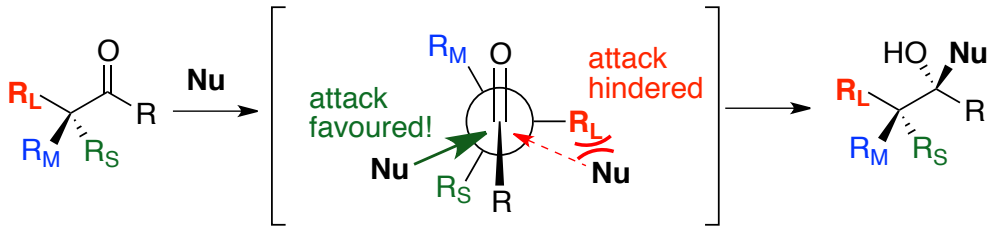
Introduction: Selectivity

3. Stereoselectivity / Stereospecificity: We may need to control stereochemistry in a given step

Stereoselective: One stereochemical outcome is favoured over two (or more) possible outcomes

Examples: generally stepwise (non-concerted) processes

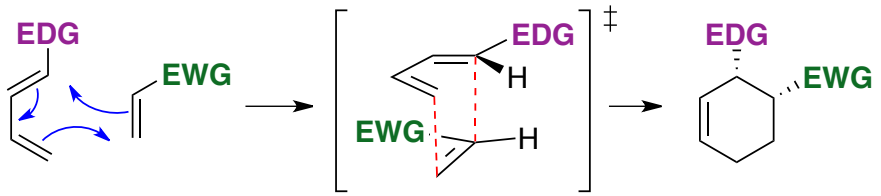
- **E1** elimination
- **Felkin-Anh model** (addition to α-chiral carbonyls)
- **Chiral auxiliary-mediated reactions**
- **Carbonyl olefination** (e.g. Wittig, etc.)
- **The facial selectivity of reactions of alkenes**
- **The facial selectivity of reactions of bicyclic systems**
- **Diels-Alder reaction (endo vs exo)**
- **Aldol reactions** (syn vs anti)



Stereospecific: A reaction where only one stereochemical outcome is possible due to the reaction mechanism.

Examples: generally concerted processes

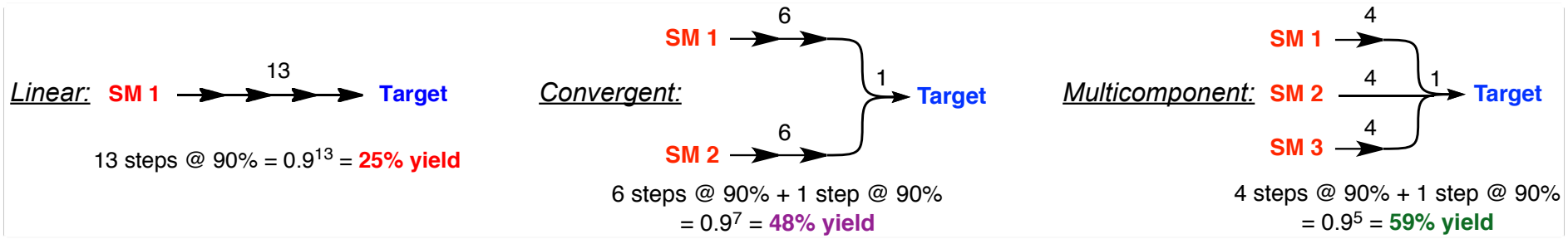
- **S_N2**
- **E2**
- **Ring-opening of epoxides**
- **Diels-Alder reaction** (and pericyclics in general)
- **Electrophilic addition to alkenes**
- **Hydrogenation of alkenes**
- **Many rearrangements** (e.g. Baeyer-Villiger)



Stereo- and regioselective reaction, but stereospecific reaction mechanism

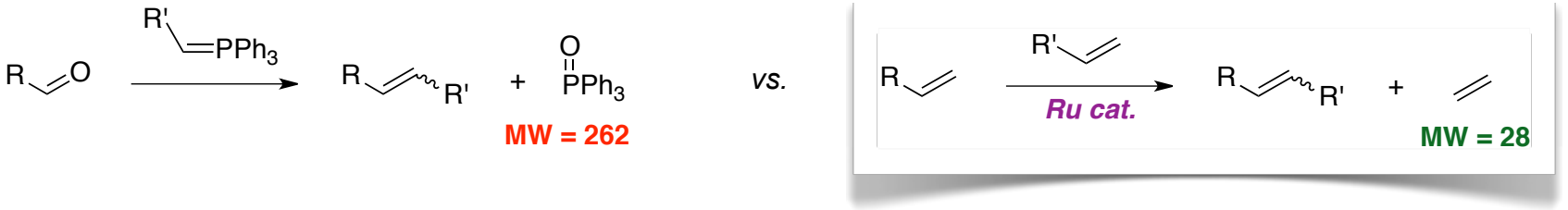
The ideal synthesis

1. Linear vs. convergent strategies: ***Key Principle:*** ***make disconnections in the middle of molecules!***



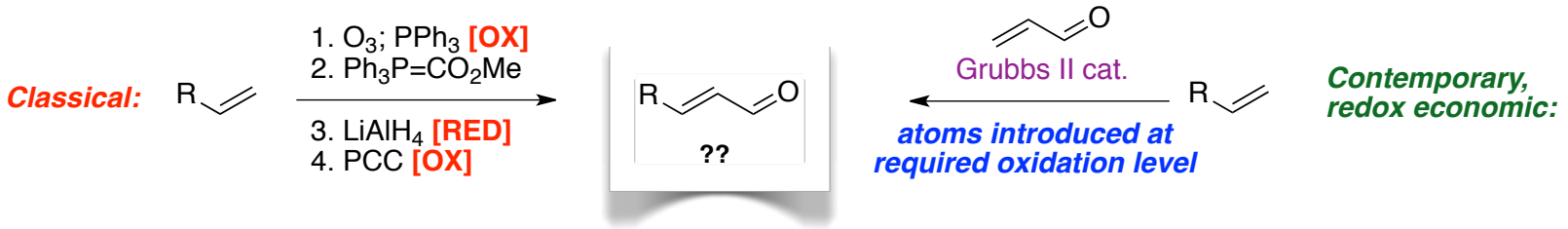
2. Stereocontrol: Substrate stereocontrol, chiral auxiliaries, **catalyst stereocontrol**, chiral pool, enzymes

3. Atom economy: (B. M. Trost, *Science* **1991**, *254*, 1471) and **Green chemistry** – minimise waste! Compare Wittig / olefin metathesis – Catalytic vs stoichiometric:



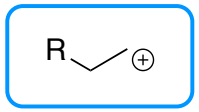
4. Step economy: Use of **cascade strategies, multicomponent reactions, no protecting groups**. Aim for e.g. 10 steps in total from cheap starting materials (not possible for really complex molecules).

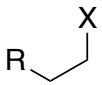
5. Redox economy: (N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 2854): Installing functional groups at the required oxidation state avoids excessive manipulations and protecting groups strategies.



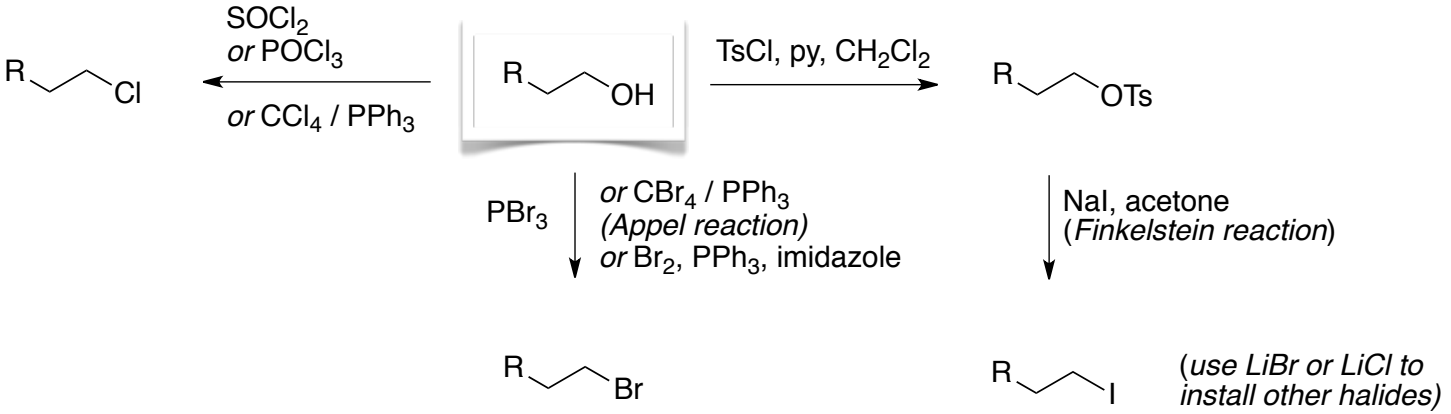
Acceptor synthons

a synthons: Essentially alkyl halides, etc.

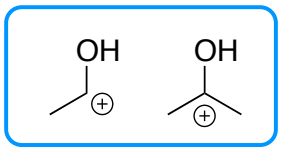
Synthon: 

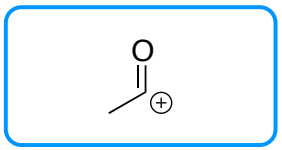
Reagents:  X = I, Br, Cl, **OTs**

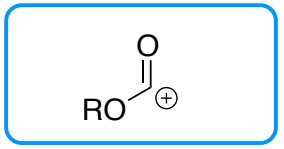
Synthesis of these reagents is most commonly achieved from alcohols:



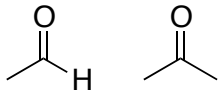
a¹ synthons

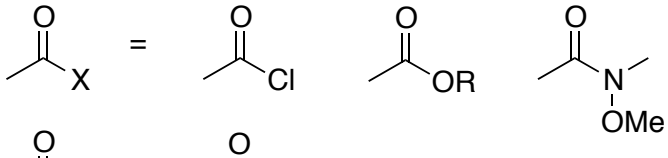


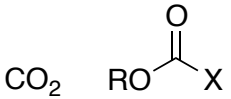


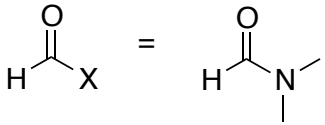


Reagents





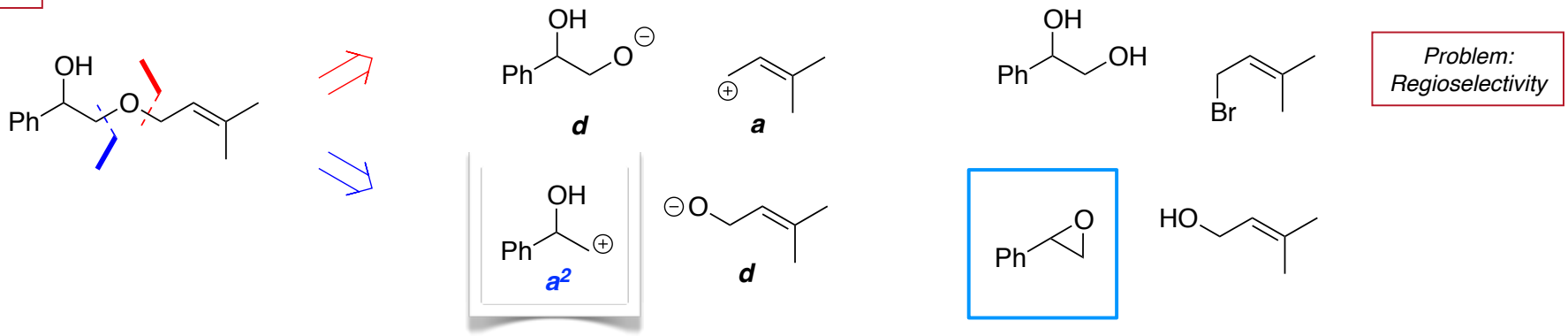




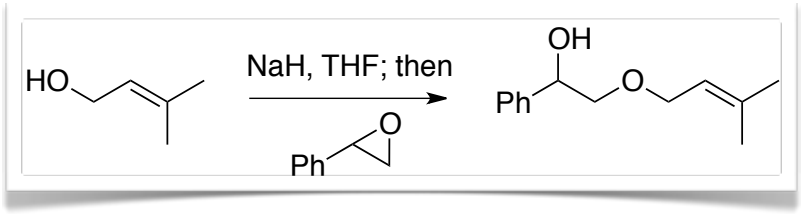
Acceptor synthons

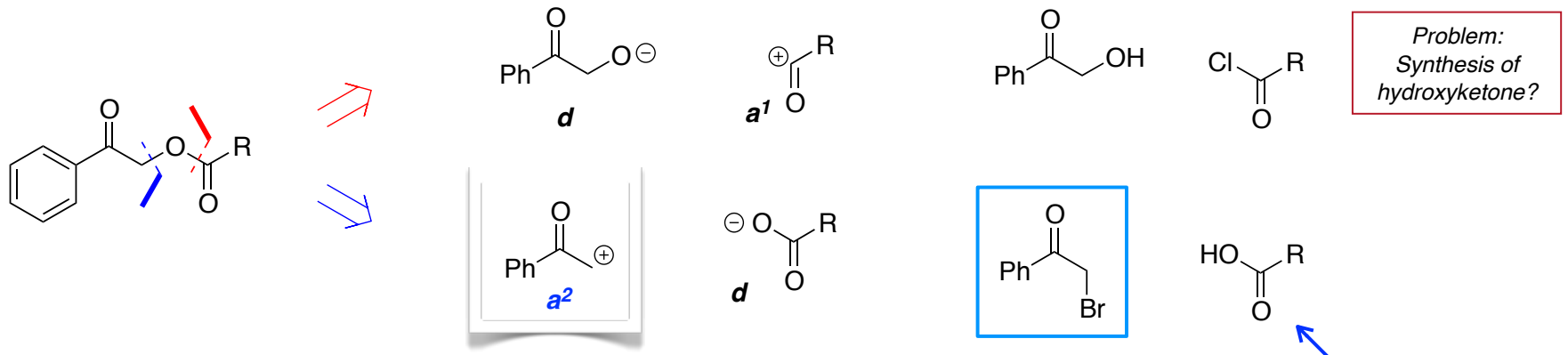
a^2 synthons

Synthons ***Reagents***

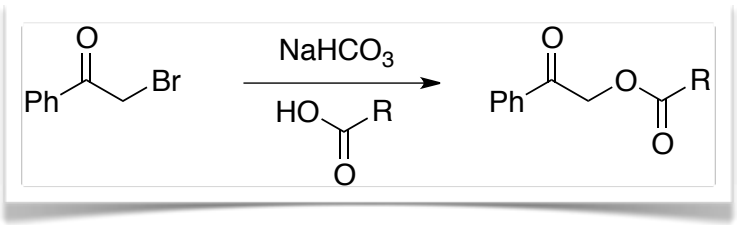


Synthesis:



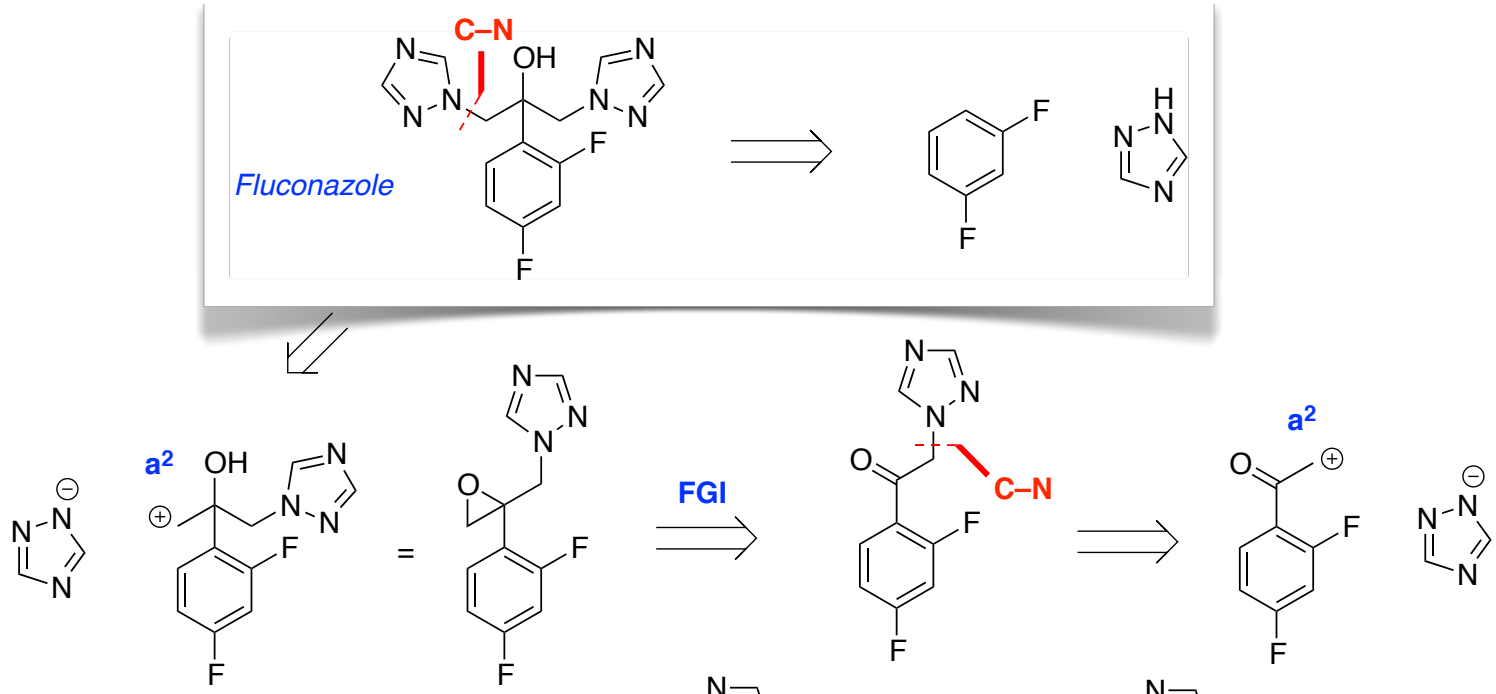


Synthesis:

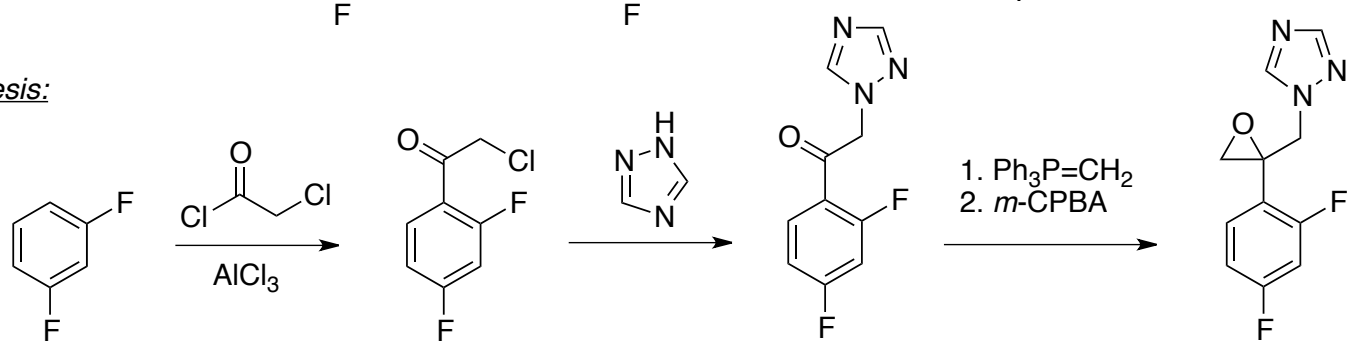


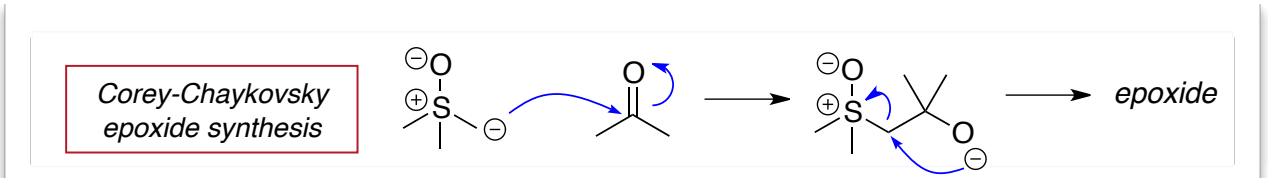
Exercise

Plan a synthesis of the the Pfizer anti-fungal agent fluconazole from 1,3-difluorobenzene and 1,2,4-triazole using two **a²** disconnections



Synthesis:





US Patent 4,404,216

Donor synthons

d synthons: These are typically carbanions or anionic / neutral heteroatoms. Here we have two considerations: is the reagent hard or soft (i.e. does it match the electrophile); and, can multiple reactions occur?

Carbon nucleophiles:

***Hard*:** organolithium, organomagnesium.

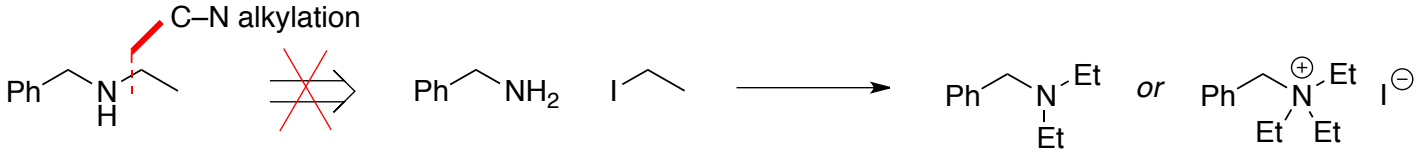
***Soft*:** cuprates, malonate, nitroalkane anion

Heteroatom nucleophiles:

***Hard*:** alkoxides, amide anions.

***Soft*:** sulfides, thiolate anions, amines, alcohols

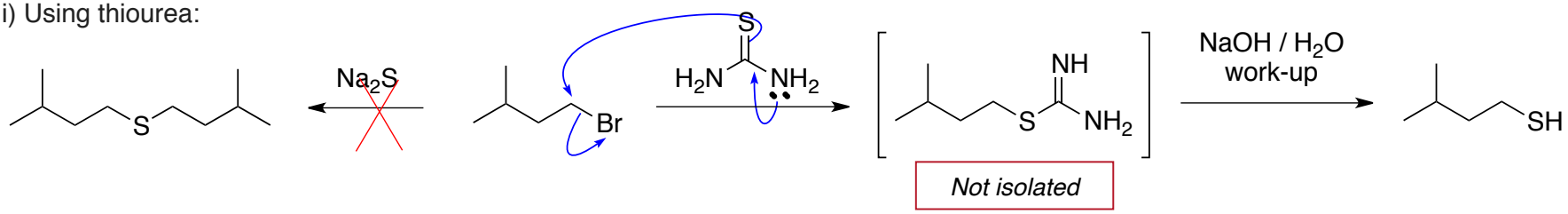
Amine synthesis: As amines are such good nucleophiles, polyalkylation is a big risk!



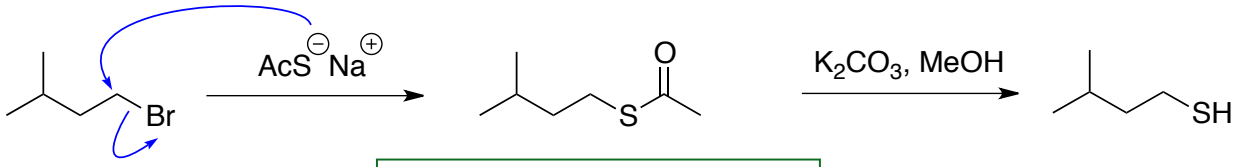
... different solutions are required for the synthesis of highly nucleophilic amines and sulfides!

a) Synthesis of sulfides:

i) Using thiourea:



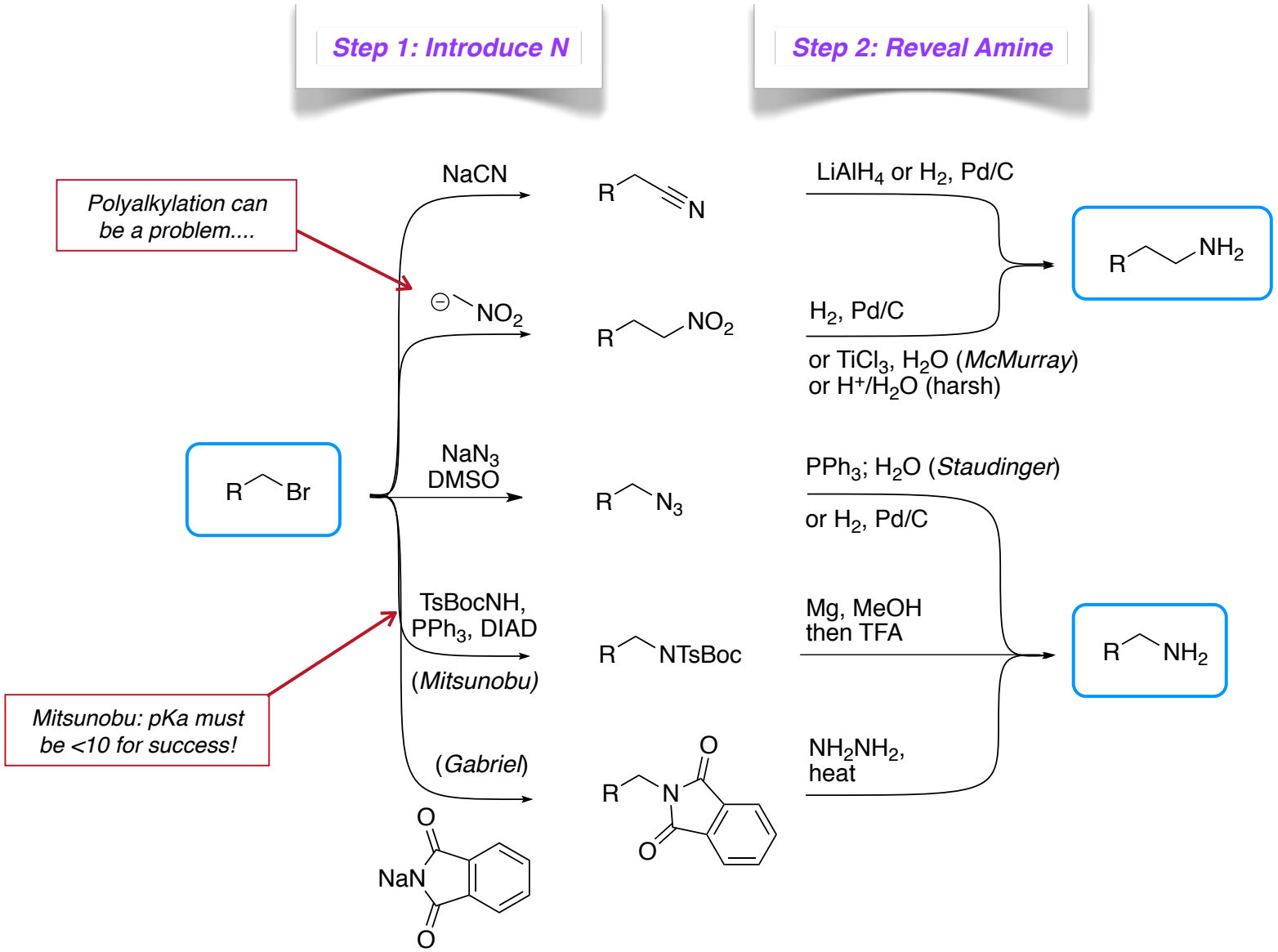
ii) Using thioacetate:



Can be isolated! (and does not smell) – protected thiolate anion

Donor synthons

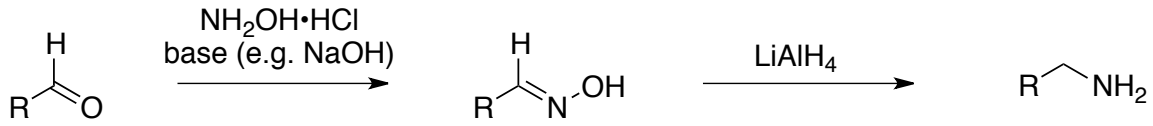
b) Synthesis of 1° amines:



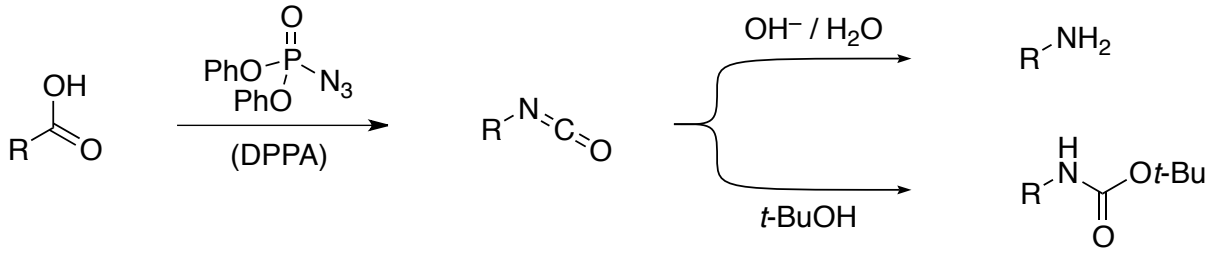
Donor synthons

b) Synthesis of 1° amines:

• *From oximes:*



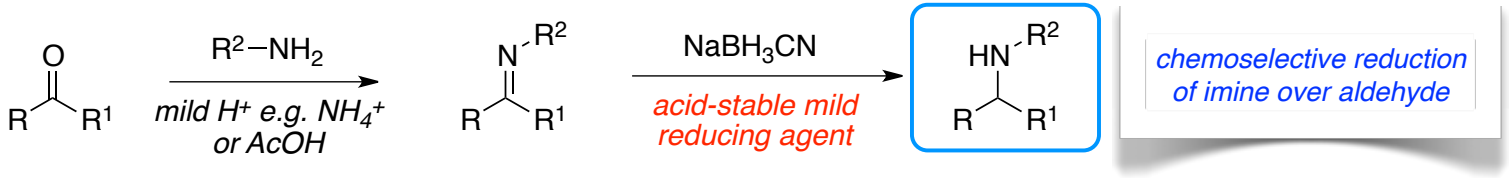
• *From acids (Curtius):*

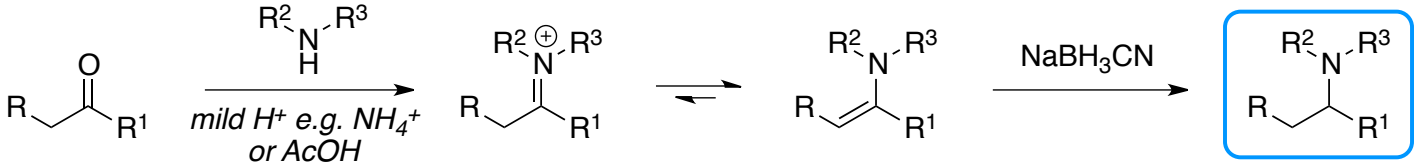


c) Synthesis of 2° and 3° amines:

There are two important methods for the synthesis of secondary amines, both of which feature reductive processes that again avoid revealing the amine too early in the reaction.

i) Reductive amination of aldehydes and ketones

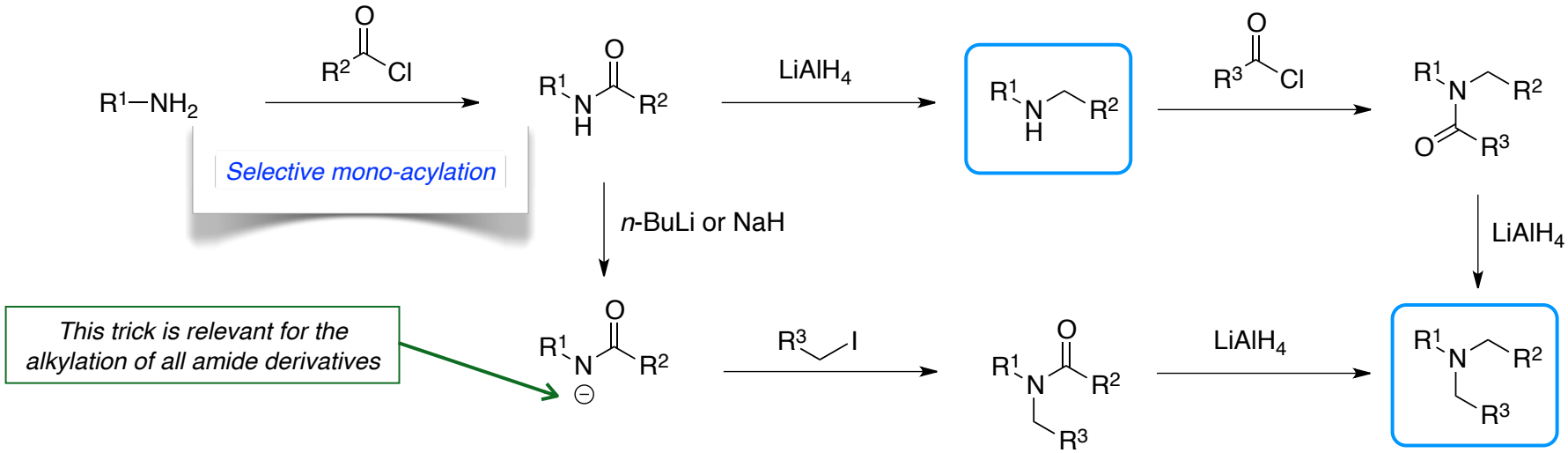




Review of synthesis of 2° amines: Salvatore et al., *Tetrahedron* **2001**, *57*, 7785.

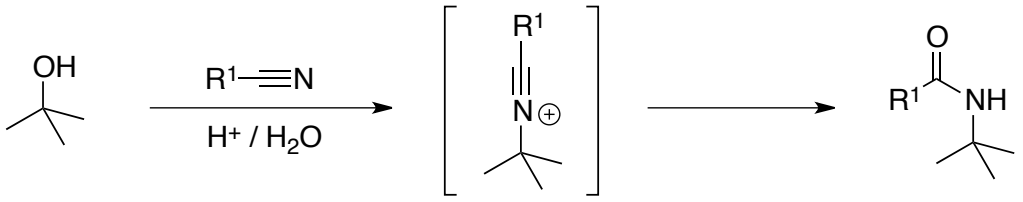
Donor synthons

ii) Reduction of amides

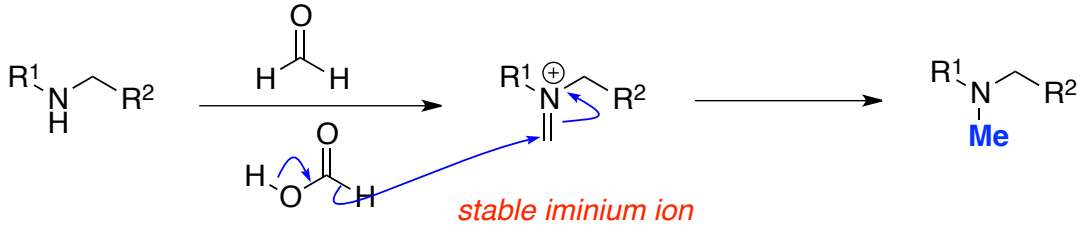


iii) Other methods:

Branched amine synthesis: the Ritter reaction

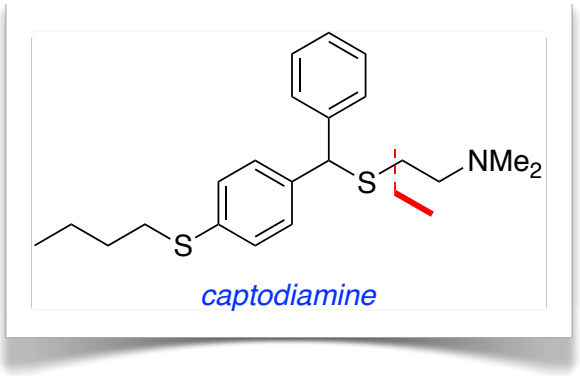


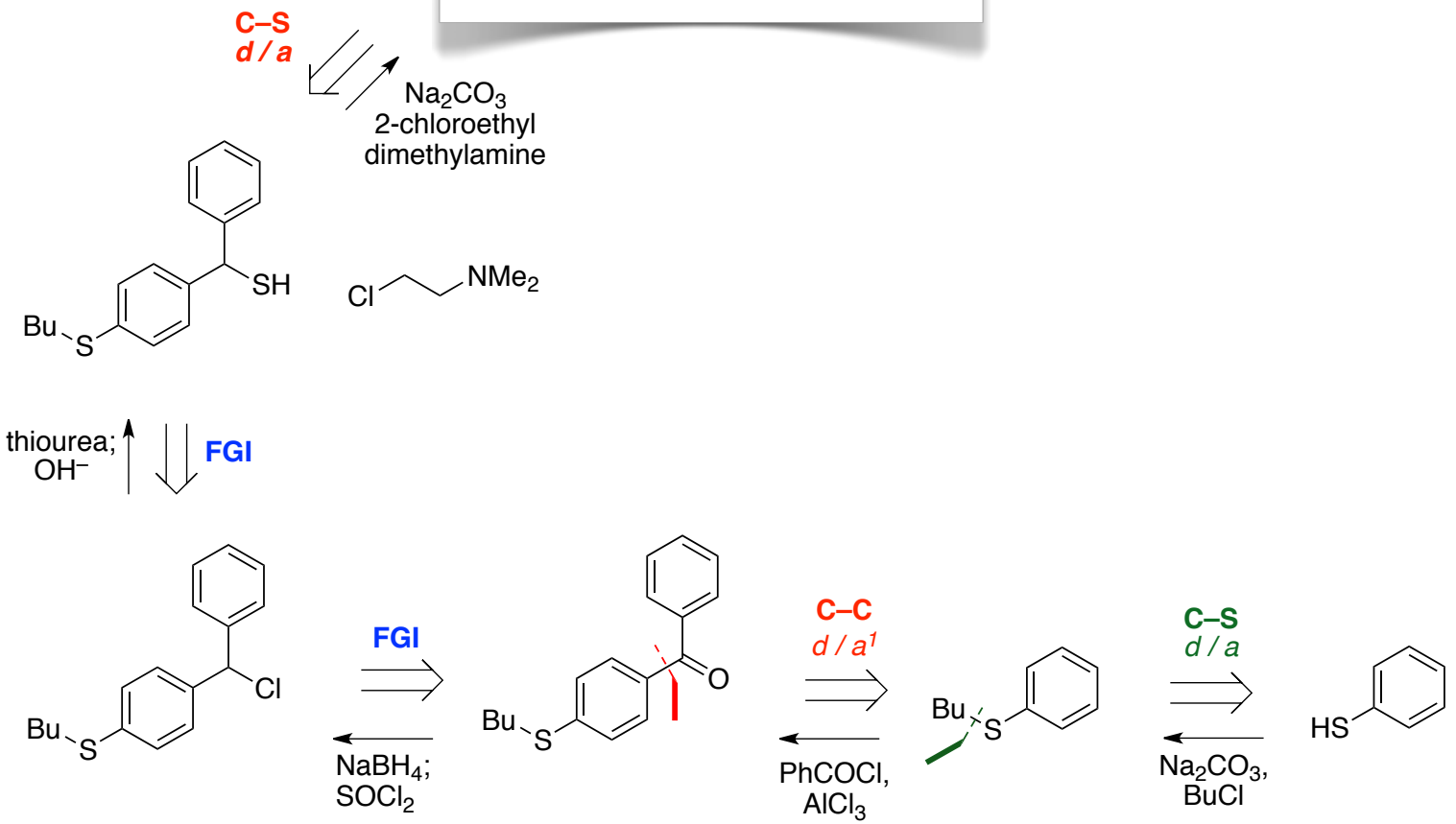
Methylamine synthesis: the Eschweiler-Clarke reaction



Exercise

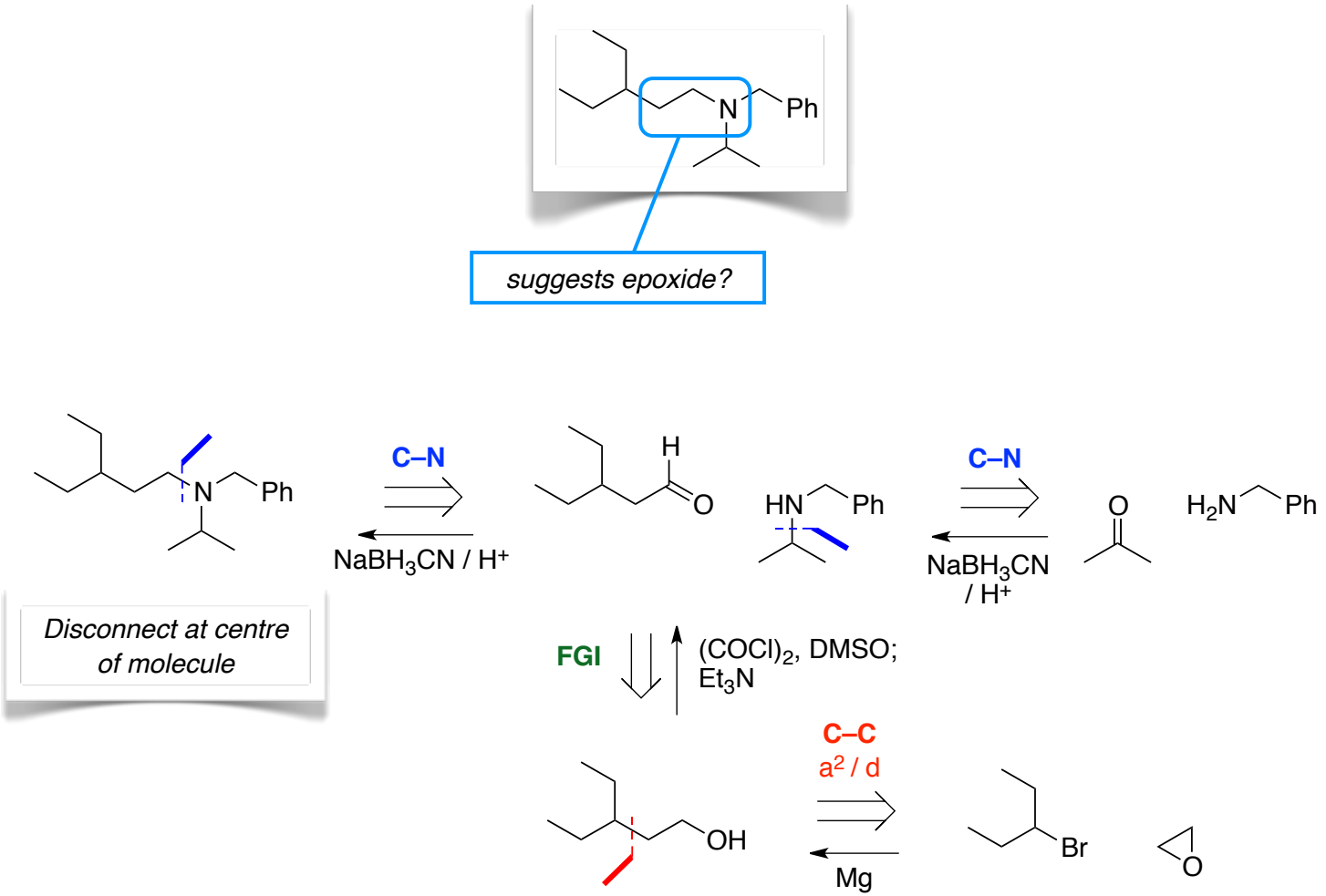
Plan a synthesis of the sedative captodiamine from thiophenol, HSC_6H_5





Exercise

Plan a synthesis of the following amine from any available starting materials!

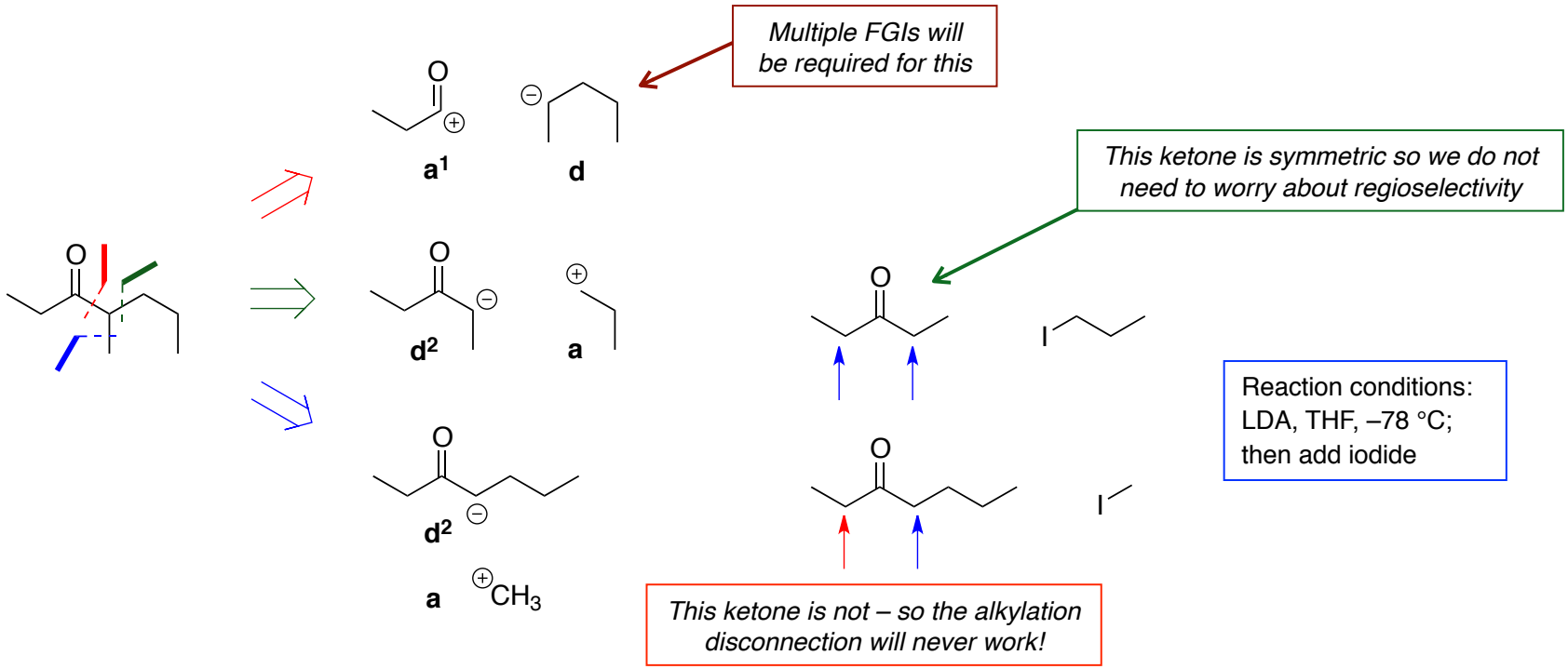


Donor synthons 2: Enolates

d^2 synthons:

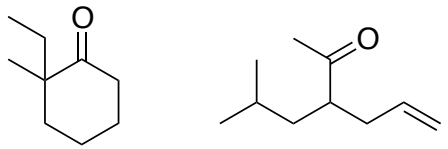
An extremely useful disconnection of carbonyls via the enolate. Enolates of almost all carbonyl derivatives are used for both alkylation, aldol, and Michael addition chemistry.

Alkylation



Key principle: Look for symmetry to help with disconnections!

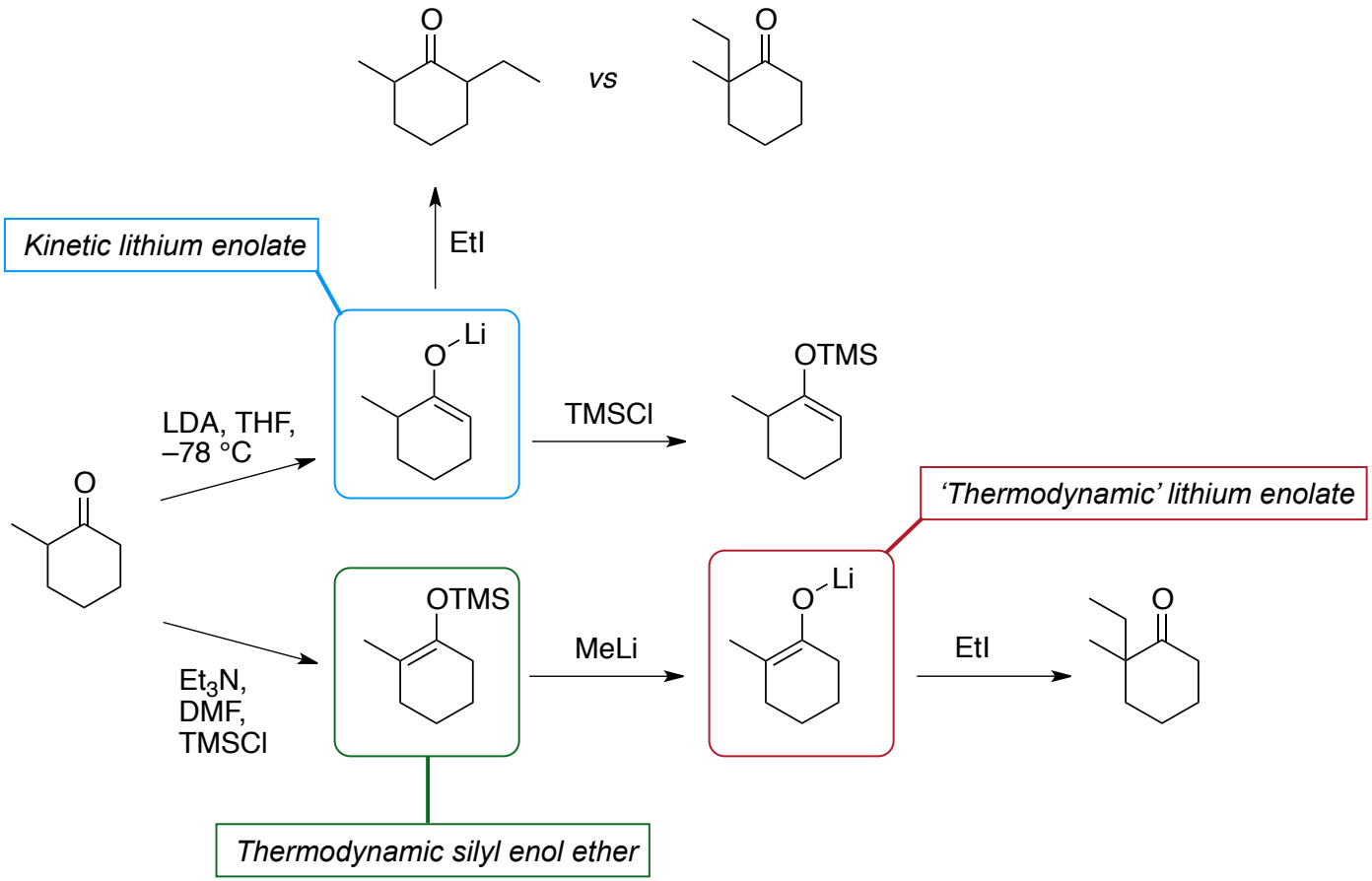
Note that alkylation doesn't always work: the following two compounds are challenging for 'normal' enolate alkylation...



Donor synthons 2: Enolates

Specific enol equivalents: When the direct alkylation won't give good selectivity, or in the absence of symmetry, we need to improve the regioselectivity of alkylation. For this, we can use a '**specific enol equivalent**' – a compound with the reactivity of an enol that affords control.

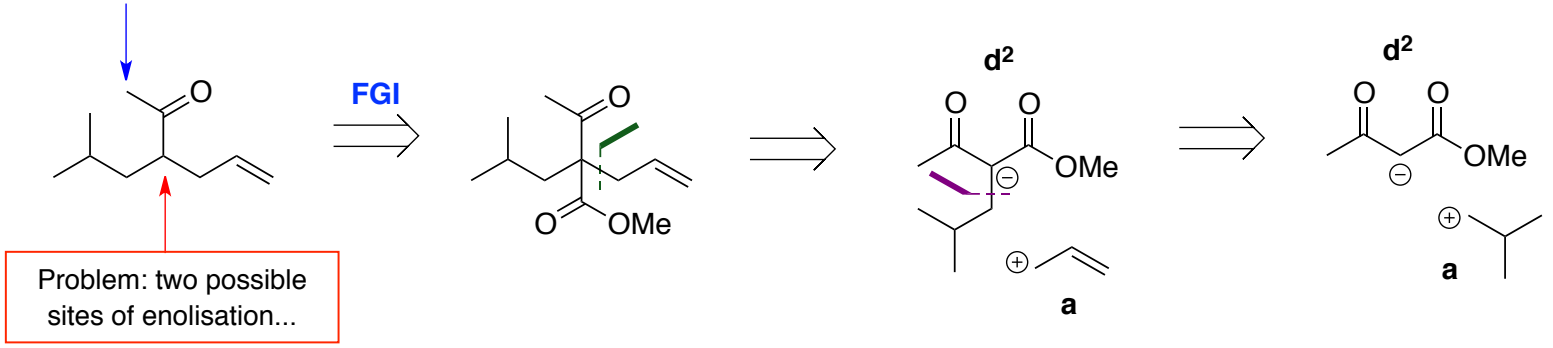
a) Silyl enol ethers



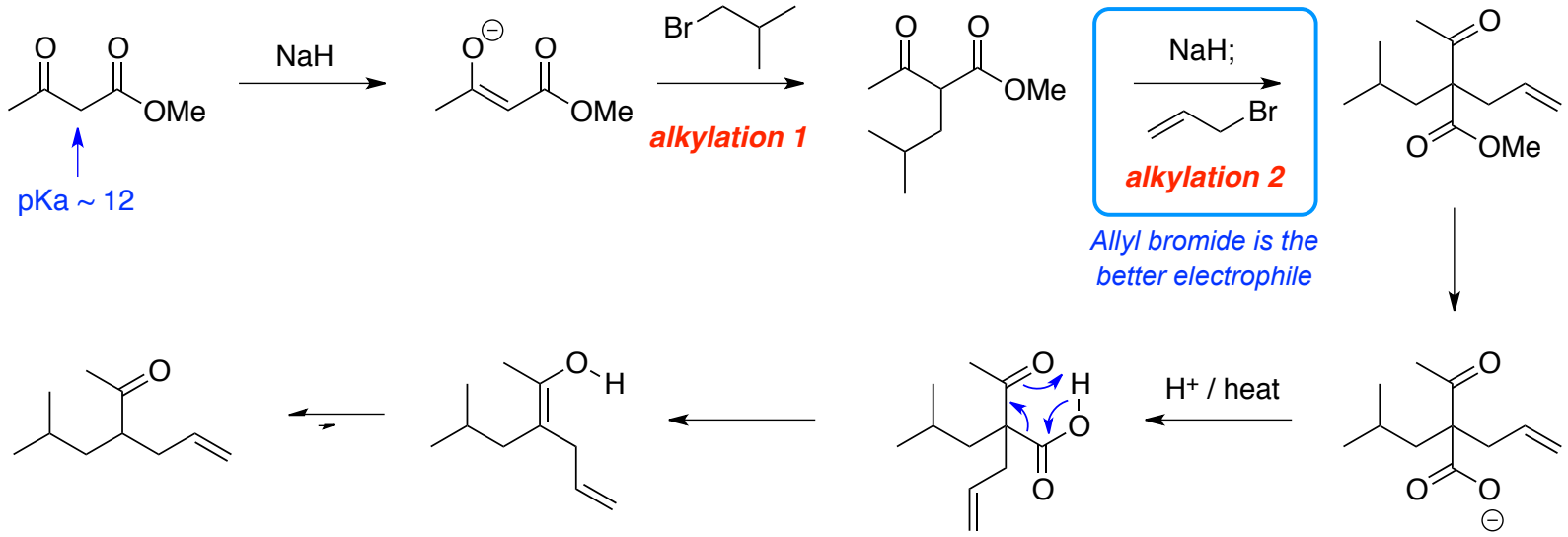
• Silyl enol ethers are also useful (required!) for (Mukaiyama) aldol chemistry...

Donor synthons 2: Enolates

b) 1,3-dicarbonyls (malonates and beta-ketoesters). These enable regioselective enolisation and are also 'soft' (i.e. good!) nucleophiles



Key principle: Re-introducing a directing functionality can greatly facilitate a synthesis!

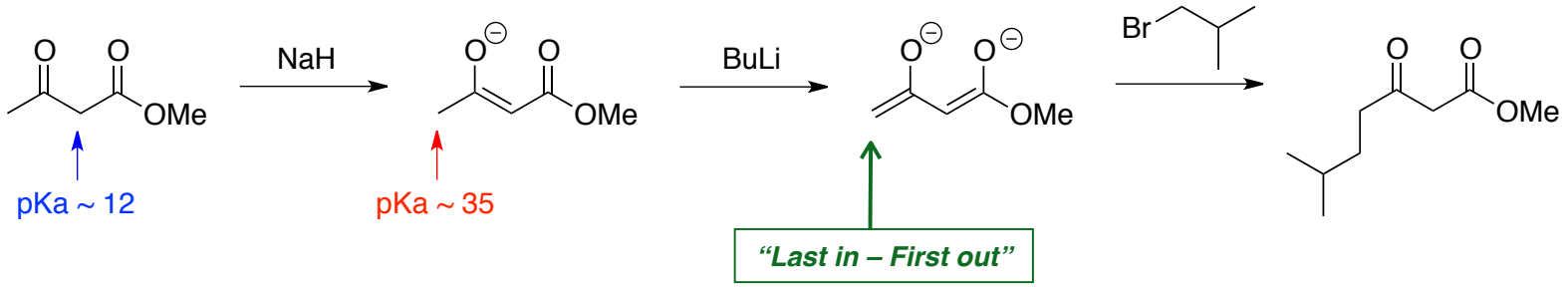


Key principle: Introduce the better electrophile / nucleophile in the more difficult step

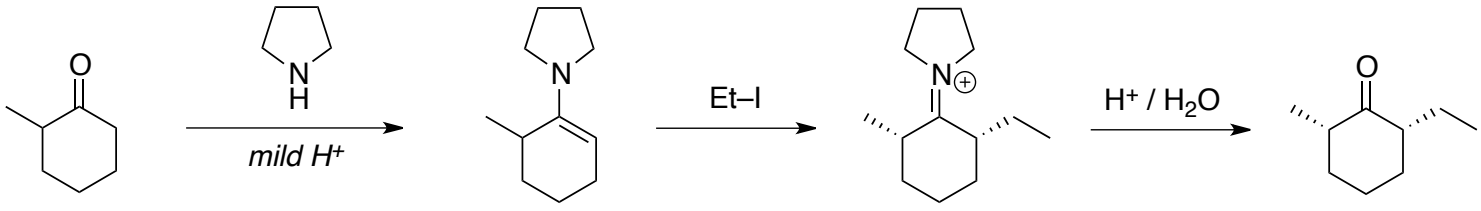
Donor synthons 2: Enolates

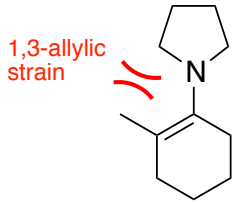
b) 1,3-dicarbonyls (malonates and beta-ketoesters)

Note: A trick for alkylation at the other position: ***form the dienolate:***



c) enamines. These 'soft' enol equivalents can be isolated, and are useful to control site selectivity of alkylation. The resultant iminium ions hydrolyse on work up. For aldehydes, they provide an attractive alternative to aldehyde enolates, which are prone to undergo self-aldol reaction.





This isomer is disfavoured by 1,3-allylic strain

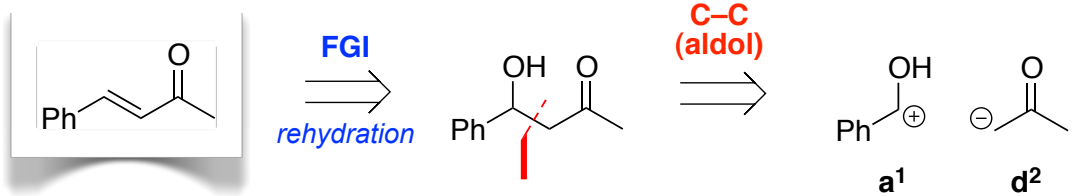
...although enamines can be useful for alkylation, they are potentially more useful to control selectivity in aldol- or Michael-type processes...

Donor synthons 2: Enolates

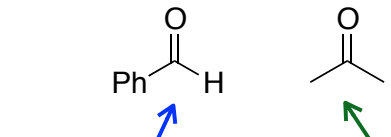
The Aldol and Michael Reactions

This will be one of the main methods by which we assemble heterocycle precursors!

Example 1:



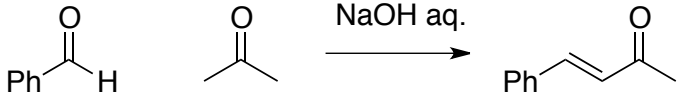
Reagents:



This aldeyde is non-enolisable!

This ketone is symmetrical!

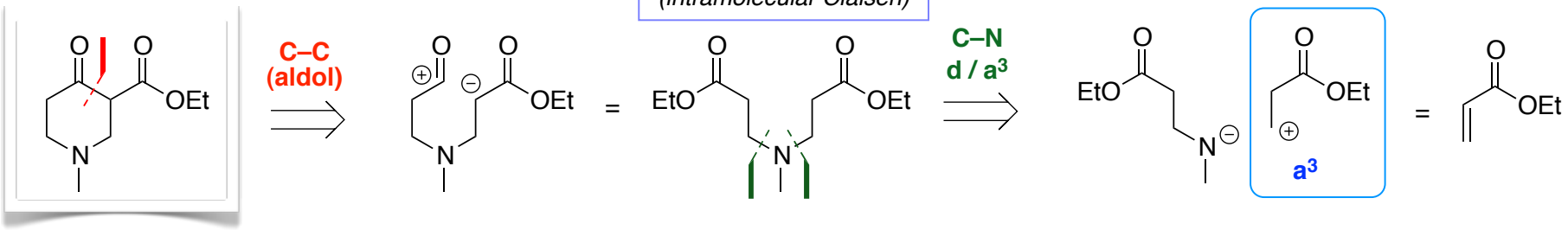
Synthesis:



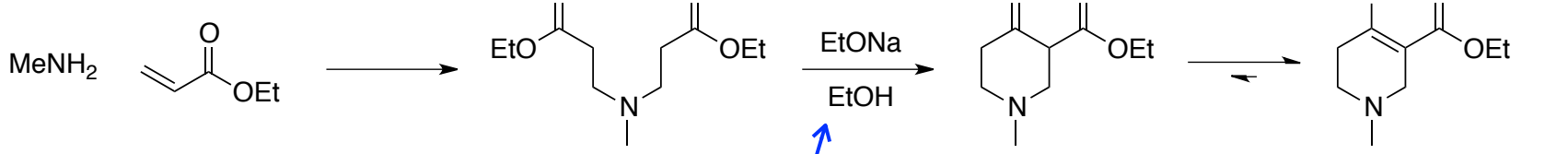
This is a good aldol disconnection as we have excellent control over the reacting partners.

Example 2:

Dieckmann cyclisation (intramolecular Claisen)



Synthesis:



Note: EtO^- used as base to 'avoid' transesterification

Note: Reaction driven by product deprotonation

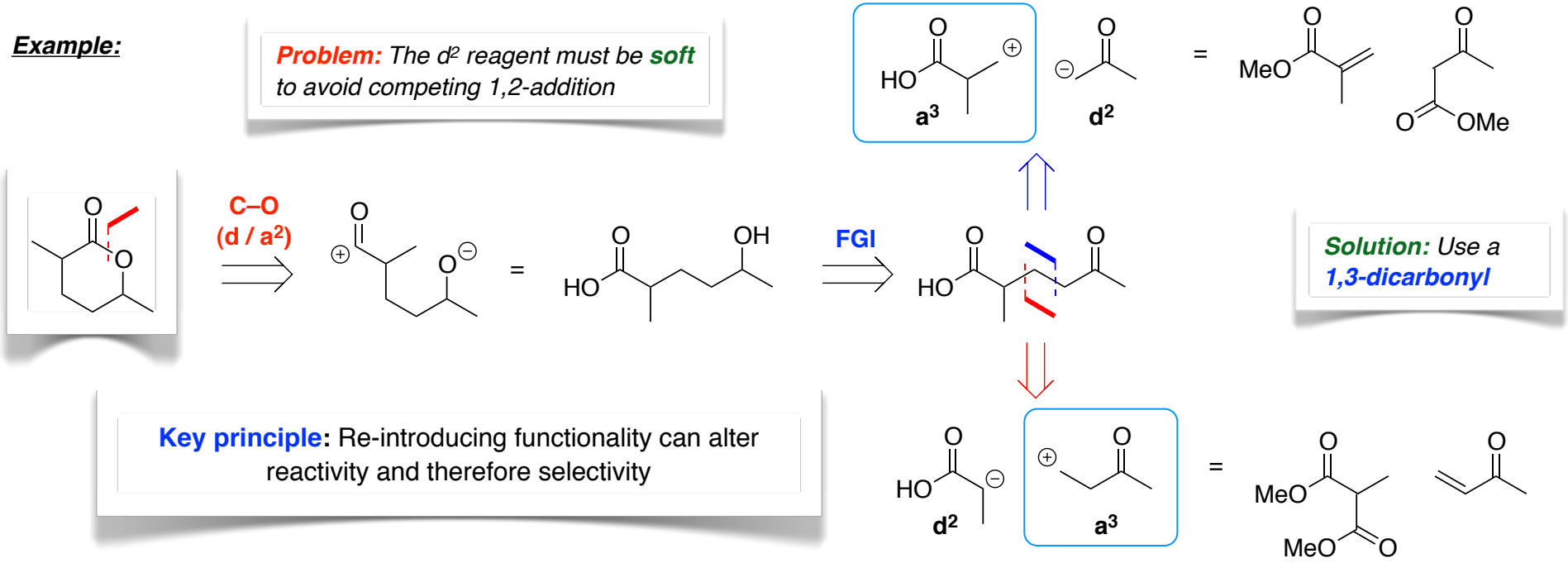
Acceptor synthons 2: Conjugate Addition

a³ synthons:

In the previous slides, we used a conjugate addition reaction of an amine and an α,β-unsaturated ester to construct a piperidone. We also used a 1,5-dicarbonyl as a source of a 6-membered ring via aldol chemistry. Where did this 1,5-dicarbonyl come from? In both cases we needed an **a³ synthon** – a Michael acceptor.

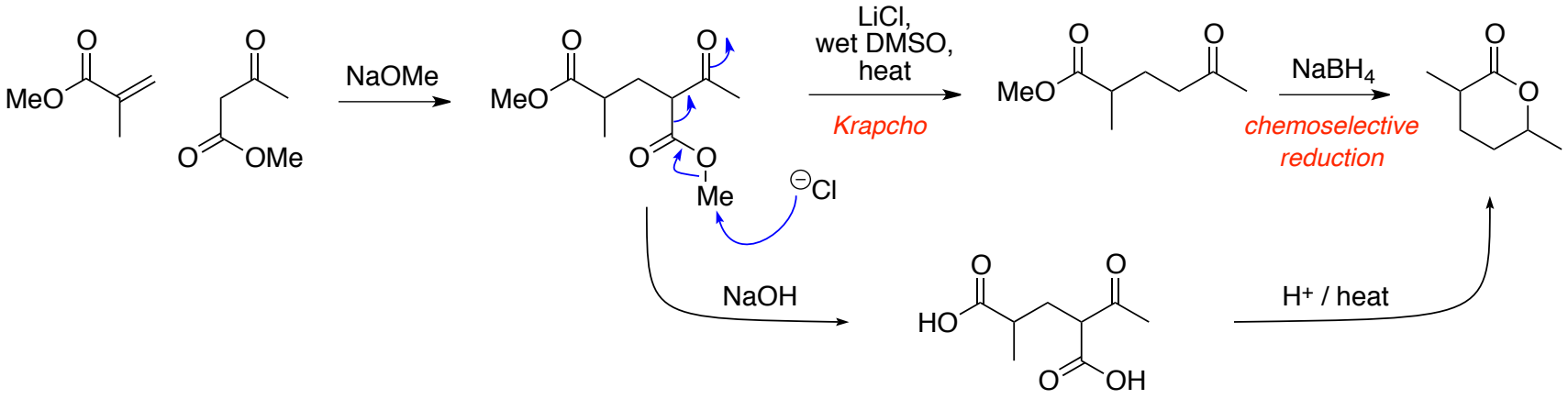
Example:

Problem: *The d² reagent must be* ***soft*** *to avoid competing 1,2-addition*



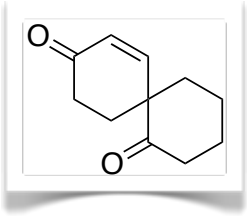
Key principle: Re-introducing functionality can alter reactivity and therefore selectivity

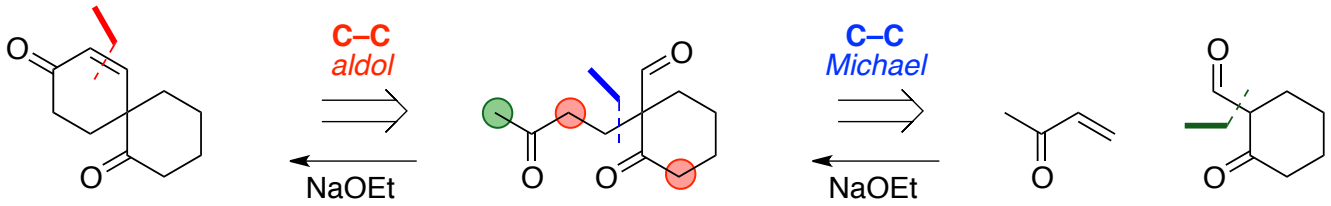
Synthesis:



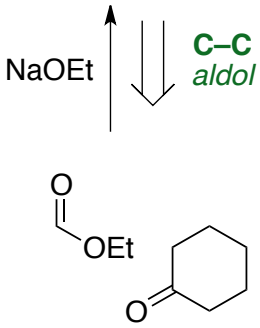
Exercise

Plan a synthesis of the following diketone from any available starting materials!

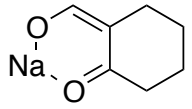




Note: Aldol is under TD control. Enolisation at other sites leads to strained rings (i.e. reversible)



Note: NaOEt 'matches' ester, which is non-enolisable

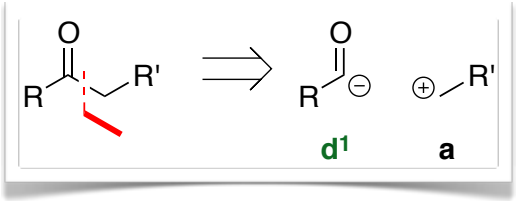


Note: product 'protected' as enolate

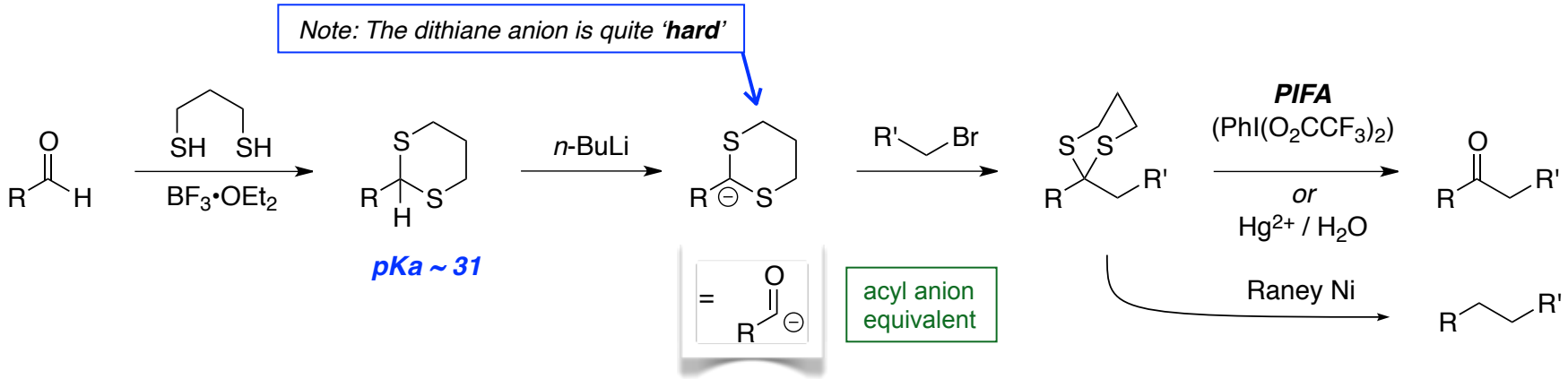
Donor synthons 3: Umpolung

d¹ synthons

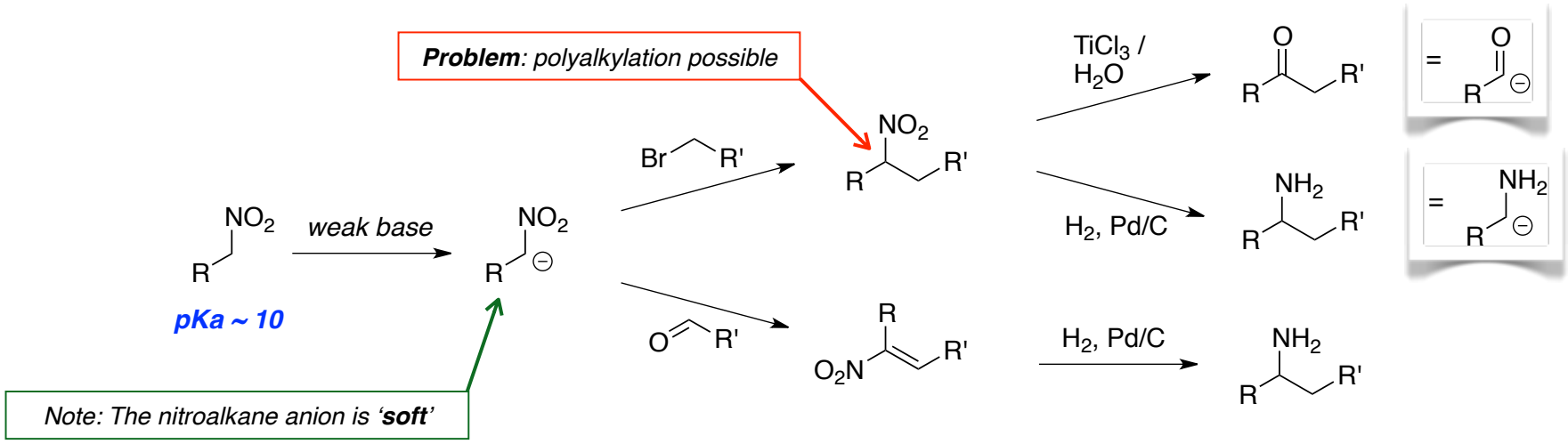
Synthons such as d¹ represent the reversal of natural polarity of the functional group. These synthons are very useful as they increase the number of methods available for bond formation!



a) Dithiane: A classical umpolung reagent, which truly converts a carbonyl into the umpolung synthon, then back to C=O.



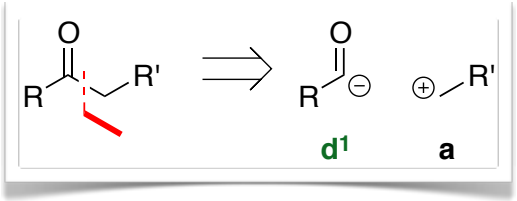
b) Nitroalkanes: A nitroalkane, although not prepared from the original carbonyl or amine, can serve as a versatile d¹ equivalent.



Donor synthons 3: Umpolung

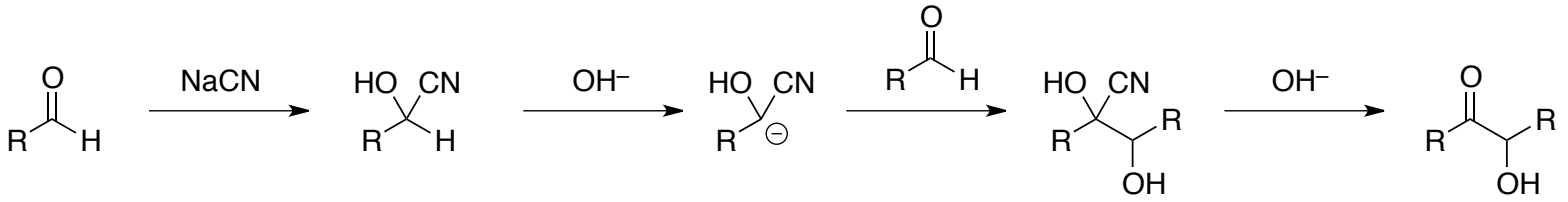
d¹ synthons

Synthons such as d¹ represent the reversal of natural polarity of the functional group. These synthons are very useful as they increase the number of methods available for bond formation!

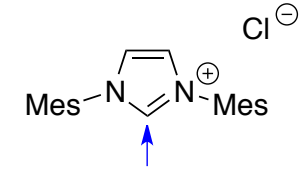


c) Cyanohydrin and related umpolung agents (Thiazolium salts, other heterocyclic carbenes)

Recall the benzoin condensation:

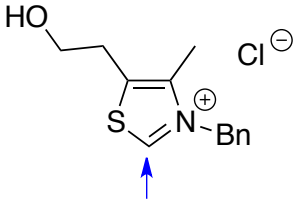


This classical reaction has been superseded by soft carbene nucleophiles such as:

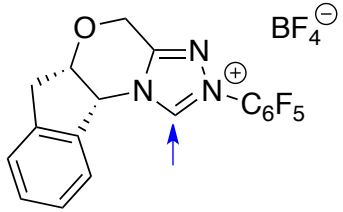


N-Heterocyclic carbenes

Readily deprotonated at ↑



Thiazolium salts
(thiamine mimics)



Triazolium salts

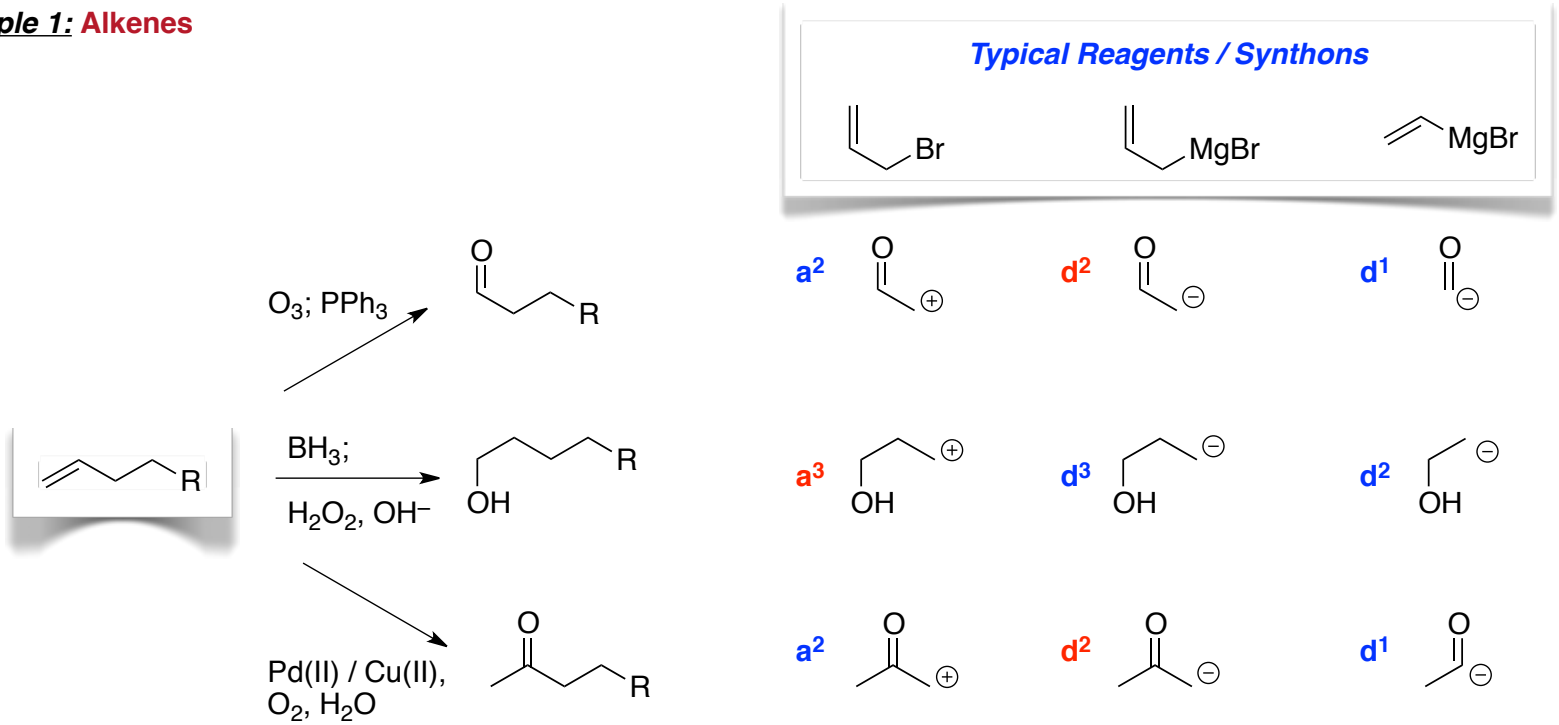
These reagents can effect benzoin type reactions, Stetter reactions (d1 conjugate addition), Baylis-Hillman type reactions, and so on. See 1,4-dicarbonyl synthesis, later....

Reviews: K Scheidt et al., *Angew. Chem. Int. Ed.* **2012**, *51*, 11686.
A. Grossmann and D. Enders, *Angew. Chem. Int. Ed.* **2012**, *51*, 314

Latent functionality

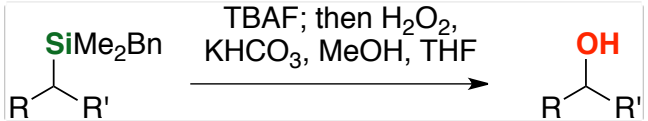
In the previous section, we saw the nitro group serving as an umpolung reagent which was later 'revealed' to be a ketone (or amine). Although on the face of it this is just an FGI, the nitro group was serving as a 'latent' carbonyl. A more accurate definition of 'latent' functionality is *the introduction of a reactive functional group in* ***unreactive form***, that can be revealed at a chosen stage of a synthesis.

Example 1: **Alkenes**



The alkene serves as a latent carbonyl or alcohol, and as an acceptor or donor synthon; it is unreactive towards conditions which the carbonyls and alcohols are reactive.

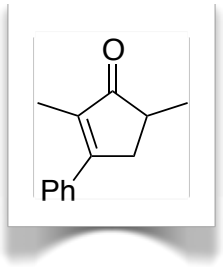
Example 2: **Silanes**

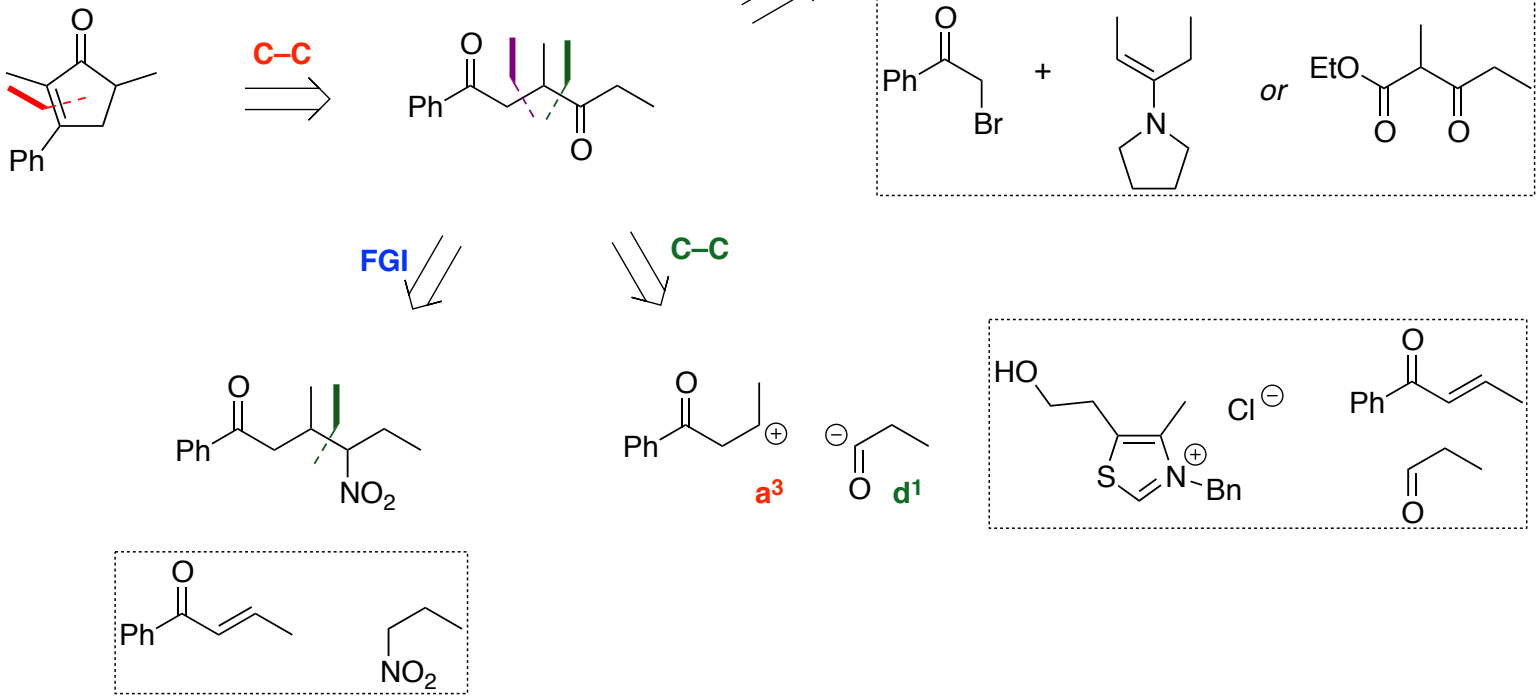


...note analogy to protecting groups...

Exercise

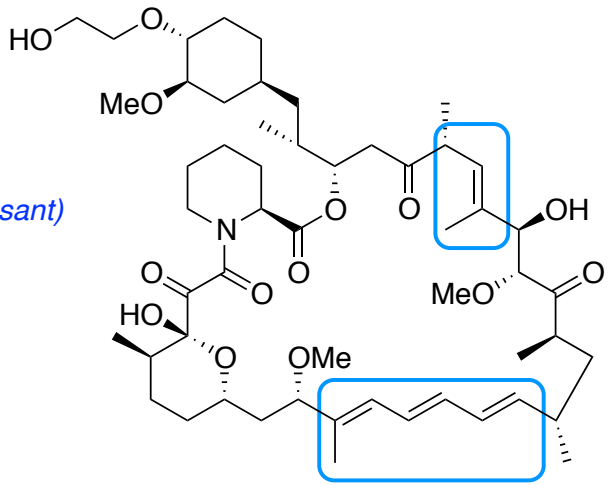
Plan a synthesis of the following enone from any available starting materials!





Alkene / Alkyne synthesis

Alkenes are not only useful as masked functionality, or as a source of diols, epoxides, etc., but are also found in many bioactive targets, particularly natural products. An example of this is Novartis' **everolimus**. Although not directly prepared by synthesis, its parent rapamycin has been synthesised a number of times, and chemists need to address this alkene synthesis. Here we recap some important methods for doing just that.



Everolimus
(immunosuppressant)
(Novartis)

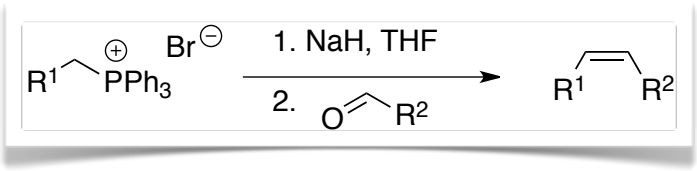
Olefination methods:

- Aldol / dehydration
- Heteroatom mediated: Wittig, Horner-Wadsworth Emmons, Julia, Peterson
- Metathesis
- Cross-coupling (for dienes etc.), Heck reaction
- Alkyne semihydrogenation
- Metal-mediated olefinations: (Takai, etc.)

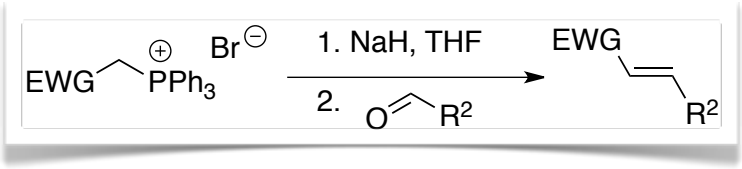
Key Principle: Aside from metathesis, aldehydes are key precursors to alkenes and alkynes

Alkene / Alkyne synthesis

Heteroatom Method 1: Wittig



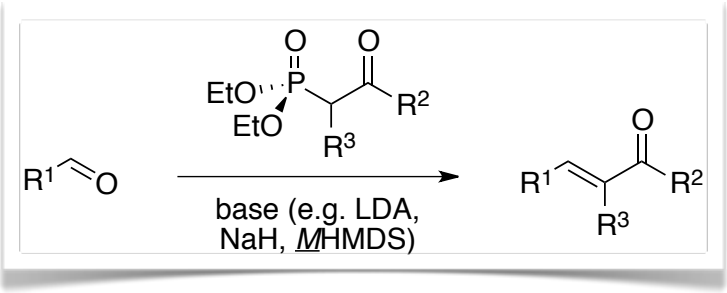
Non-stabilized ylid:
(*Z*)-selective



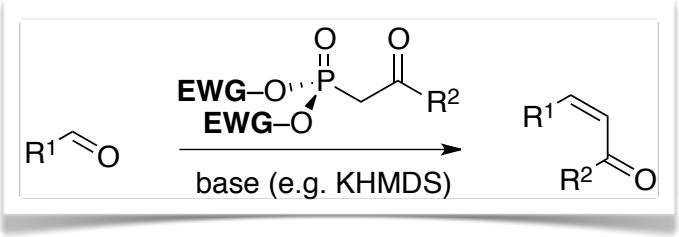
Stabilized ylid:
(*E*)-selective

EWG = ester, ketone, aldehyde, nitrile, aryl

Heteroatom Method 2: Horner-Wadsworth-Emmons: **A VERY NICE WAY TO MAKE MICHAEL ACCEPTORS!**



electron-rich
phosphonate:
(*E*)-selective



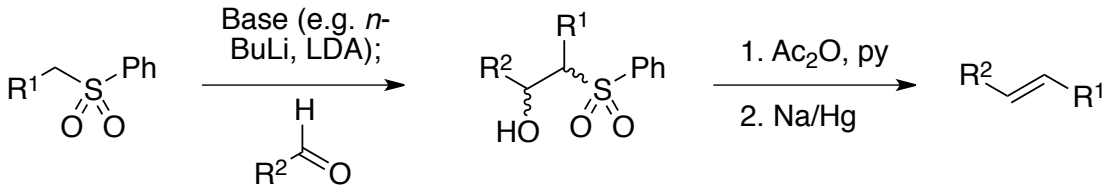
electron-poor
phosphonate:
(*Z*)-selective

EWG = CH_2CF_3 *Still-Gennari*
EWG = Ph *Ando*

For mechanisms:
See Appendix

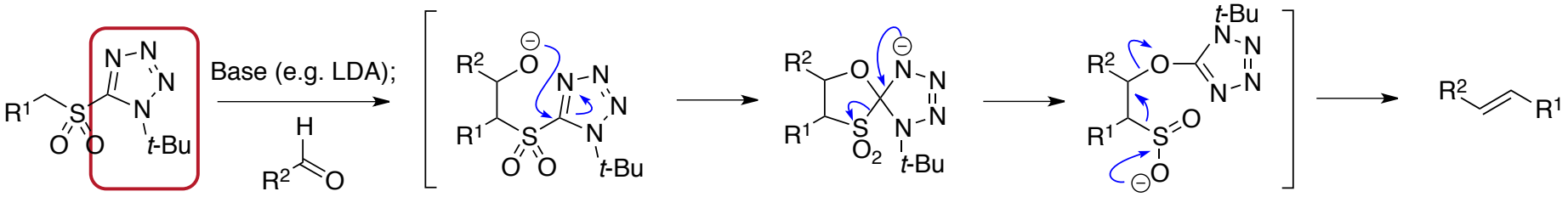
Alkene / Alkyne synthesis

Heteroatom Method 3: Julia



Highly (*E*)-selective

Heteroatom Method 4: Modified Julia



One step – but selectivity can be variable

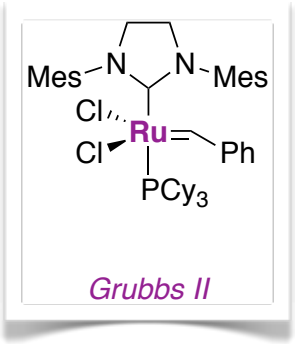
A heteroaromatic group capable of acting as an electrophile. Commonly phenyltetrazole (PT), benzothiazole (BT), t-butyltetrazole (TBT)

Recent review: C. Aïssa, *Eur. J. Org. Chem.* **2009**, 1831

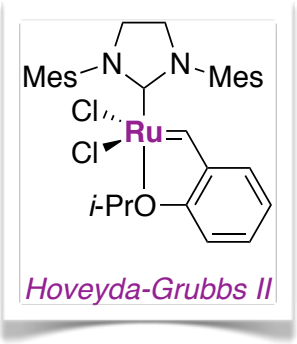
Alkene / Alkyne synthesis

Metal-Mediated reaction 1: Metathesis

Catalysts of choice:



Grubbs II

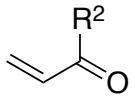


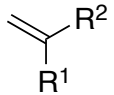
Hoveyda-Grubbs II

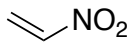
Drawback:

Classes of alkene for cross-metathesis:

Type 1: Rapid homodimerization, homodimers consumable ***e.g.*** 

Type 2: Slow homodimerization, homodimers sparingly consumable ***e.g.*** 

Type 3: No homdimerization ***e.g.*** 

Type 4: Olefins inert to CM but do not deactivate catalyst ***e.g.*** 

Examples of reactions for which metathesis is particularly useful:

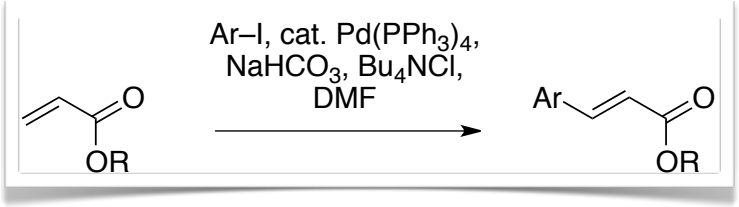
RCM for ring sizes ≥5. Particularly useful for medium ring synthesis, and macrocycles. And normal rings.

High E-selectivity. For a beneficial effect of CuI on this reaction (yield / rate) see *JOC* **2011**, *76*, 4697

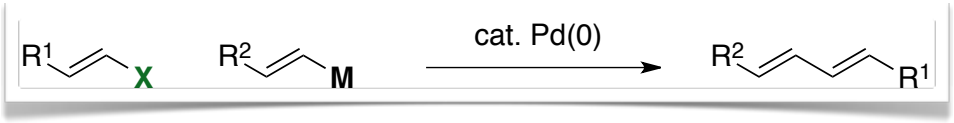
For classification of alkenes in cross-metathesis, see: Grubbs et al. *JACS* **2003**, *125*, 11360
For a review of cross-metathesis, see: Blechert and Connon, *Angew. Chem. Int. Ed.* **2003**, *42*, 1900

Alkene / Alkyne synthesis

Metal-Mediated reaction 2: Heck Reaction



Metal-Mediated reaction 3: Cross-coupling



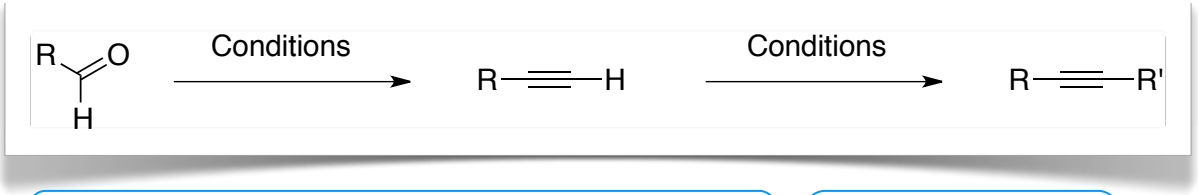
See appendix for synthesis of alkenyl halides and metals

Metal-Mediated reaction 4: Lindlar Hydrogenation

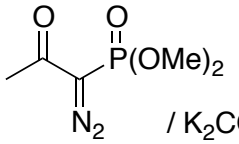
Catalysts: H_2, $Pd/BaSO_4$ *or* $Pd/CaCO_3$
Poisons: quinoline, ethylenediamine

P-2-Ni: $Ni(OAc)_2 + NaBH_4$, MeOH

Synthesis of Alkynes:

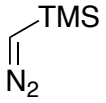


- *Corey Fuchs:* CBr_4 / 2 PPh_3 *(often w/ Zn or Et_3N)*
- *Ohira-Bestmann:*



/ K_2CO_3, MeOH

- *Gilbert-Seyferth:*



/ *n*-BuLi

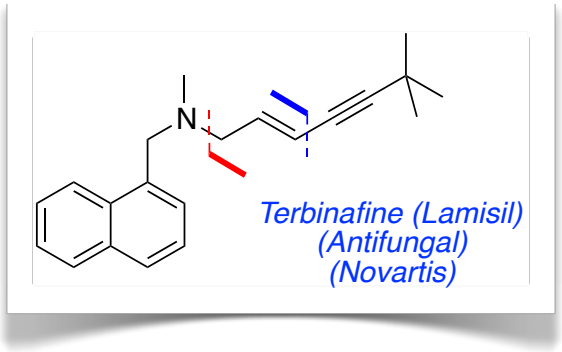
n-BuLi; R'–I
(or other electrophile)

Pd(0), CuI, Ar–I
(*Sonogashira*)

See appendix for other methods

Exercise

Plan a synthesis of terbinafine (lamisil).



e.g. X = Br: K_2CO_3
e.g. X = OAc: Pd(0)

C–C
allylation

C–C
Sonog.

cat. $PdCl_2(PhCN)_2$
cat. CuI
piperidine

expensive

NHMe

X

N

Cl

expensive

FGI

PBr_3

E/Z imperfect

K_2CO_3, KI,
DMF

OH

NHMe

Cl

Cl

C–C

toxic

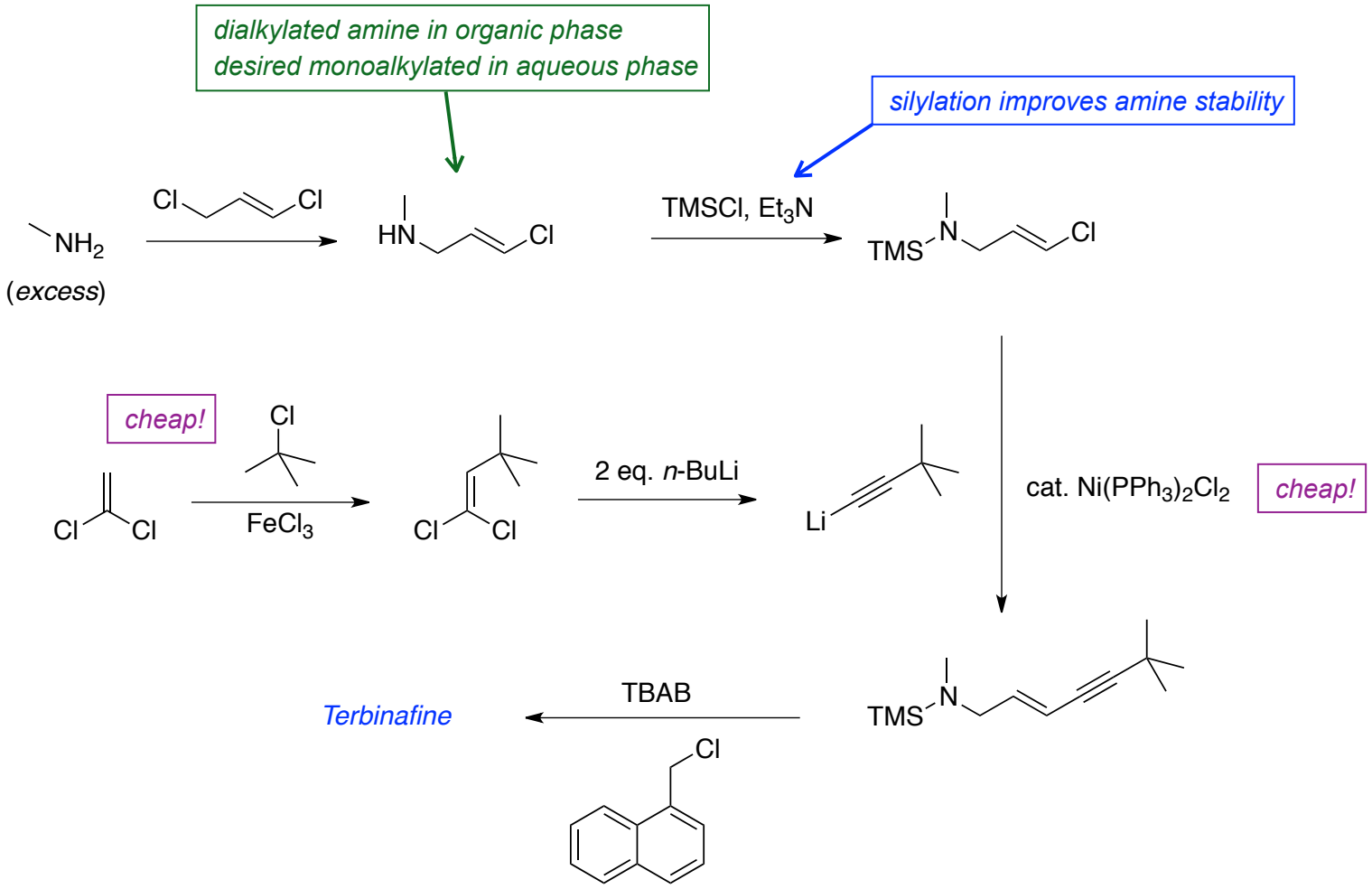
O

expensive

TL **1996**, *37*, 57.
EP1753770

Exercise

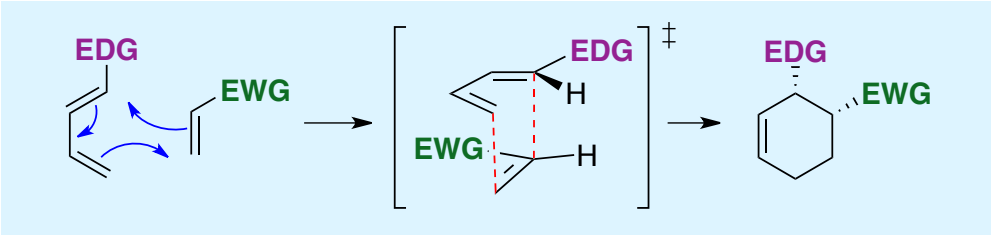
Process route:



TL **1996**, *37*, 57.
EP1753770

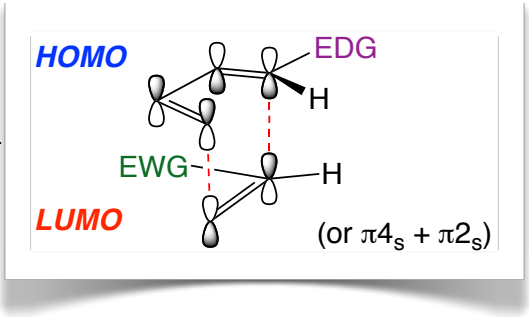
Diels-Alder disconnection

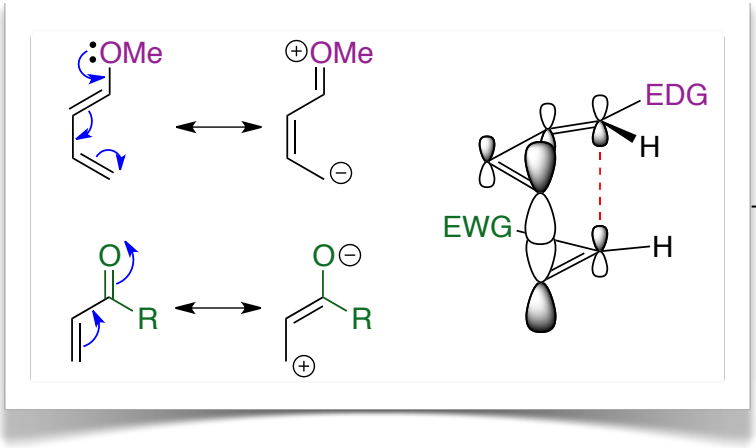
Diels-Alder chemistry allows us to construct cyclohexene systems with high efficiency and stereocontrol:



Selectivity:

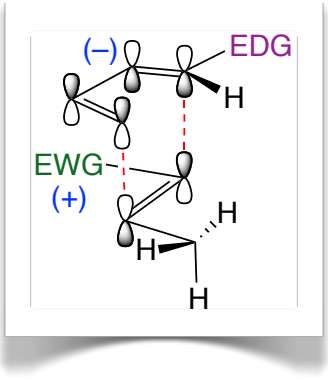
• Orbital energy considerations mean ideal DA setup is electron rich diene (HOMO) + electron poor dienophile (LUMO)





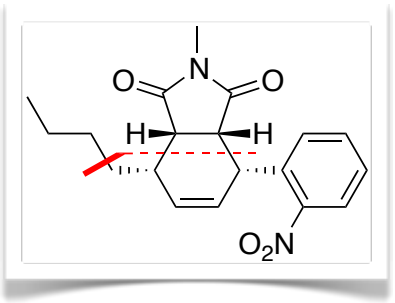
• Regioselectivity reflects overlap of the largest coefficients of these orbitals

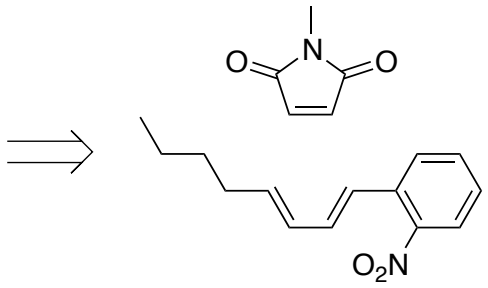
• *Endo*-stereoselectivity classically explained by secondary orbital effects, but is more likely due to electrostatic or steric effects

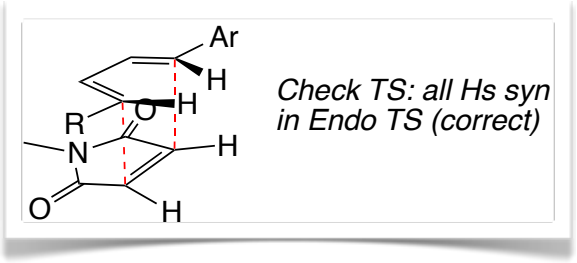


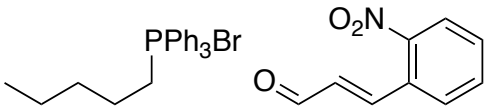
Diels-Alder disconnection

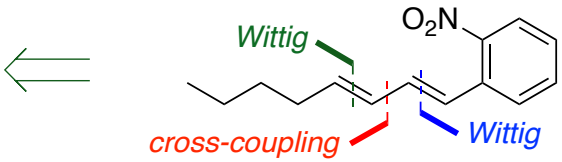
Example 1:

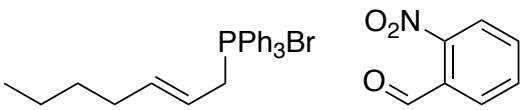






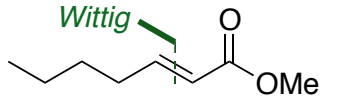


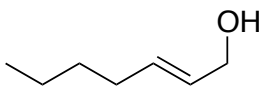




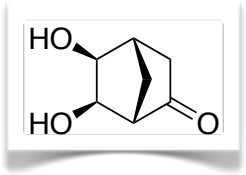
- enal easy to make by aldol / dehydration
- stereoselectivity of Wittig is wrong!

FGI



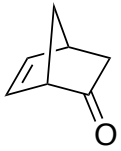


Example 2:



FGI

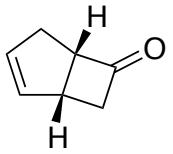
cat. OsO_4, NMO



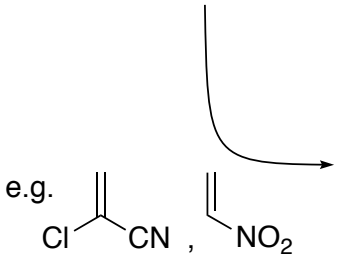
Note: stereoselective exo-face dihydroxylation

D-A??

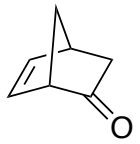
[2+2]



- We need a 'ketene equivalent'

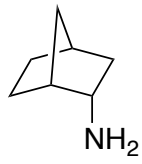


$TiCl_3$, H_2O



'ketene DA equivalent'

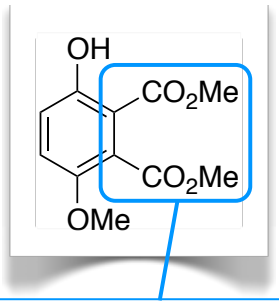
H_2, Pd/C



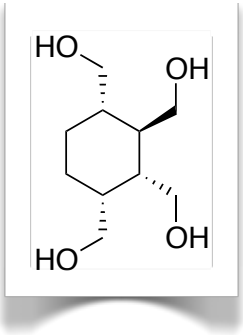
'enamine DA equivalent'

Exercise

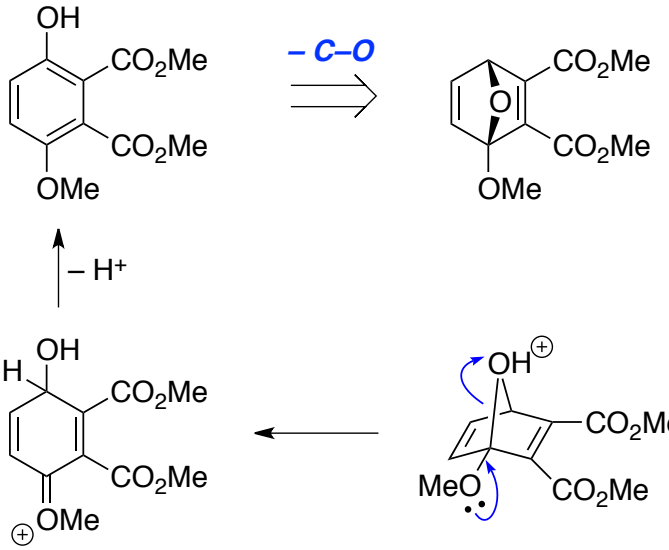
Plan a synthesis of the following molecules using Diels-Alder chemistry



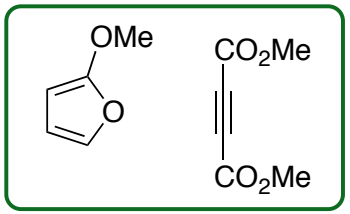
Recognise potential dienophile

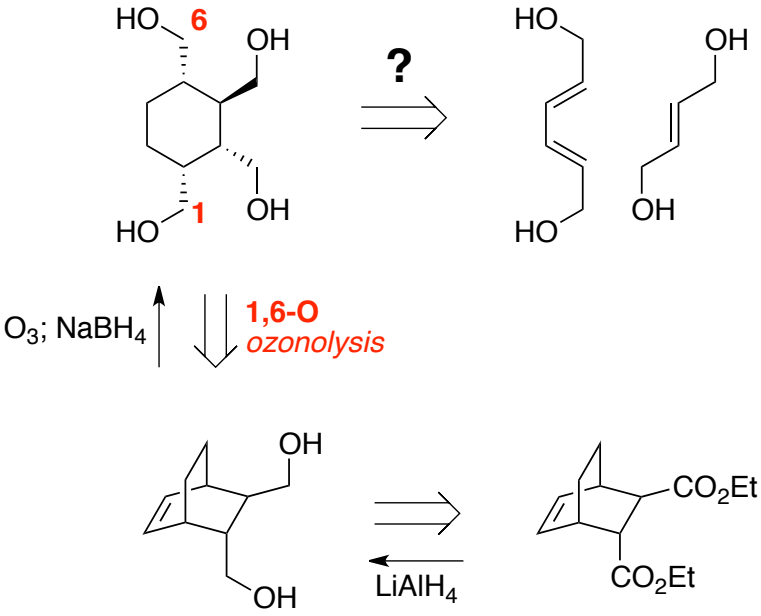


Whilst we could probably do FGIs to make this work, there is an alternative....



Good electronics! (furan e-rich)



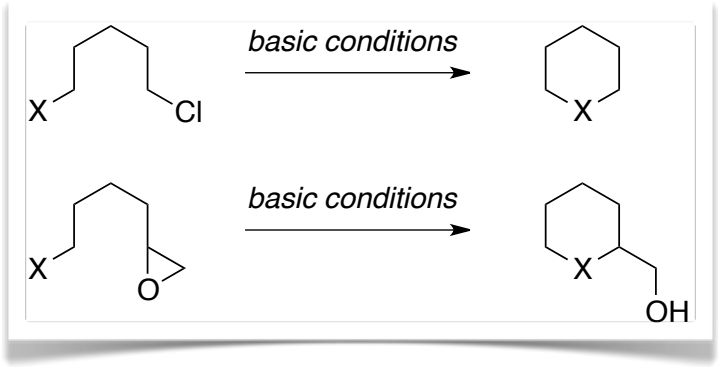


Alkene ozonolysis can reconnect 1,6-dioxygenation

Saturated Heterocycles

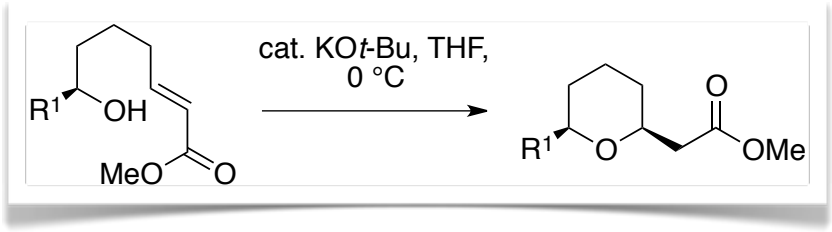
The synthesis of saturated heterocycles can be achieved in many ways; the common theme to most of these is to use the nucleophilicity of the heteroatom.

1. S_N2 Cyclisation onto halides, epoxides, etc.



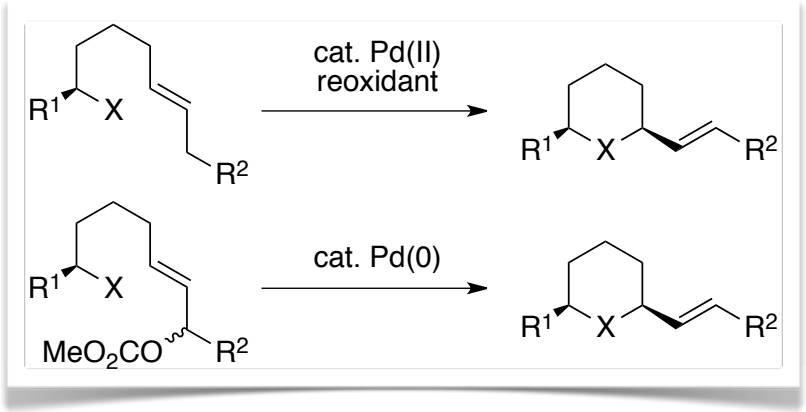
- Works well for 3, 5, 6 and 7-membered rings, and azetidines
- Irreversible – S_N2 reactivity – stereochemistry of sm converted into products
- However this means stereochem of sm must be controlled

2. Cyclisation onto Michael acceptors



- Particularly good for pyran synthesis.
- Usually operates under thermodynamic control, so equatorial product is favoured.

3. Palladium-mediated cyclisations



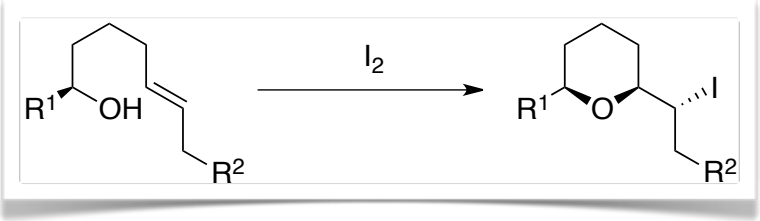
- Wacker or Tsuji-Trost type reactivity; stereochemistry controlled by equatorial disposition of sidechain; or potentially by carbonate stereochemistry

Reviews: Muzart, *J. Mol. Cat. A: Chemical* **2010**, *319*, 1
Wolfe, *Eur. J. Org. Chem.* **2007**, 571

General reviews of oxacycle synthesis:
Larossa, Romea, Urpi, *Tetrahedron* **2008**, *64*, 2683
Wolfe, *Tetrahedron* **2007**, *63*, 261

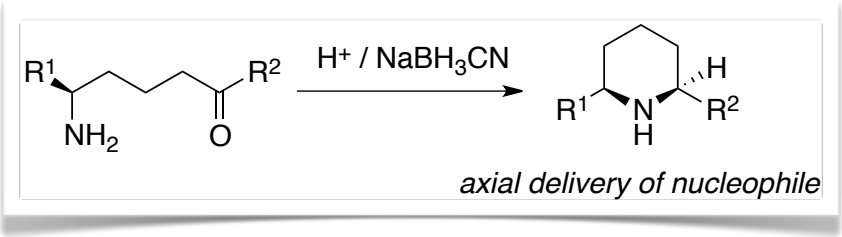
Saturated Heterocycles

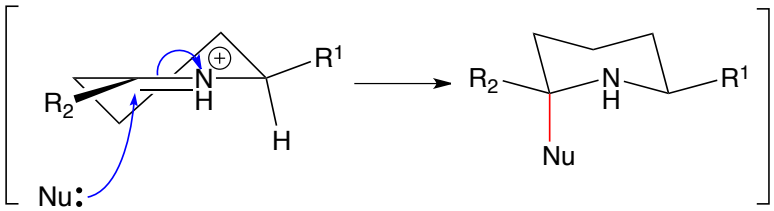
4. Electrophile-promoted cyclisation onto alkenes



• Iodoetherification or iodolactonisation, and other good electrophiles, promote this reaction. Stereoselective for equatorial sidechain.

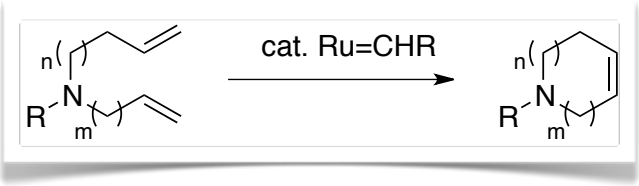
5. Reductive cyclisation processes (cyclisation onto carbonyls)





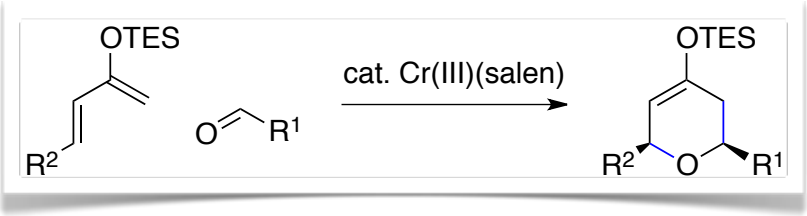
• Nucleophile delivered axial for stereoelectronic reasons

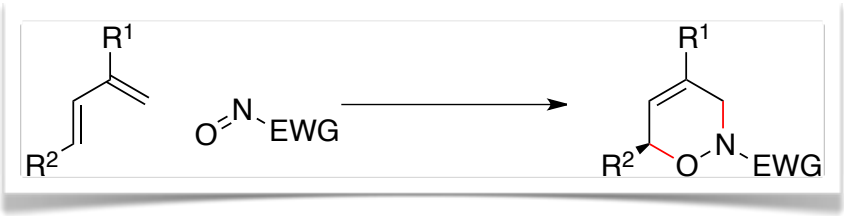
6. RCM



• Particularly useful for medium-sized rings!

7. Hetero-Diels-Alder reactions and other cycloadditions



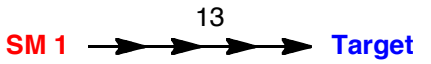


For a review, see: Pellissier, *Tetrahedron* **2009**, *65*, 2839

Disconnection Strategy Summary

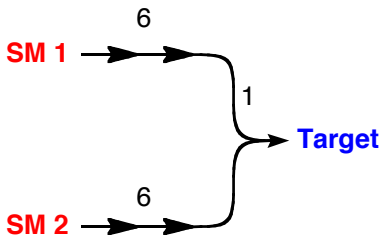
1. Make the synthesis as short as possible!

Linear



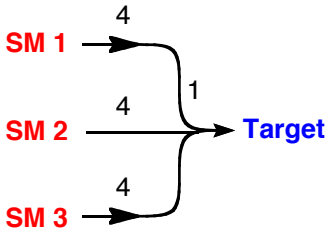
13 steps @ 90% = 0.9^{13} = **25% yield**

Convergent



6 steps @ 90% + 1 step @ 90%
= 0.9^{7} = **48% yield**

Multicomponent



4 steps @ 90% + 1 step @ 90%
= 0.9^{5} = **59% yield**

2. Use only known disconnections

3. Disconnect back to oxygen where possible (provides better control)

4. Disconnect C–C bonds using available (or reintroduced) FGs, and:

5. Disconnect near the middle of the molecule (e.g at branch points, or disconnect rings from chains)

6. Use symmetry

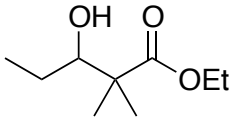
7. Use the 'best' disconnection / forward reaction as late as possible in the synthesis

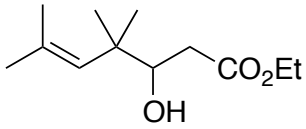
8. Use FGIs – but as few as possible

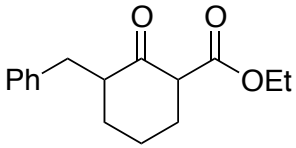
9. Look for available sms hiding in the molecule

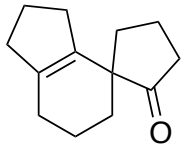
Problem Session 1

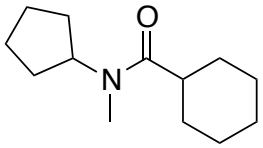
Propose syntheses of the following compounds from starting materials of your choice

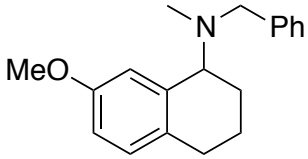
a) 

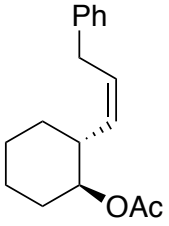
b) 

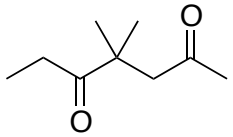
c) 

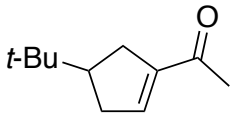
d) 

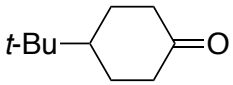
e) 

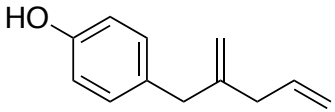
f) 

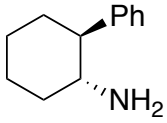
g) 

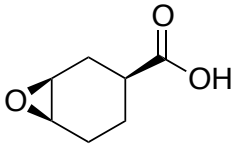
h) 

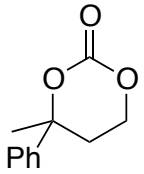
i) 

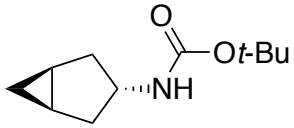
from 

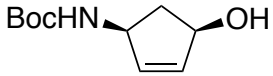
j) 

k) 

l) 

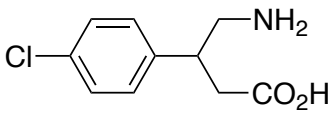
m) 

n) 

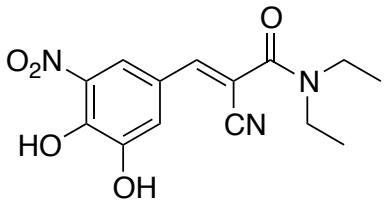
o) 

Problem Session 1

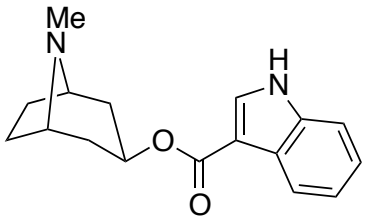
Propose syntheses of the following pharmaceutical agents from starting materials of your choice



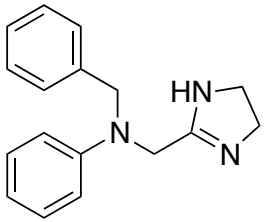
Baclofen
(Novartis)



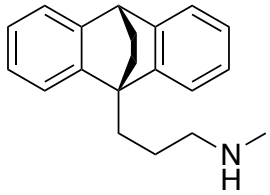
Entacapone
(Parkinson's)
(Novartis)



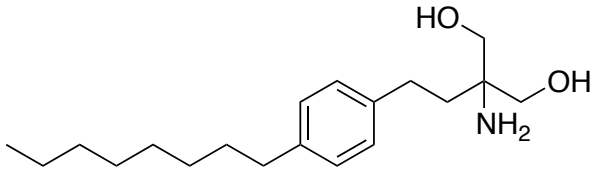
Tropisetron
(antiemetic)
(Novartis)



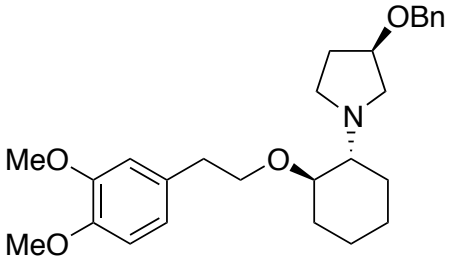
Antazoline
(Antihistamine)
(Novartis)



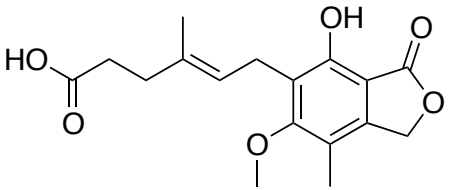
Maprotiline
(antidepressant)
(Novartis)



Fingolimod
(Immunosuppressive)
(Novartis)



Vernakalant (benzyl ether)
antiarrhythmic agent
Merck



Mycophenolic acid
(Immunosuppressant)
(Novartis)

Retrosynthesis: Course Outline

UNIVERSITY OF OXFORD

The principles of retrosynthesis

- Introduction to retrosynthesis: The origins of the subject, nomenclature, how we go about breaking up molecules
- Key strategic considerations: Functional group interconversions, selectivity, protecting groups
- Synthons and Reagents: Acceptor and Donor synthons – how to recognise these disconnections and the importance of (di)oxygenation relationships
- Focus on specific reaction types and methods to install functionality (e.g. amines, alkenes, cycloadditions, cross-coupling)
- Worked examples throughout these topics
- ***Interactive Problem session***: Extended practice with 'classical' disconnection problems

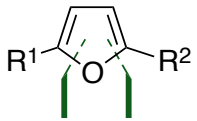
Retrosynthesis in medicinal chemistry

- Coverage of 5- and 6-membered aromatic heterocycle disconnections with worked examples
- Advanced disconnections of arenes
- Asymmetric synthesis including worked examples
- Case studies to illustrate principles
- ***Interactive Problem session***: Extended practice with a range of pharmaceuticals

Aromatic heterocycle synthesis 1: Furans, Pyrroles, Thiophenes

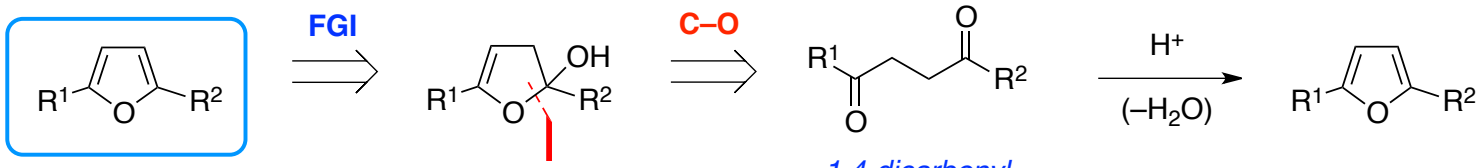
The general theme disconnecting aromatic heterocycles is to cleave C–X bonds within the ring, with a carbonyl precursor. Here we recognise these C–X bonds as being enols, or imines / enamines (for O, N heterocycles).

Furans: Recognise 2 x enol in target



2 x enol

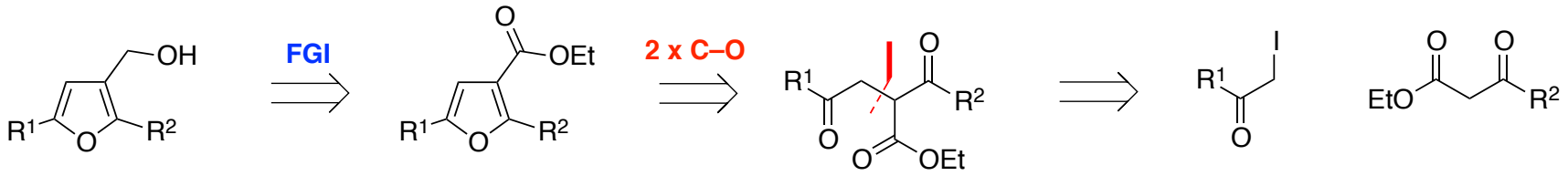
• *Although not technically correct, this manner of heterocycle analysis can be very convenient.*



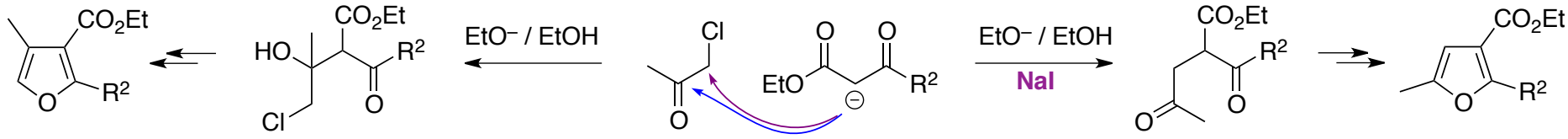
1,4-dicarbonyl

(See earlier slides on carbonyl synthesis + next section)

Extensions: As more substituents are present, modify the 1,4-dicarbonyl synthesis!



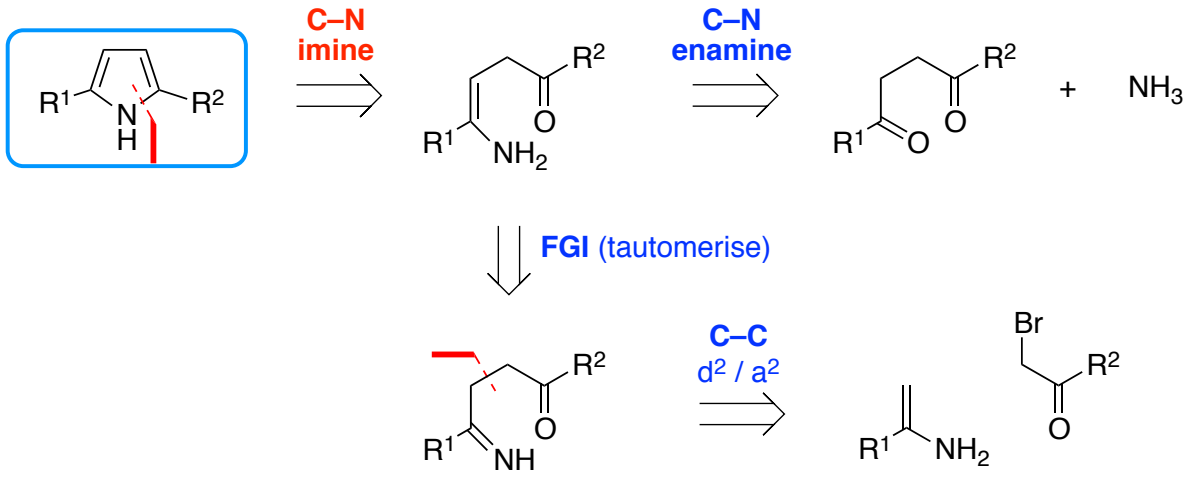
Reality!: Outcome depends on electrophile and conditions....

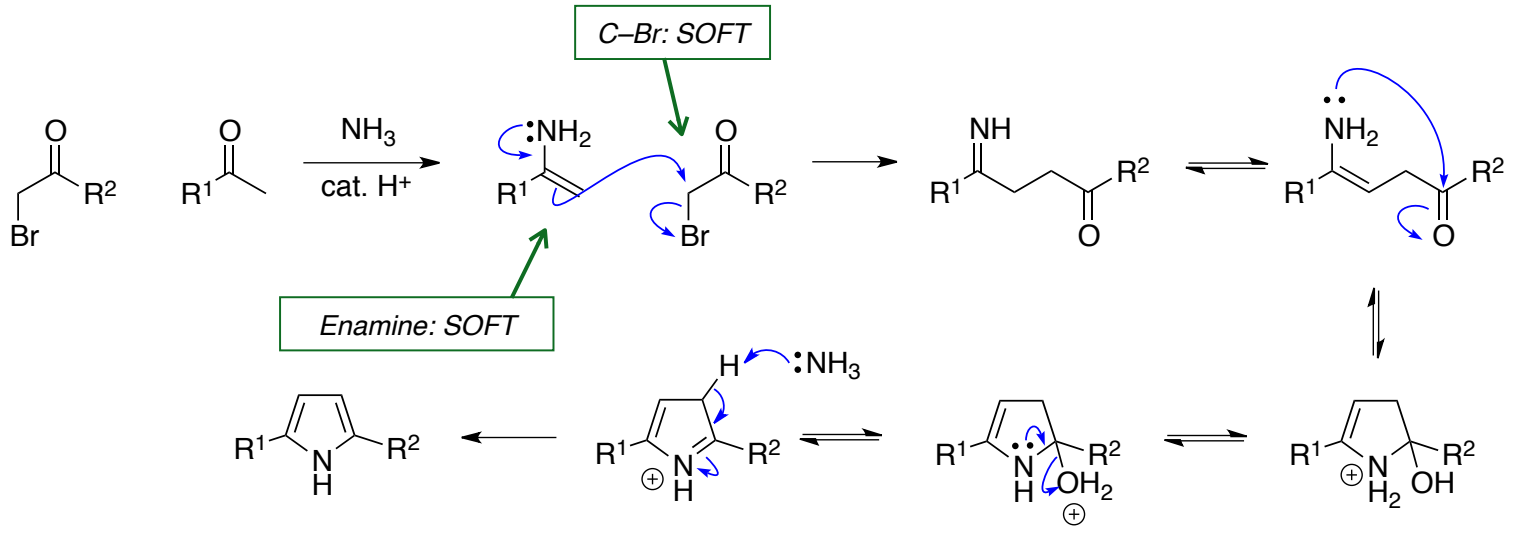


Aromatic heterocycle synthesis 1: Furans, Pyrroles, Thiophenes

The general theme disconnecting aromatic heterocycles is to cleave C–X bonds within the ring, with a carbonyl precursor. Here we recognise these C–X bonds as being enols, or imines / enamines (for O, N heterocycles).

Pyrroles: Simply use ammonia (or primary amine) to effect cyclization!

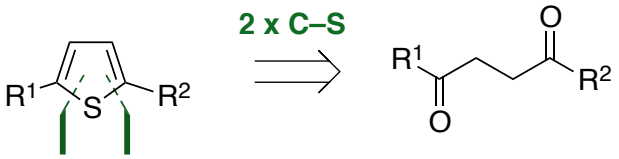




Aromatic heterocycle synthesis 1: Furans, Pyrroles, Thiophenes

The general theme disconnecting aromatic heterocycles is to cleave C–X bonds within the ring, with a carbonyl precursor. Here we recognise these C–X bonds as being enols, or imines / enamines (for O, N heterocycles).

Thiophenes: Recognise 2 x thioenol in target – disconnect back to 1,4-di-carbonyl again!



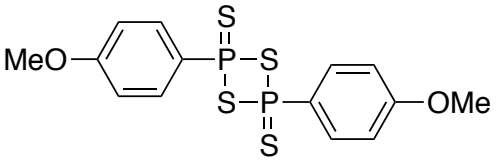
1,4-dicarbonyl

Methods to cyclise the 1,4-dicarbonyl:

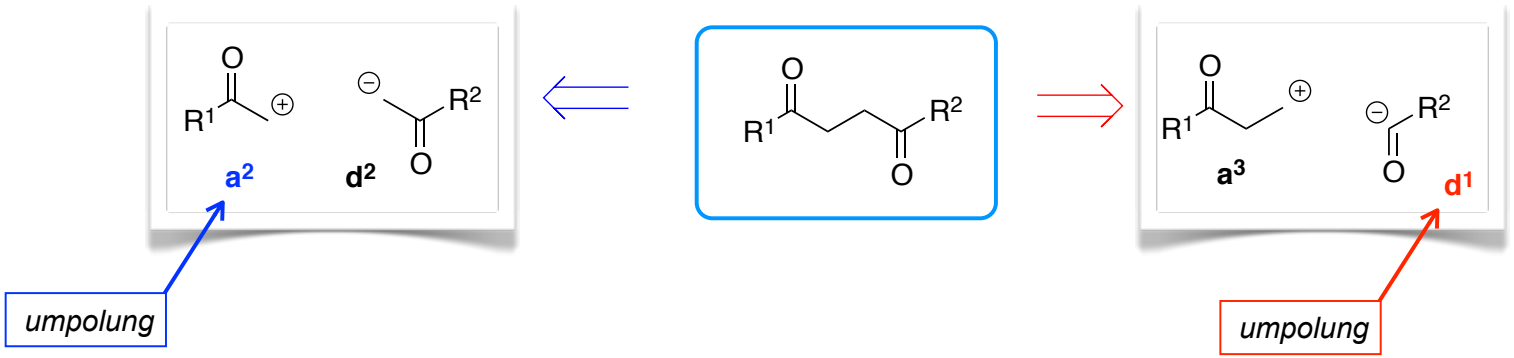
H_2S

P_2S_5

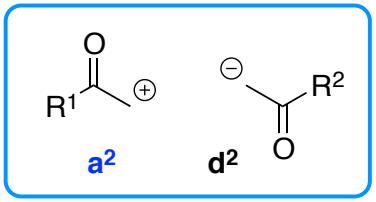
Lawesson's reagent

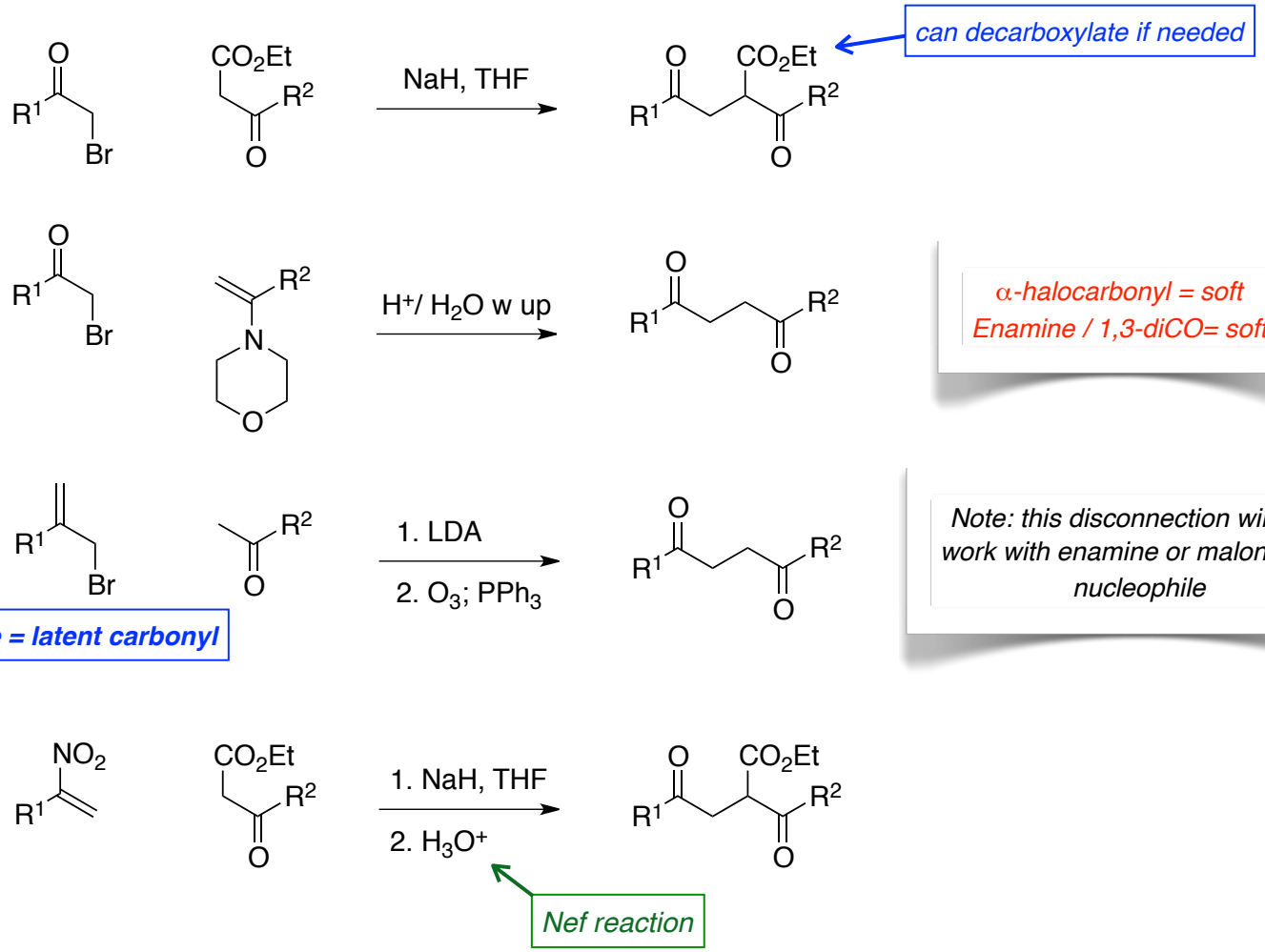


All of these heterocycles arise from 1,4-dicarbonyls, which need to be made using unnatural synthons. Two disconnections are possible:

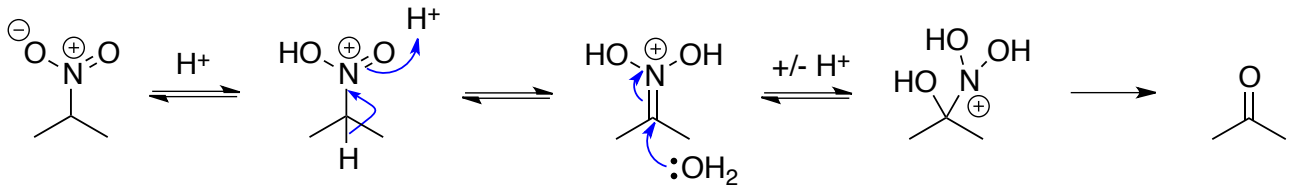


1,4-dicarbonyl synthesis revisited

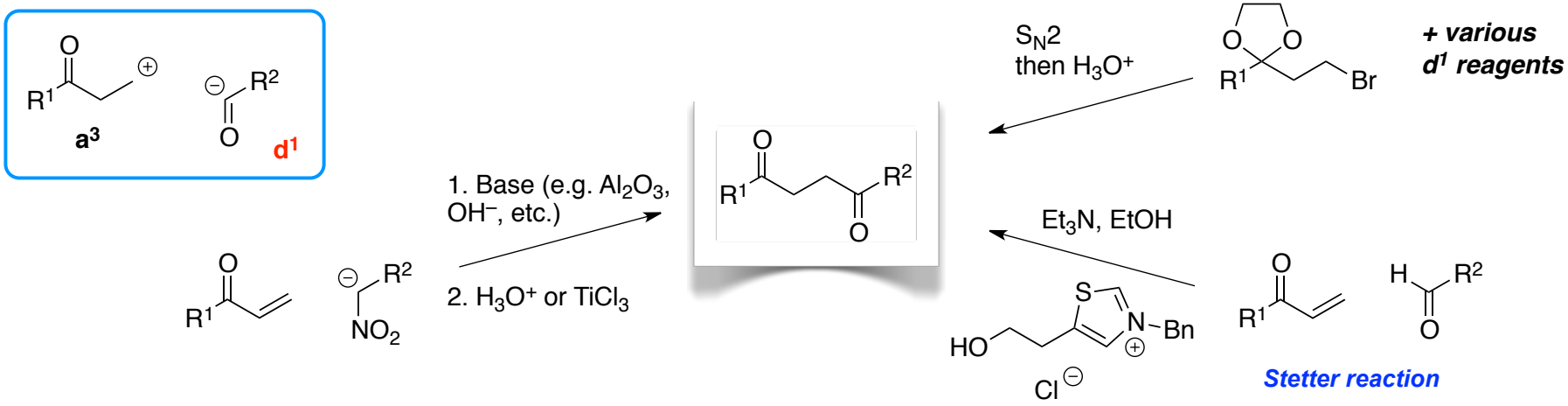




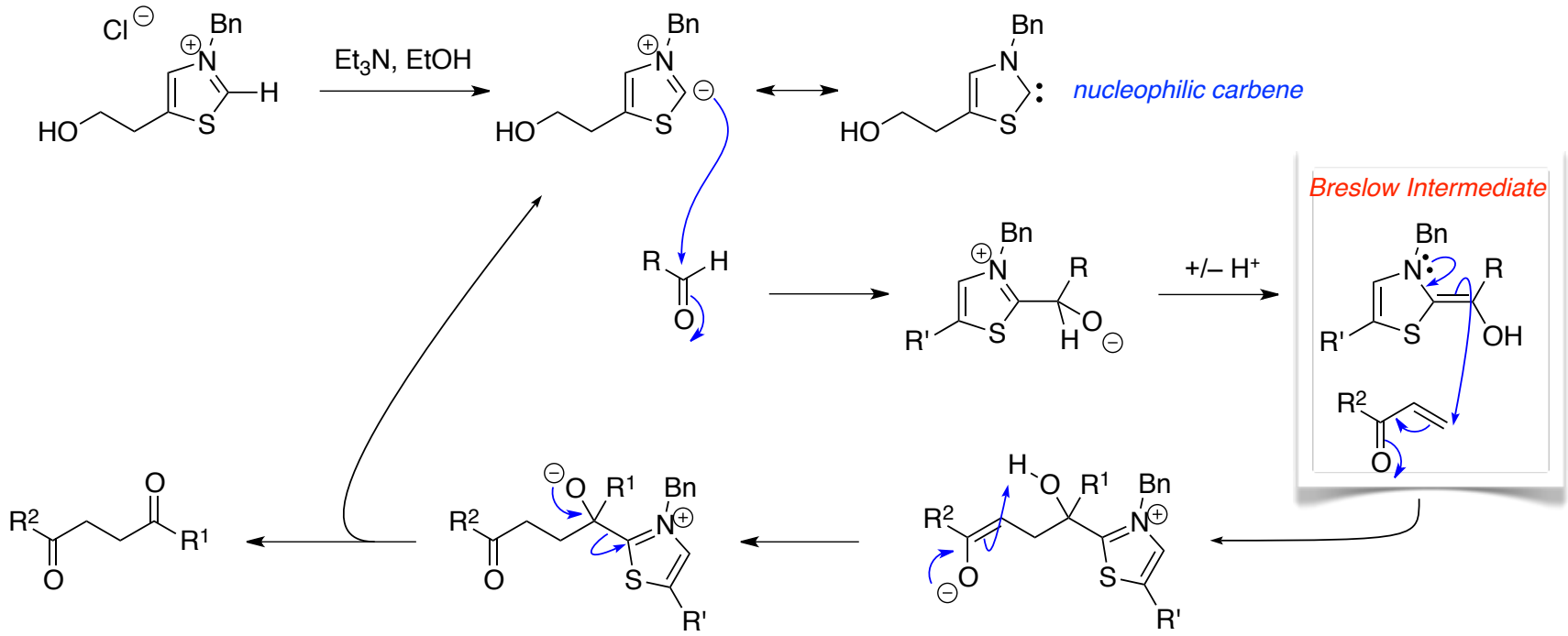
- *Mechanistic focus: Nef reaction*



1,4-dicarbonyl synthesis revisited



• *Mechanistic focus: Stetter reaction*

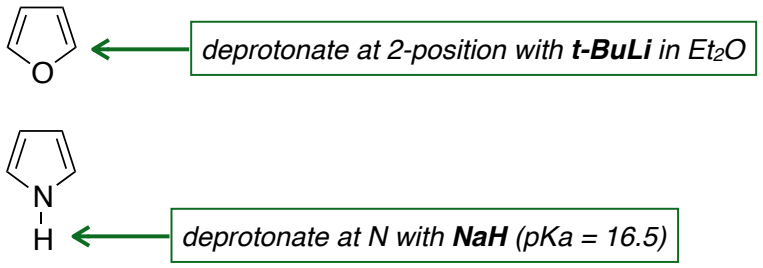


Review of nitroalkane conjugate addition: Ballini et al., *Chem. Rev.* **2005**, *105*, 933.
For recent leading references on the Stetter reaction, see: *Org. Biomol. Chem.*, **2011**, *9*, 8437; *JACS* **2005**, *127*, 14675.

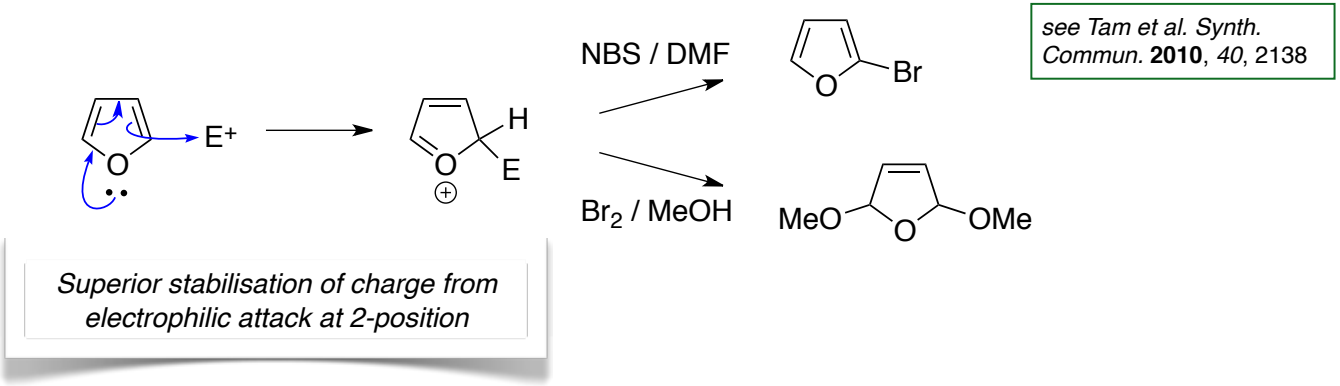
Aromatic heterocycle synthesis 1: Furans, Pyrroles, Thiophenes

Further functionalization of the heterocycle nucleus can be be achieved under a variety of conditions; these heterocycles react readily with electrophiles as they are electron rich.

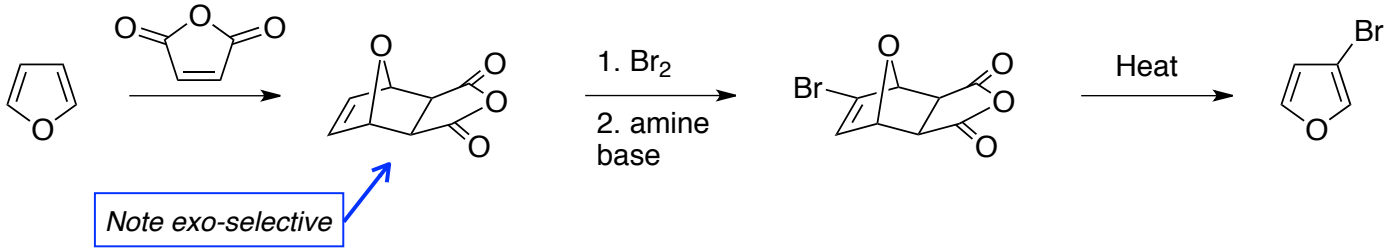
a) Direct metallation (deprotonation):



b) Reaction with electrophiles: generally at the 2-position

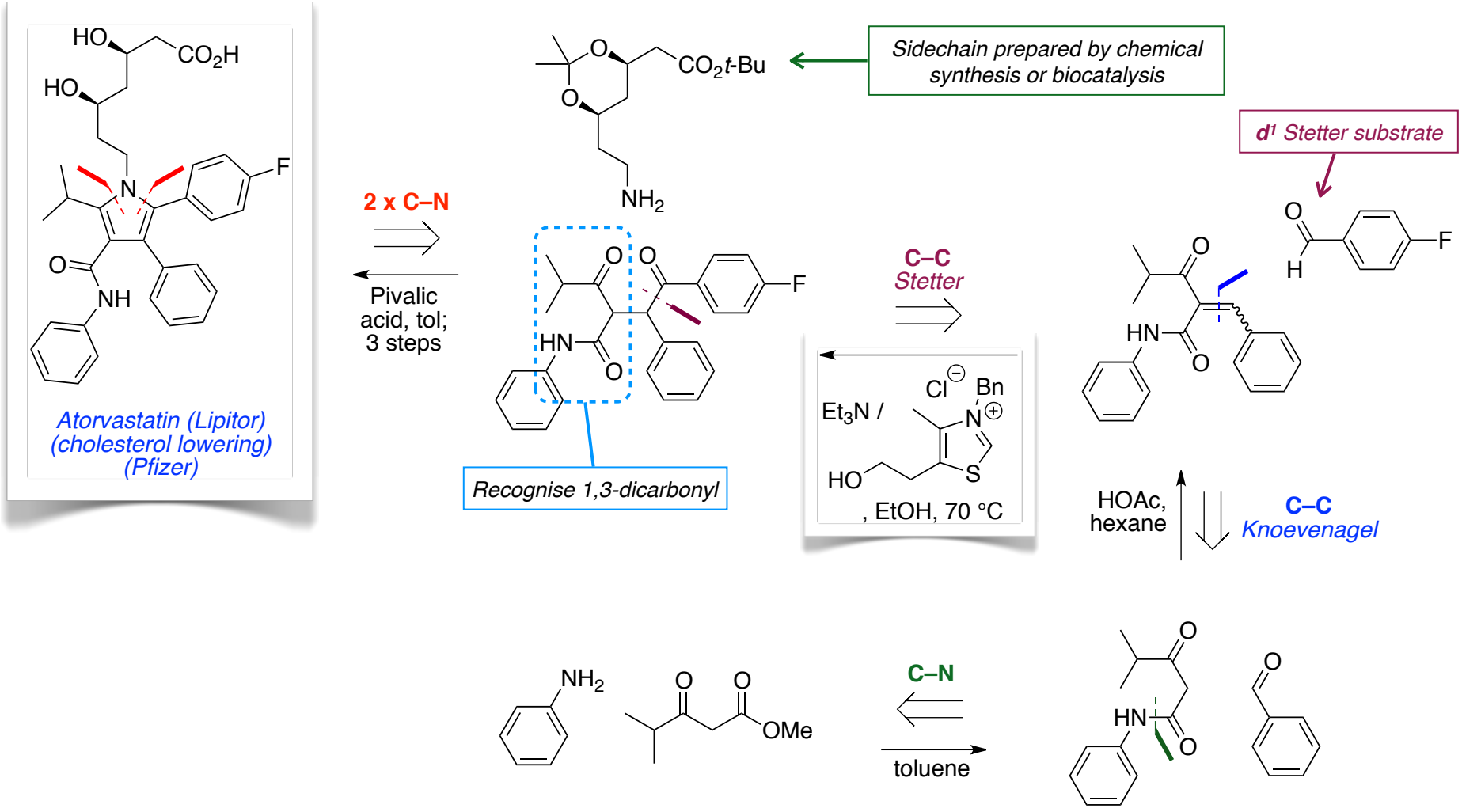


c) Diels-Alder reactions:



Case Study: Atorvastatin

The Pfizer synthesis of atorvastatin contains a classic example of Paal-Knorr pyrrole synthesis, combined with the highly efficient Stetter protocol to prepare the 1,4-dicarbonyl.

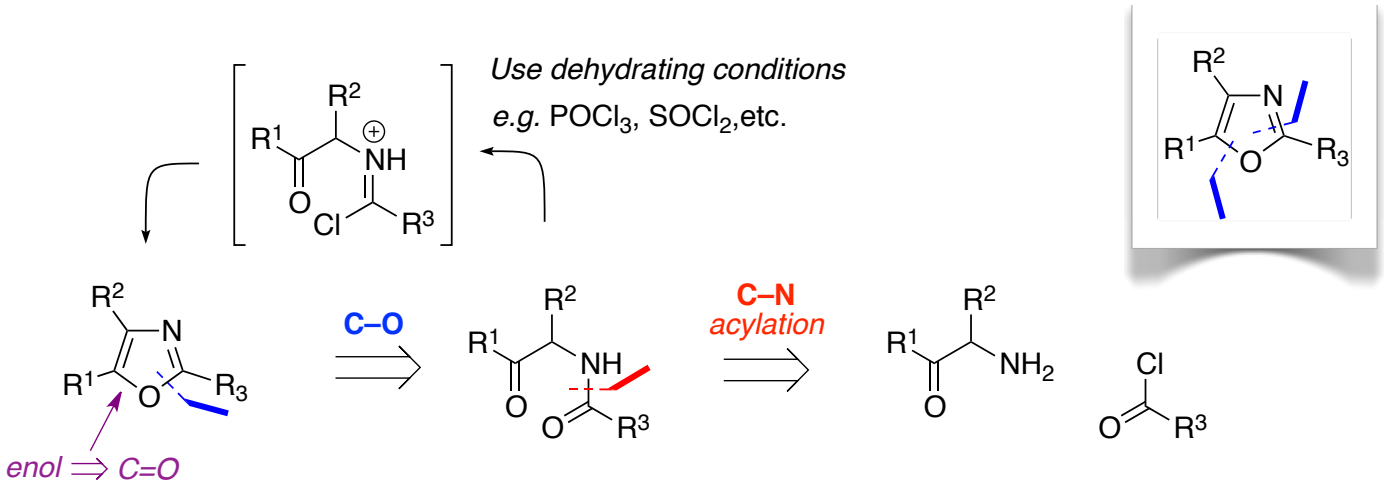


Aromatic heterocycle synthesis 2: Azoles

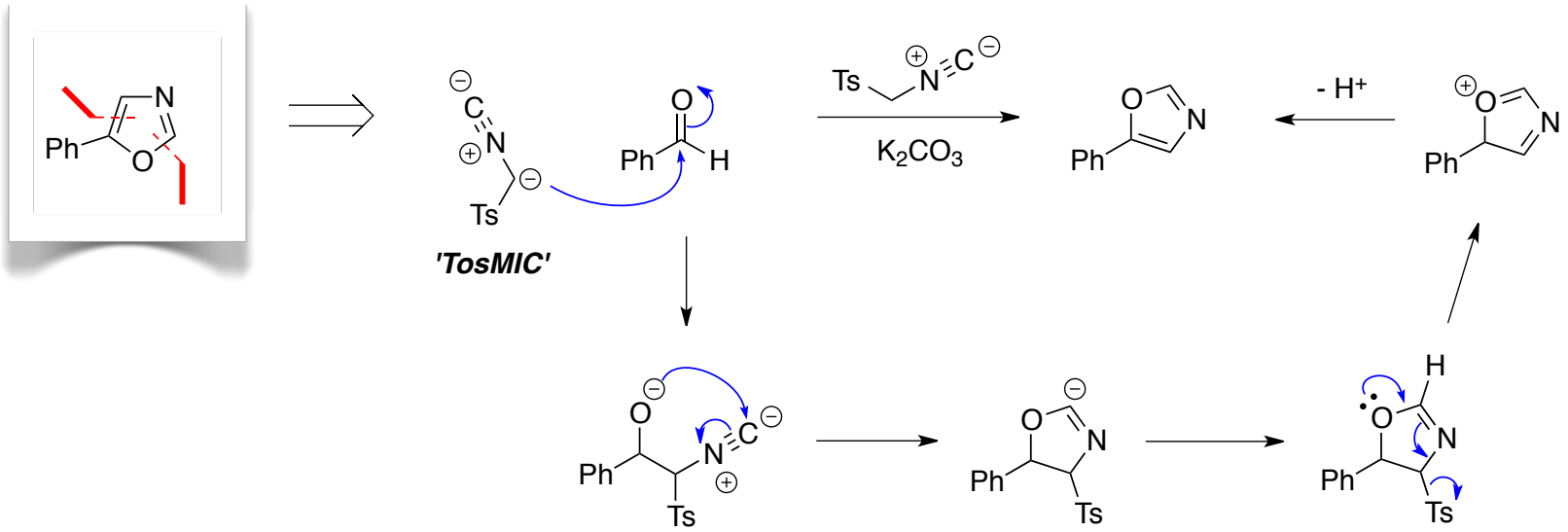
For 5-membered rings with two heteroatoms, look for ring-opening C=O disconnections which form C–Heteroatom bonds

Oxazoles:

Example 1:

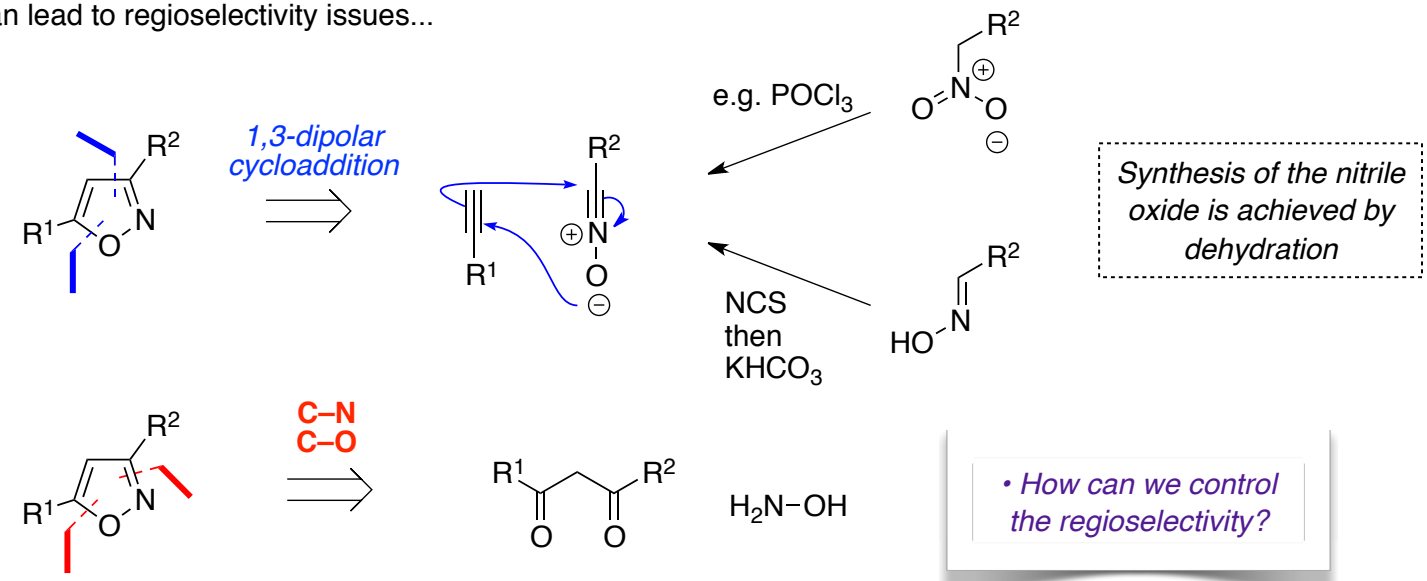


Example 2: *Using TosMIC (good for monosubstituted azoles)*

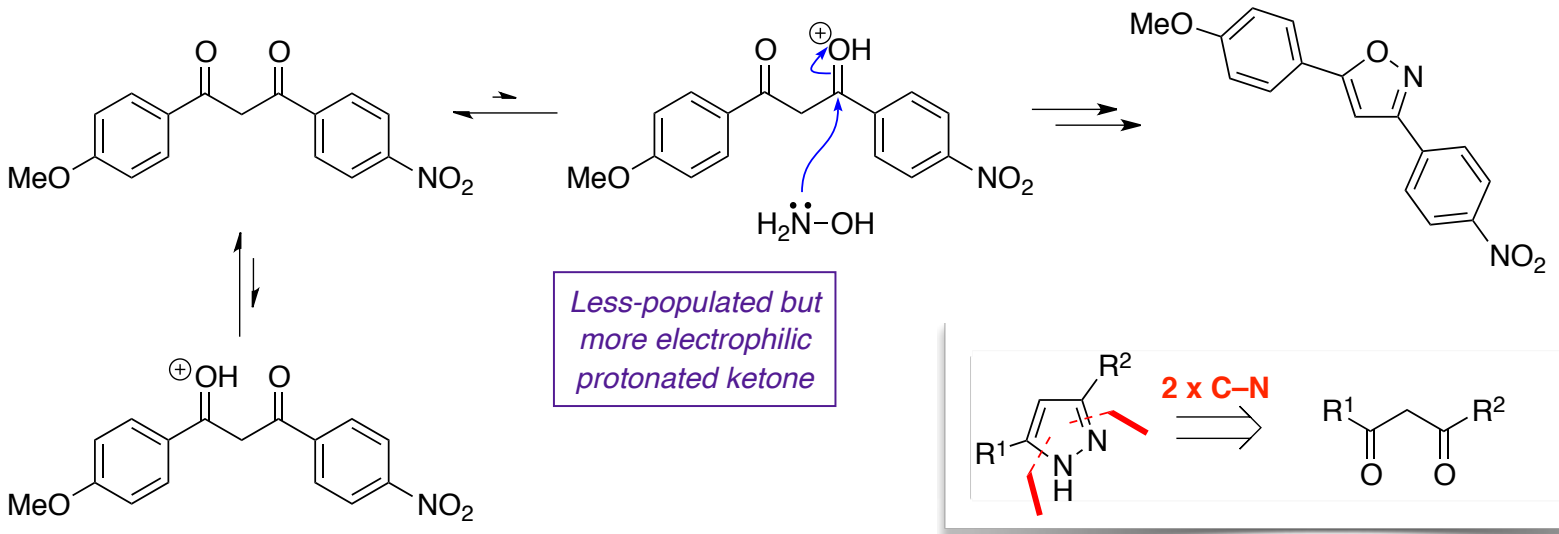


Aromatic heterocycle synthesis 2: Azoles

Isoxazoles: Isoxazole formation can lead to regioselectivity issues...



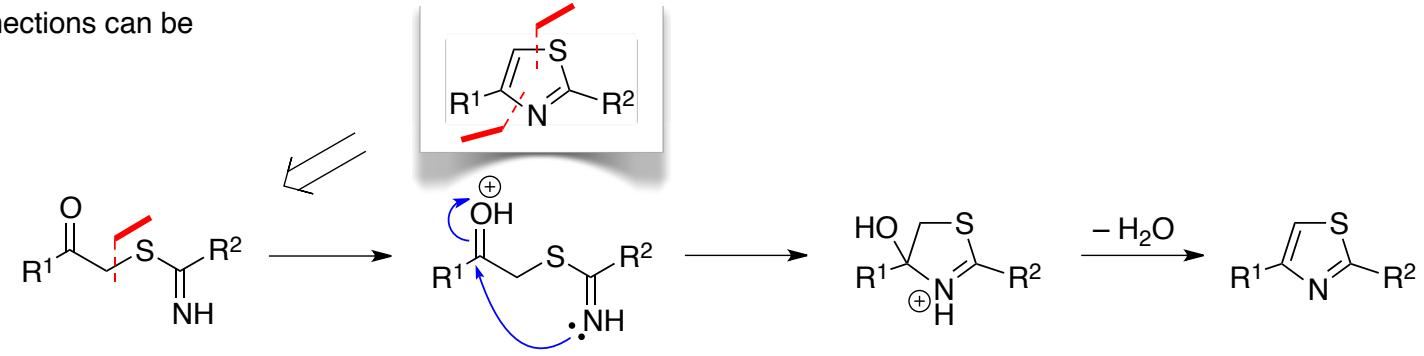
Regioselectivity: *e.g. Hydroxylamine reacts with* ***the most electrophilic*** *of the two carbonyls:*



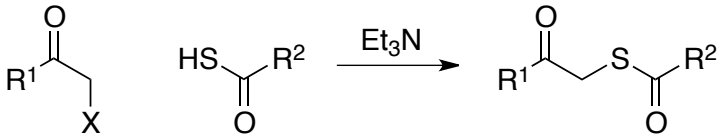
Note identical disconnection for pyrazoles

Aromatic heterocycle synthesis 2: Azoles

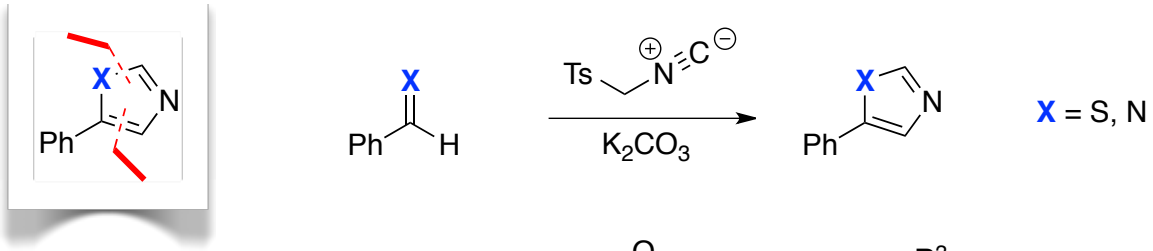
Imidazoles, Thiazoles: Similar disconnections can be used to form these heterocycles.



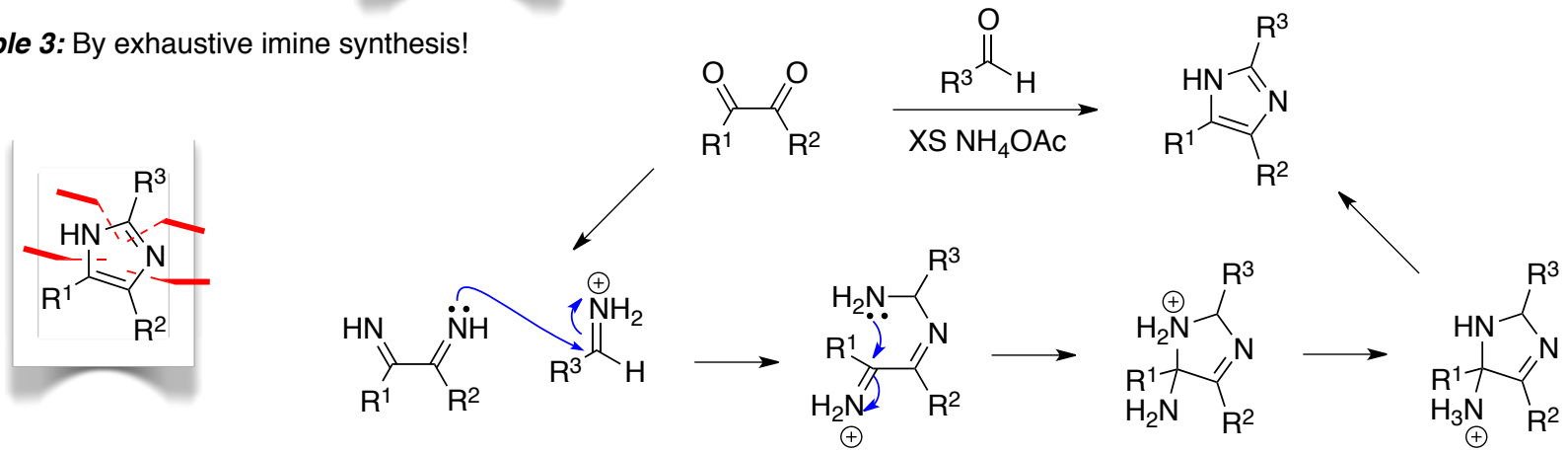
soft-soft



Example 2: TosMIC again...!



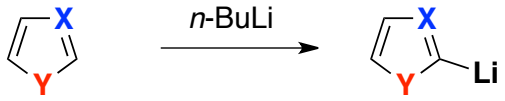
Example 3: By exhaustive imine synthesis!

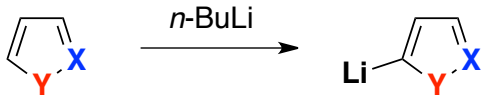


Aromatic heterocycle synthesis 2: Azoles

Further functionalization of azoles is possible with nucleophilic or electrophilic reagents:

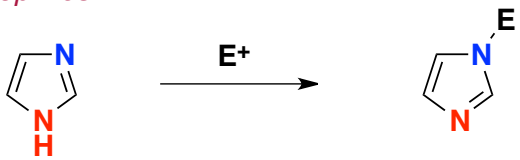
Lithiation:

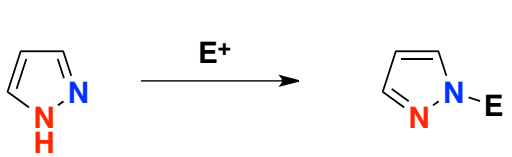




Reaction fails for isoxazoles

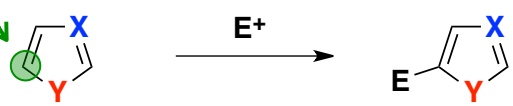
Reaction with electrophiles:

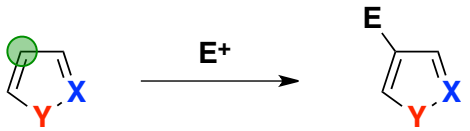




e.g. **E** = Me^+, AcCl,
Cu-cat. *N*-arylation

Largest HOMO coeff. / most stable intermediate cation

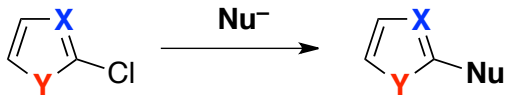


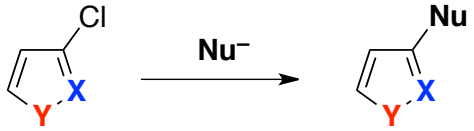


e.g. **E** = Br^+,
NO_2^+ (forcing)

Assisted by EDGs on ring

Reaction with nucleophiles:

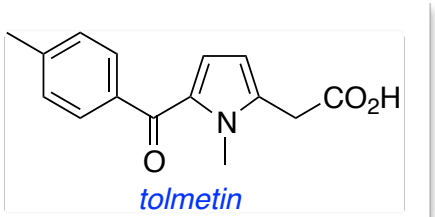




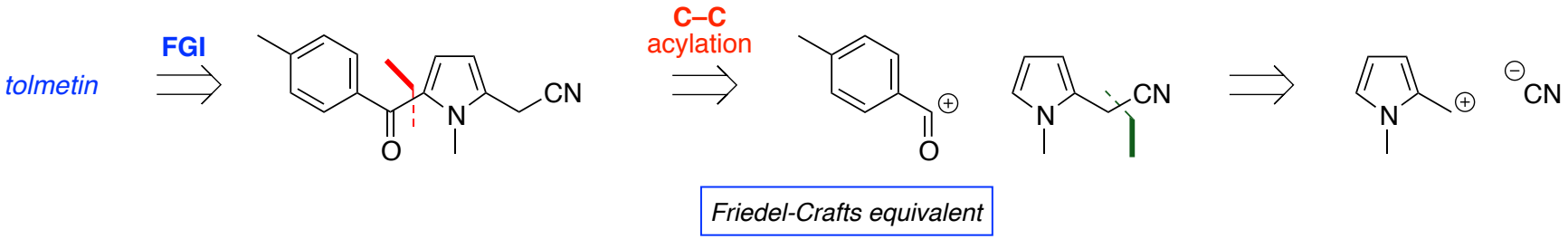
(*prepare from azolidinone*)

Exercise

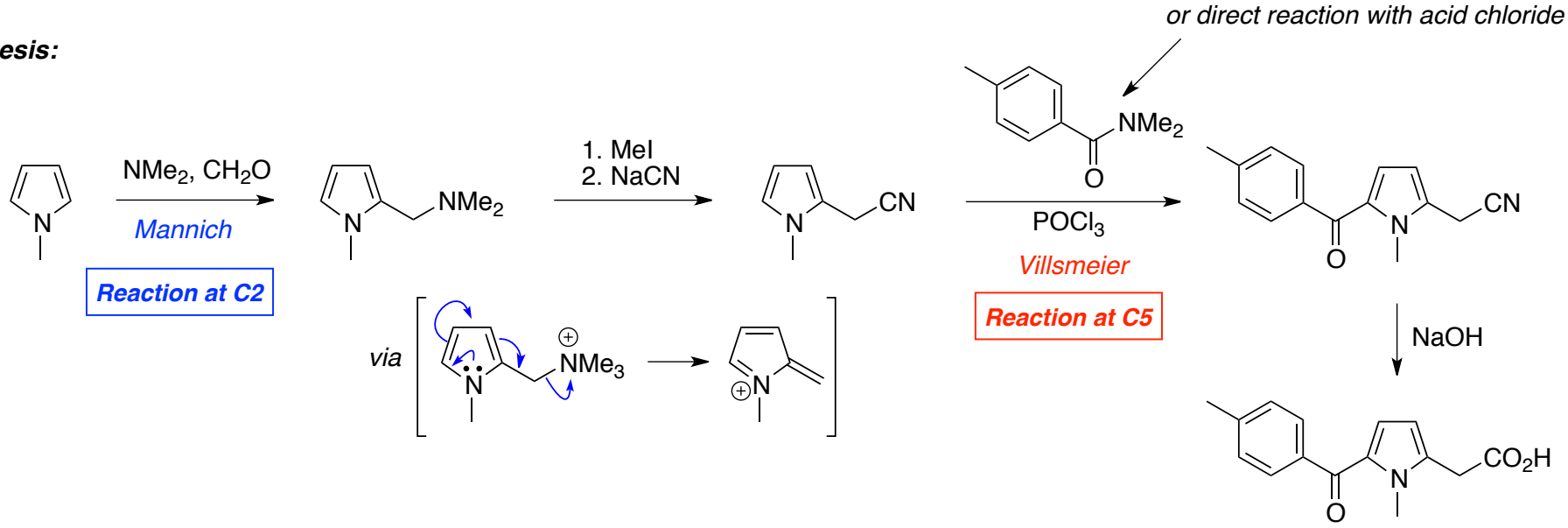
Plan a synthesis of the non-steroidal anti-inflammatory drug tolmetin, from *N*-methylpyrrole.



Retro:

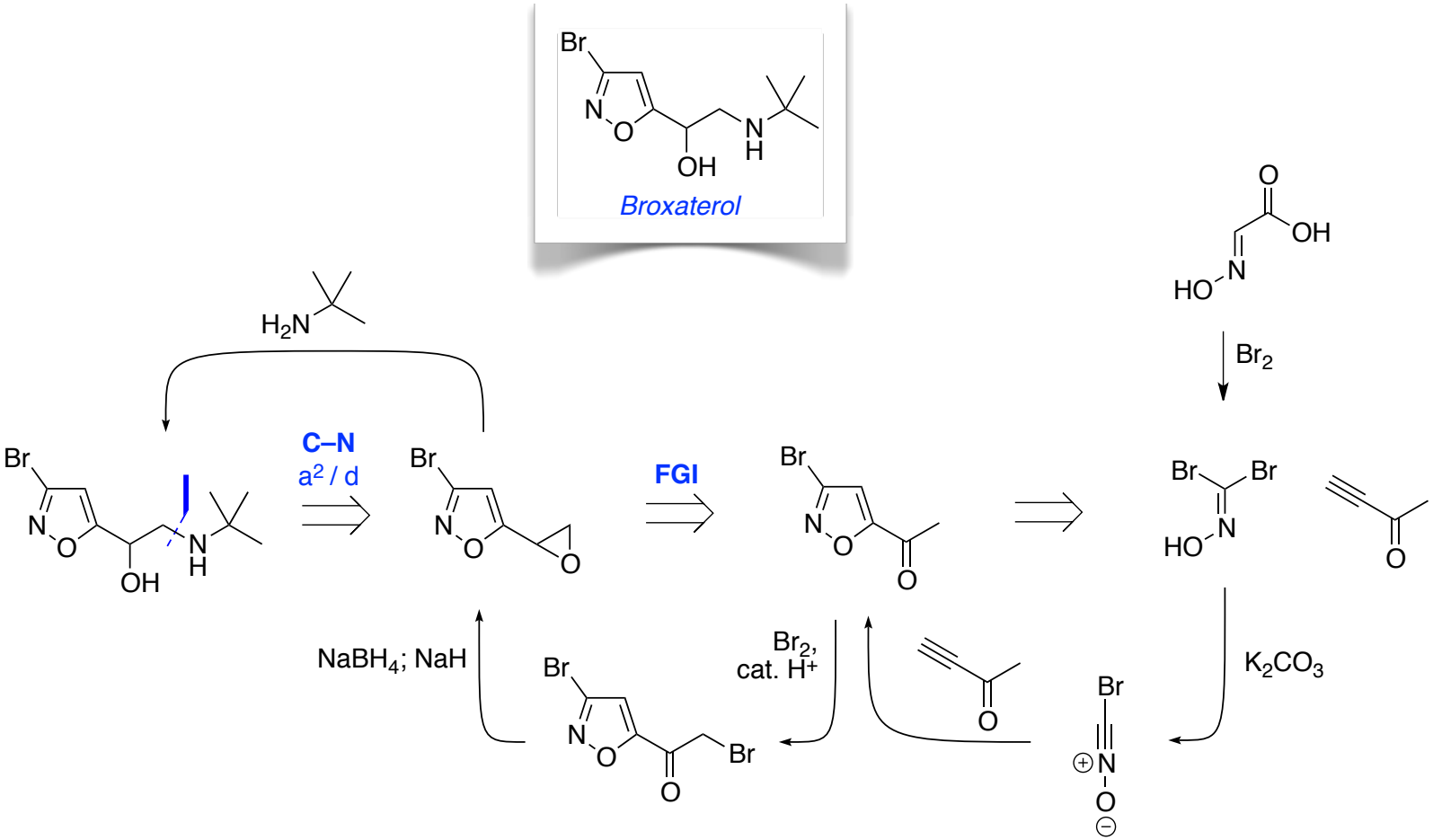


Synthesis:



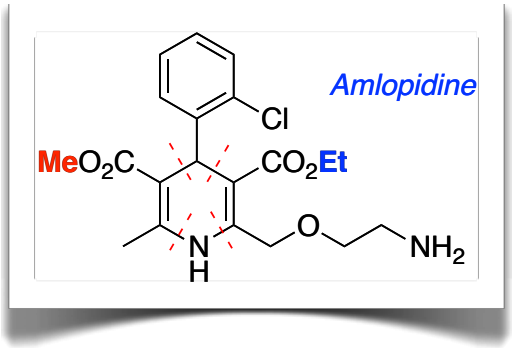
Exercise

Propose a synthesis of of the anti-asthma drug broxaterol:

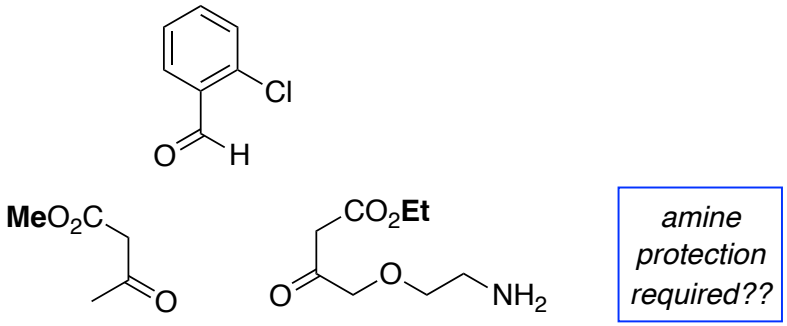


Exercise

Propose a synthesis of of the angina / hypertension drug amlopidine:

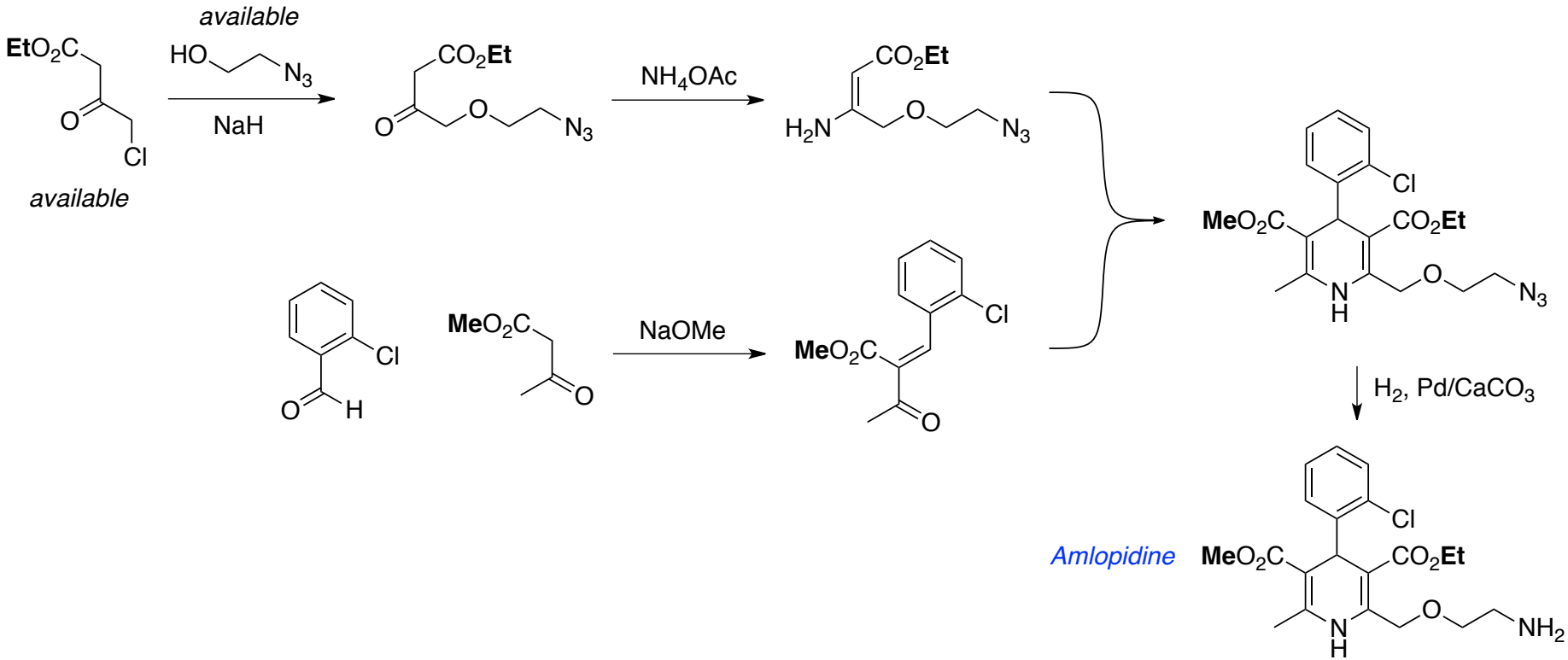


stepwise Hantzsch



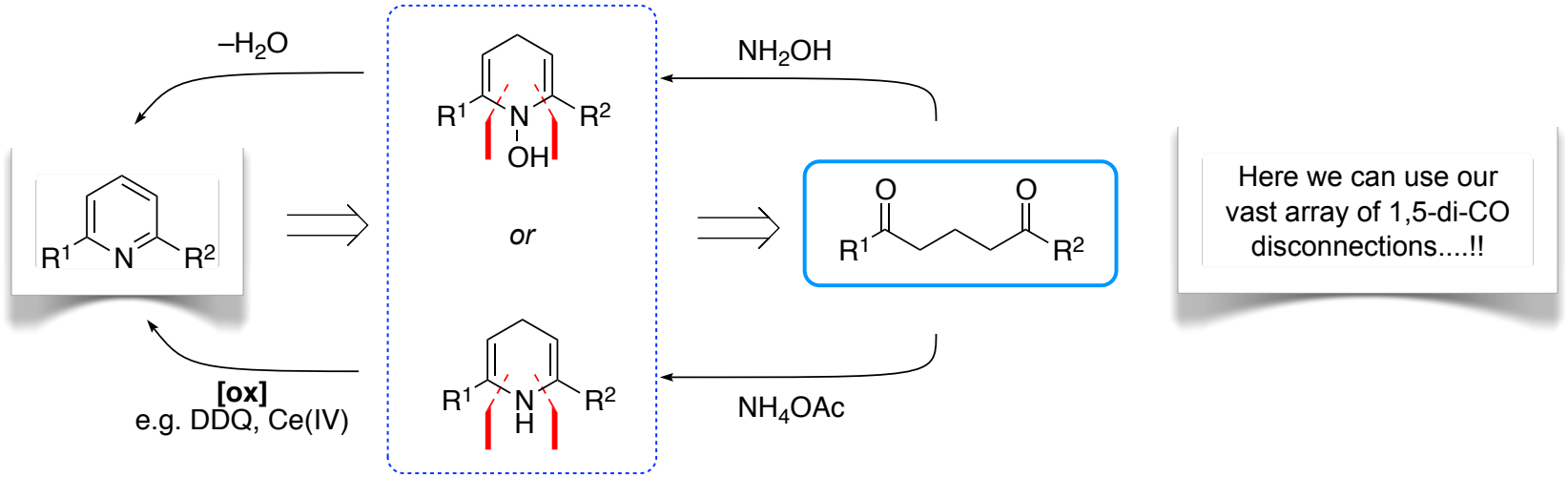
amine protection required??

Synthesis:

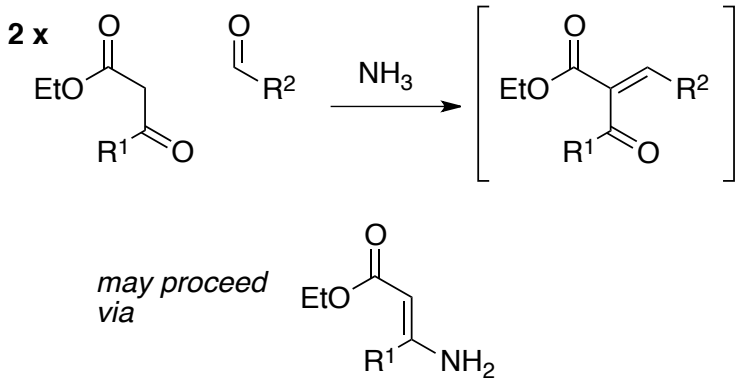


Aromatic heterocycle synthesis 3: Pyridines

The classical pyridine disconnection is to recognise a 1,5-dicarbonyl precursor:

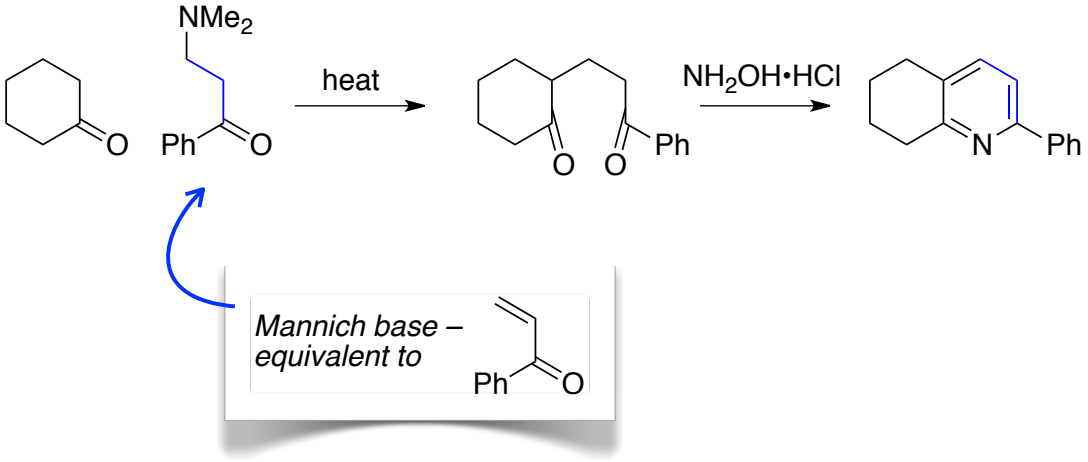


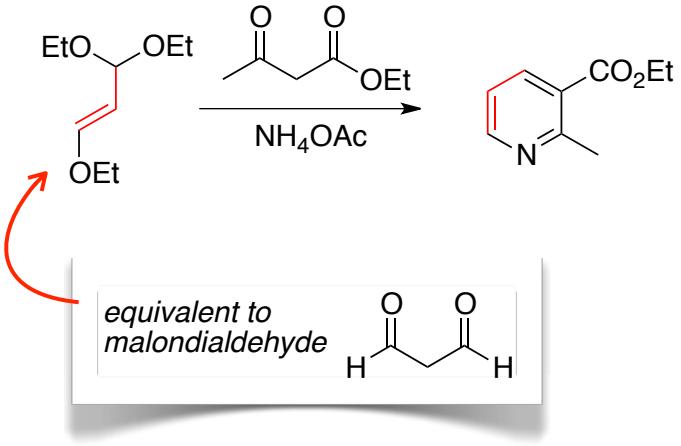
This is the basis of the classic Hantzsch dihydropyridine synthesis:



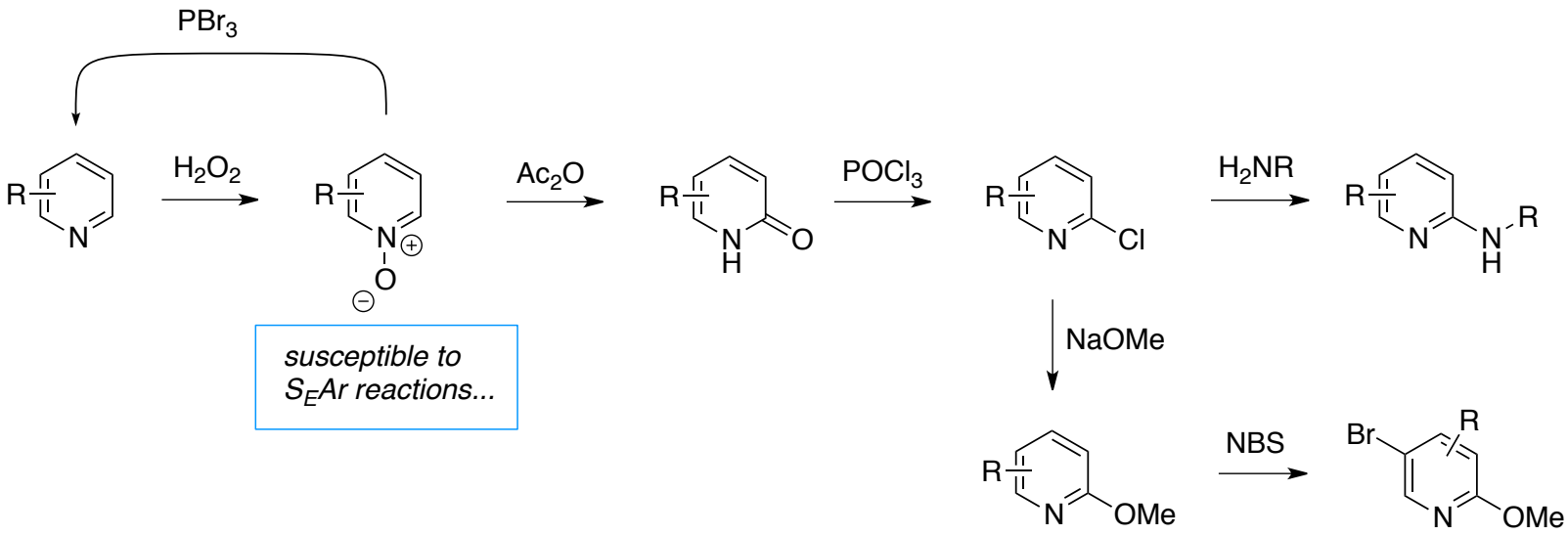
Aromatic heterocycle synthesis 3: Pyridines

Variants: To avoid the use of overly reactive Michael acceptors or aldehydes:





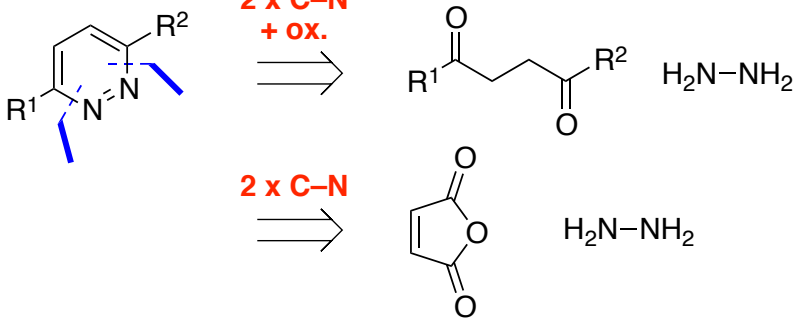
Further examples of useful pyridine chemistry...



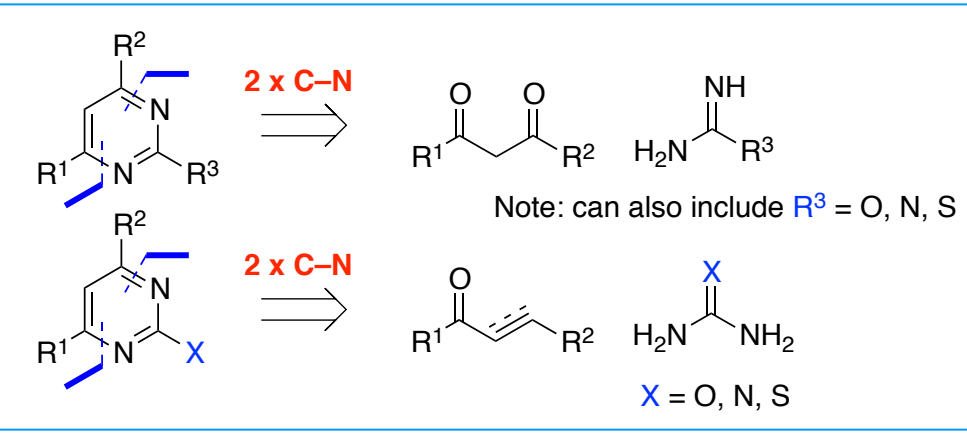
Aromatic heterocycle synthesis 4: Diazines

The synthesis of **Diazines** and derivatives simply involves putting the disconnections we have seen so far together! Also remember oxydiazines...

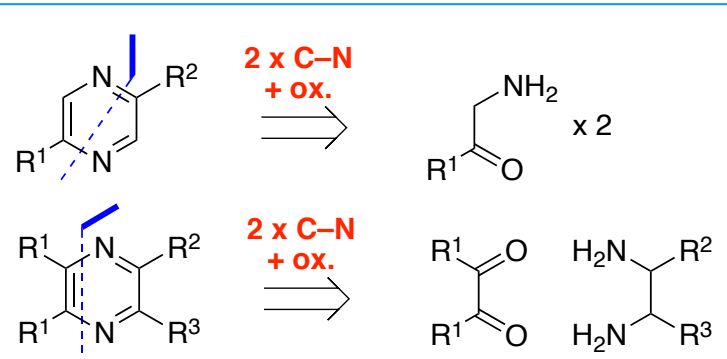
Pyridazine:



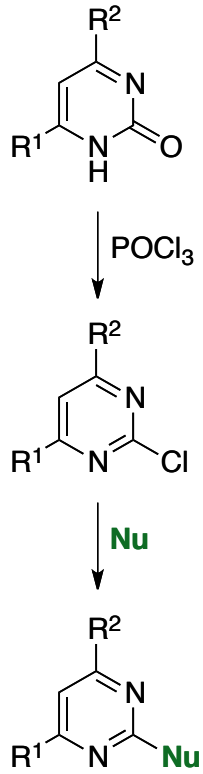
Pyrimidine:



Pyrazine:



Note: **Oxydiazines** are easy to convert to chlorides using $POCl_3$. This provides a straightforward way to perform S_NAr reactions.



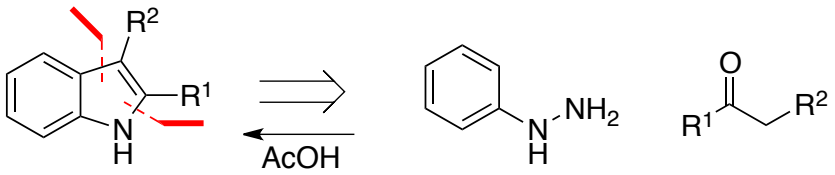
Aromatic heterocycle synthesis 5: Benzannulated heterocycles

Obviously a very important class of compounds – we will again look briefly at some trends, which can equally be applied to bis-heterocyclic systems.

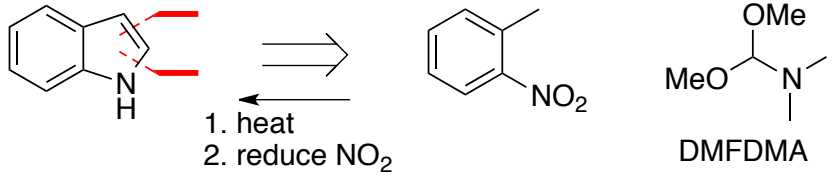
Benzannulated 5-membered rings

a) Indoles

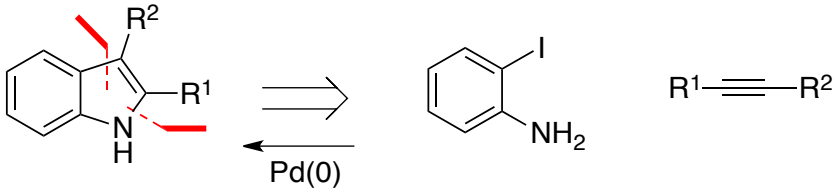
Fischer



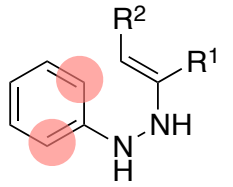
Leimgruber-Batcho

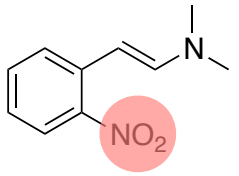


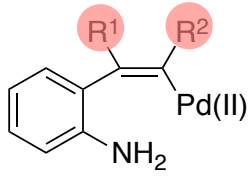
Larock



Key intermediates:







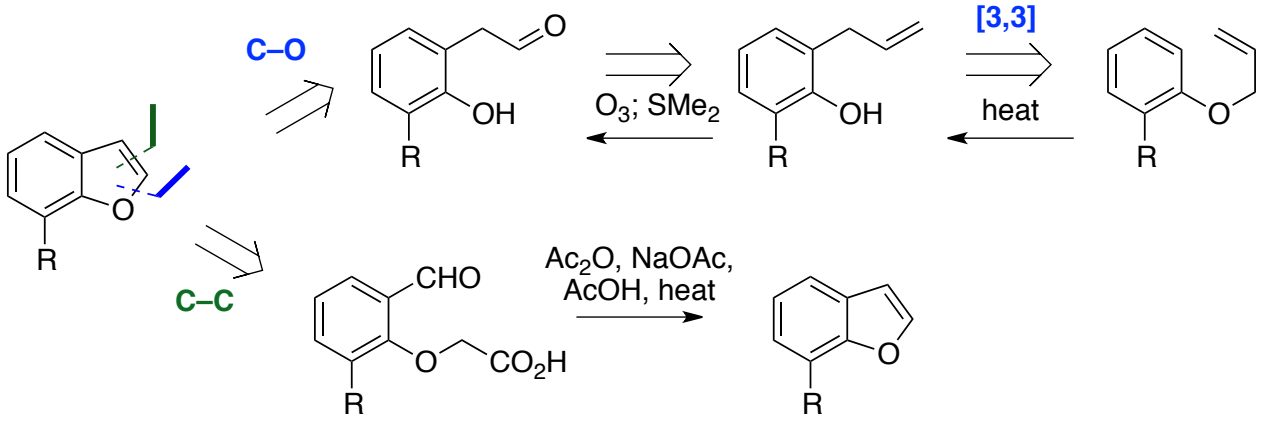
Issues:

Regioselectivity in [3,3]

Nitro reduction

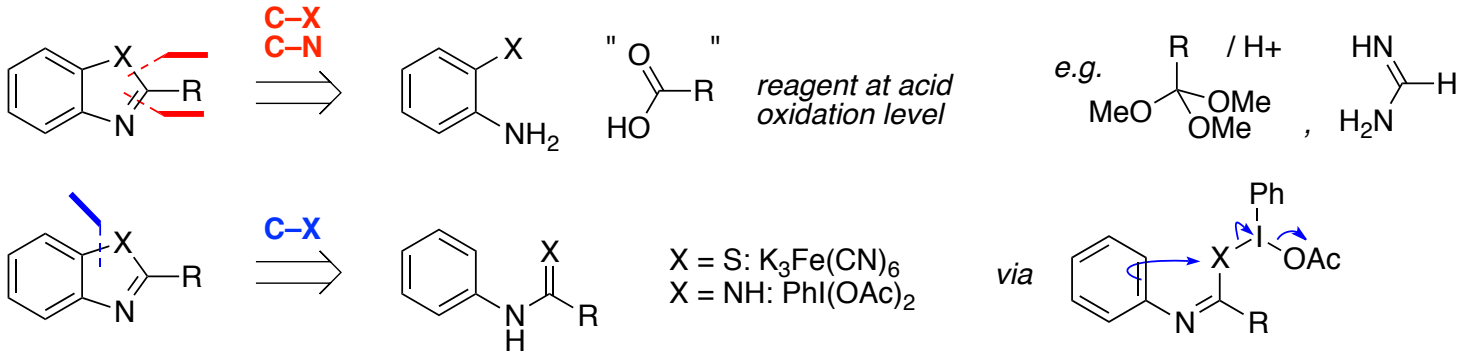
Regioselectivity in carbopalladation

b) Benzofurans

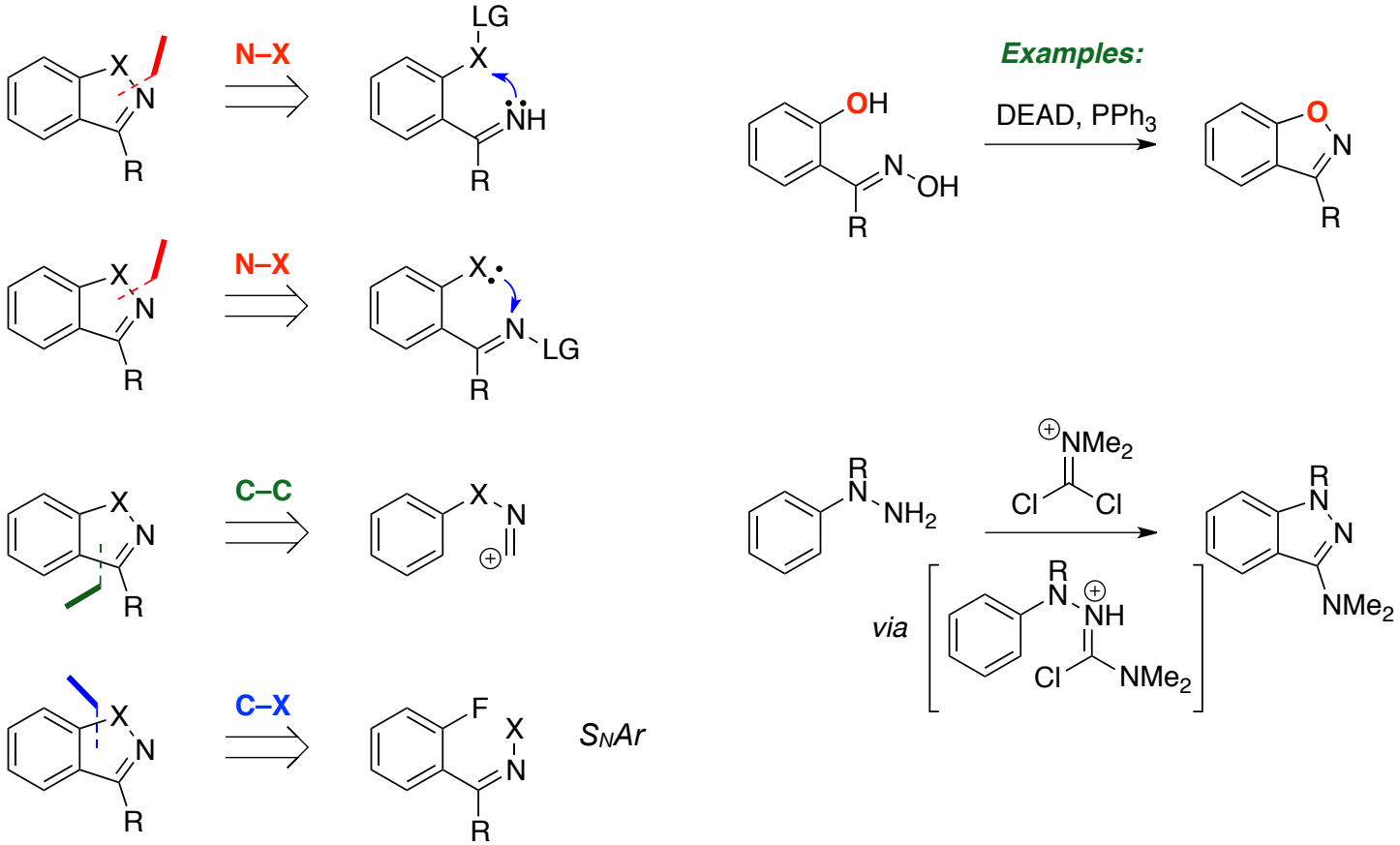


Aromatic heterocycle synthesis 5: Benzannulated heterocycles

c) 1,3-Benzimidazoles, Benzothiazoles, Benzoxazoles



d) Indazoles, Benzisothiazoles, Benzisoxazoles

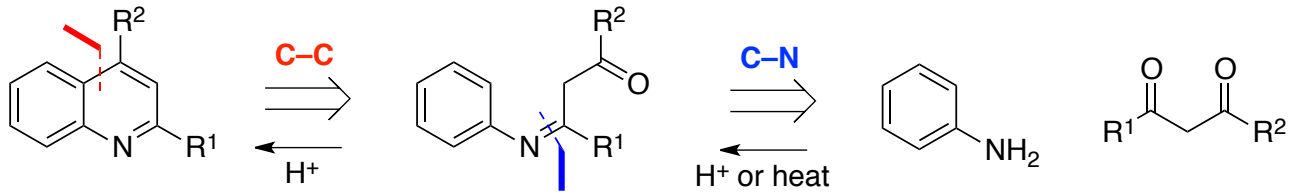


Aromatic heterocycle synthesis 5: Benzannulated heterocycles

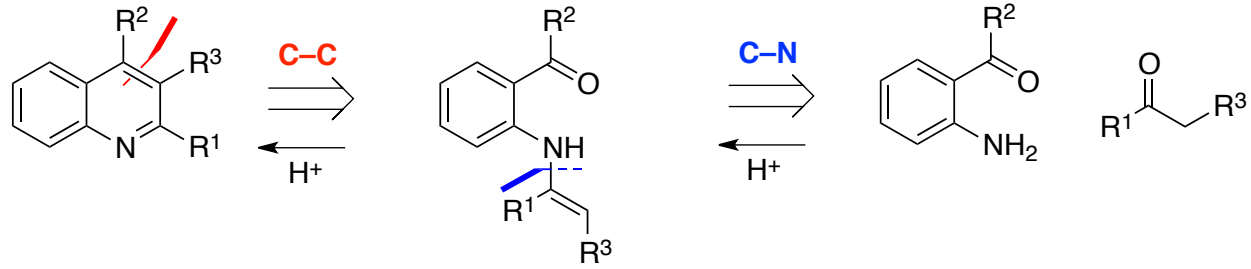
2. Benzannulated 6-membered rings

a) Quinolines

Combes

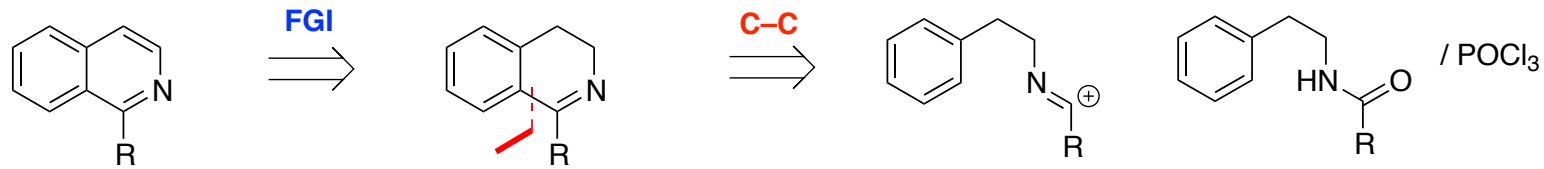


Friedländer (acid or base)



b) Isoquinolines

Bischler-Napieralski

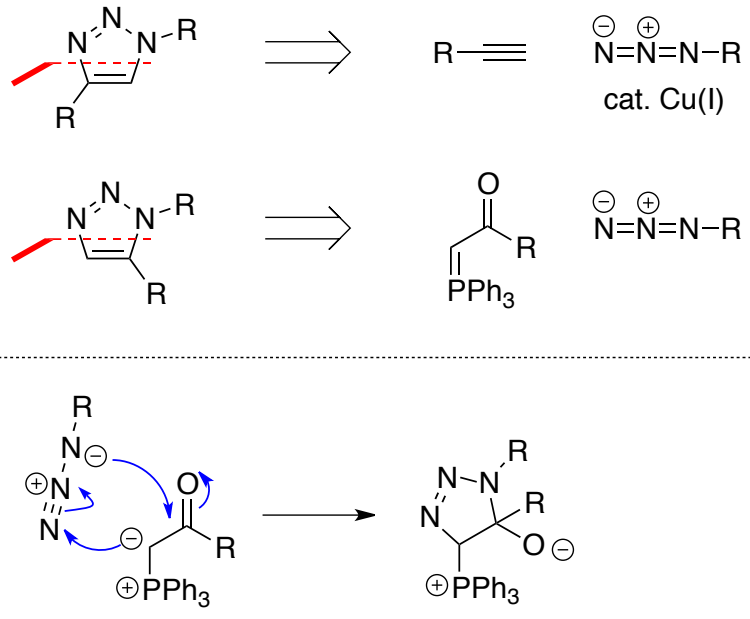


the equivalent reaction with imines is the Pictet-Spengler tetrahydroquinoline synthesis

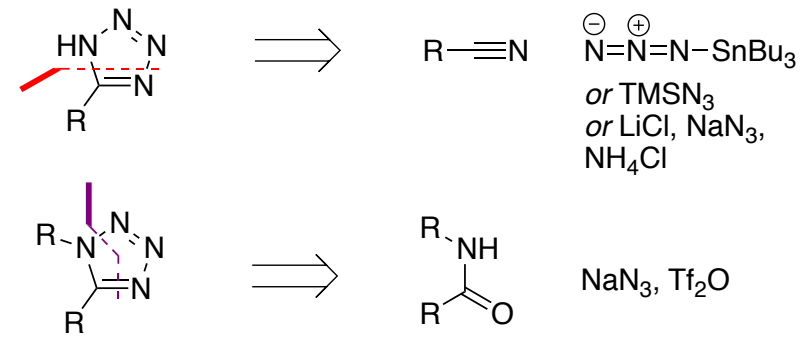
Aromatic heterocycle synthesis 6: Rings with ≥ 3 heteroatoms

To prepare triazoles, oxadiazoles, tetrazoles, etc. we simply modify our disconnections used so far with an emphasis on carbonyl recognition. The strategies below are colour coded into **cycloadditions**, **excision of a single atom**, **cyclisation (dehydration)**, and '**stepwise cycloaddition**'.

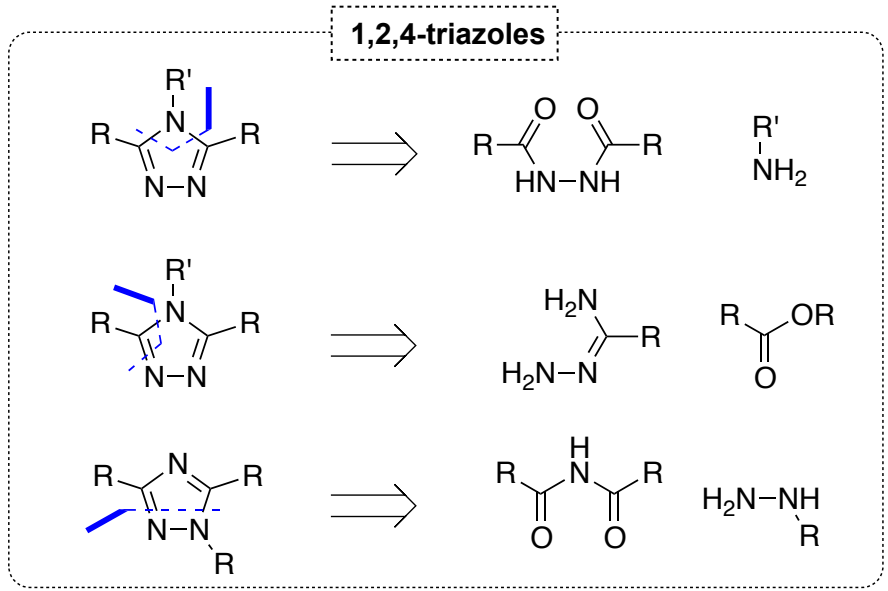
1,2,3-triazoles



tetrazoles



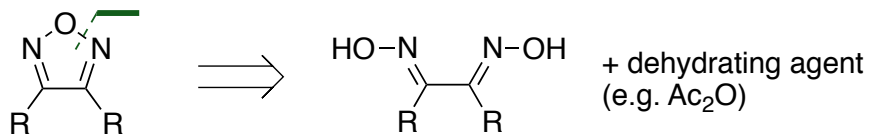
1,2,4-triazoles



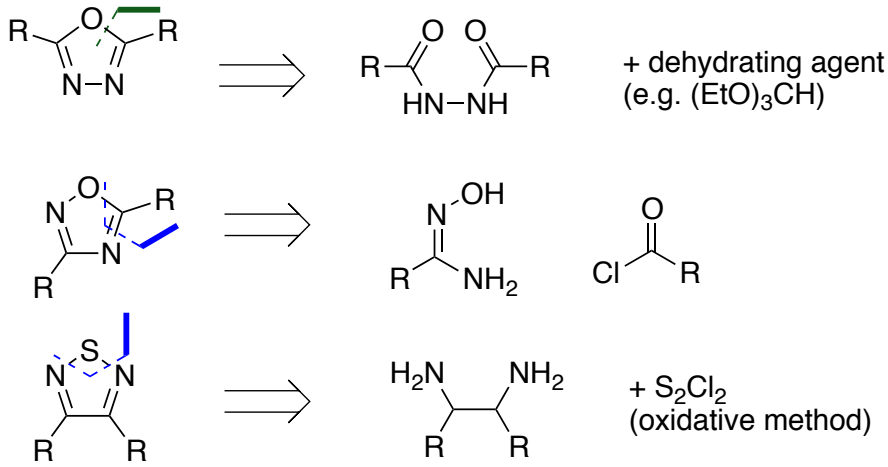
Aromatic heterocycle synthesis 6: Rings with ≥ 3 heteroatoms

To prepare triazoles, oxadiazoles, tetrazoles, etc. we simply modify our disconnections used so far with an emphasis on carbonyl recognition. The strategies below are colour coded into **cycloadditions**, **excision of a single atom**, **cyclisation (dehydration)**, and '**stepwise cycloaddition**'.

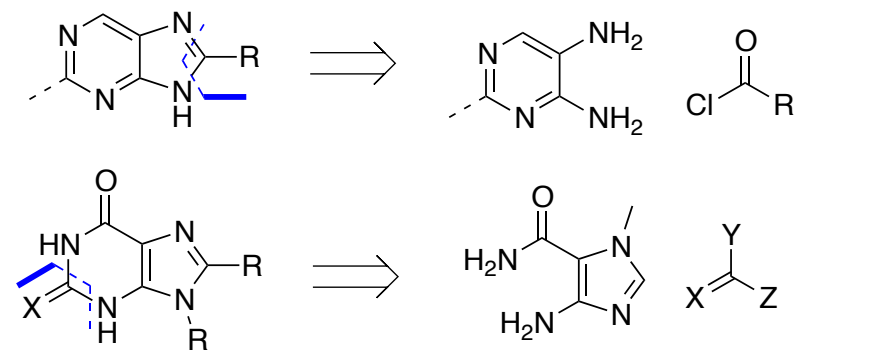
1,2,3-oxadiazoles



1,2,4-oxadiazoles and thiadiazoles

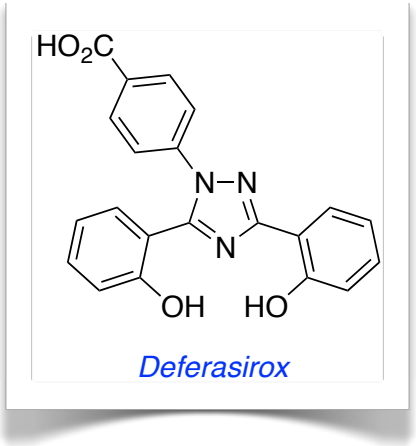


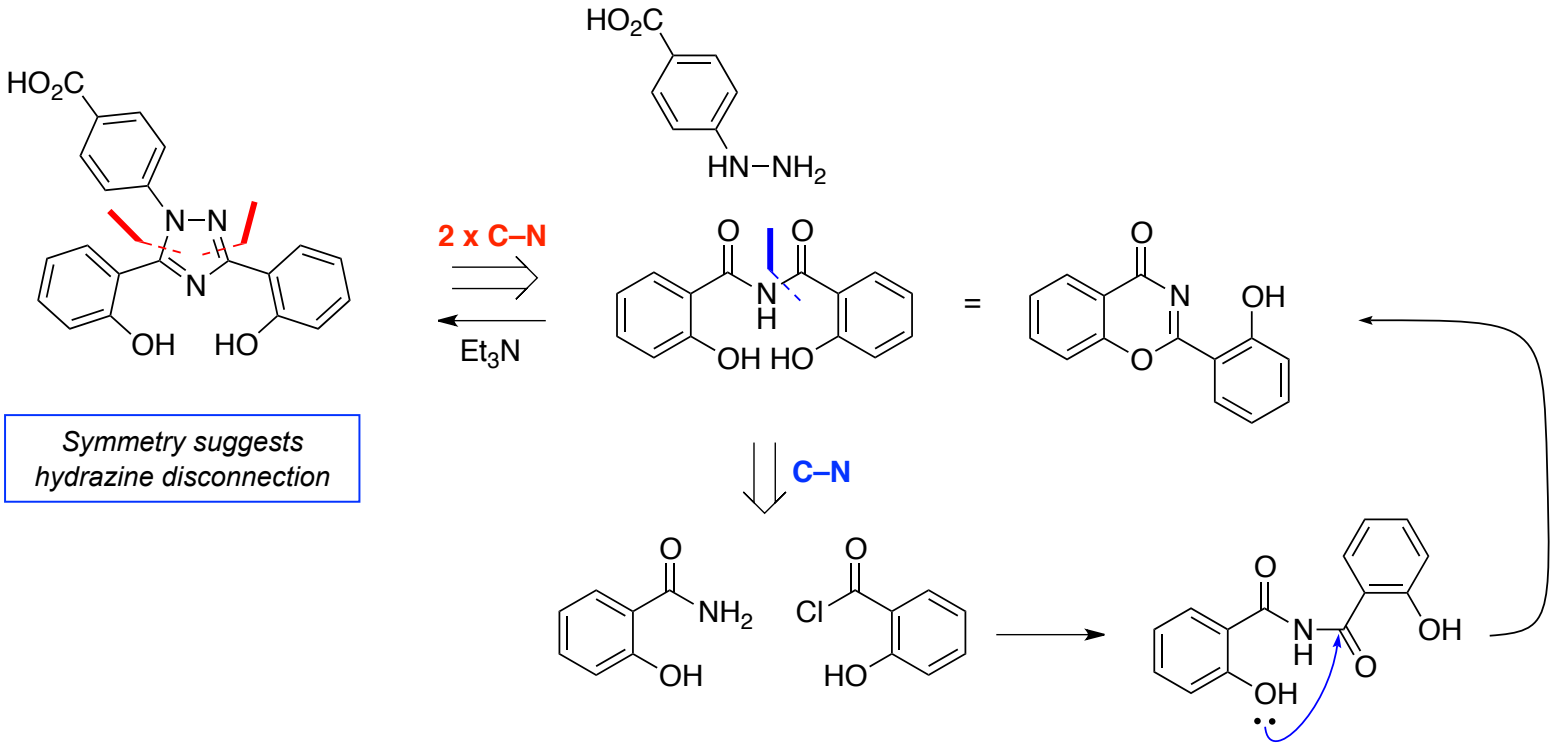
purines



Exercise

Plan a synthesis of deferasirox from starting materials of your choice

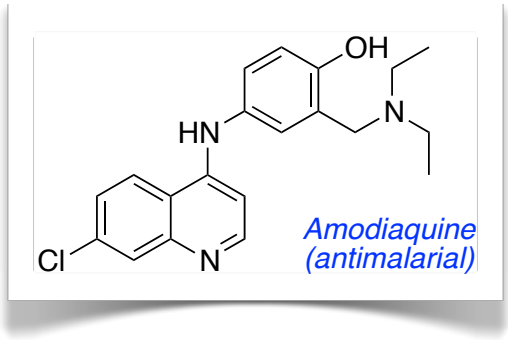


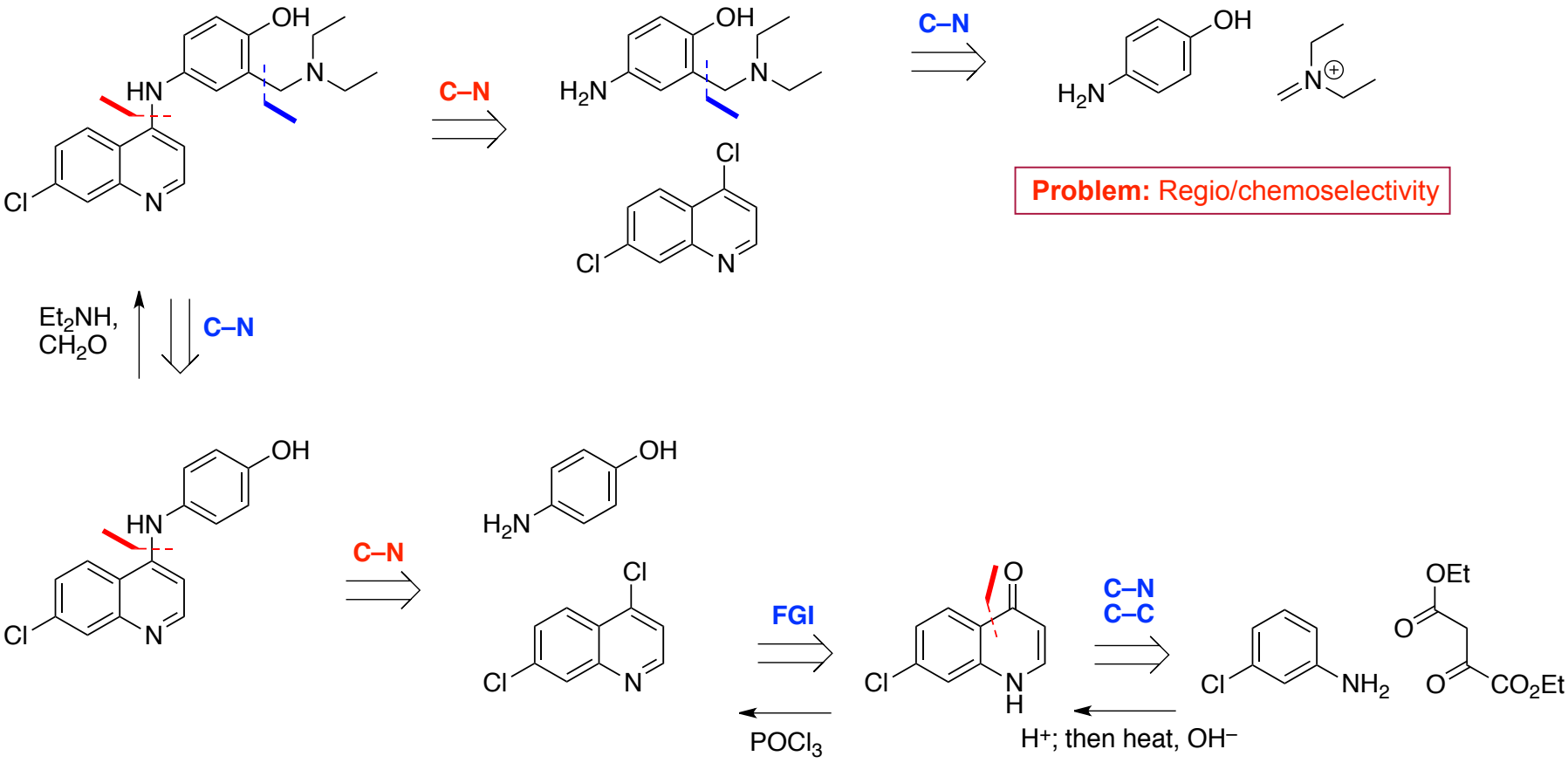


Eur. J. Inorg. Chem. **2004**, 4177

Exercise

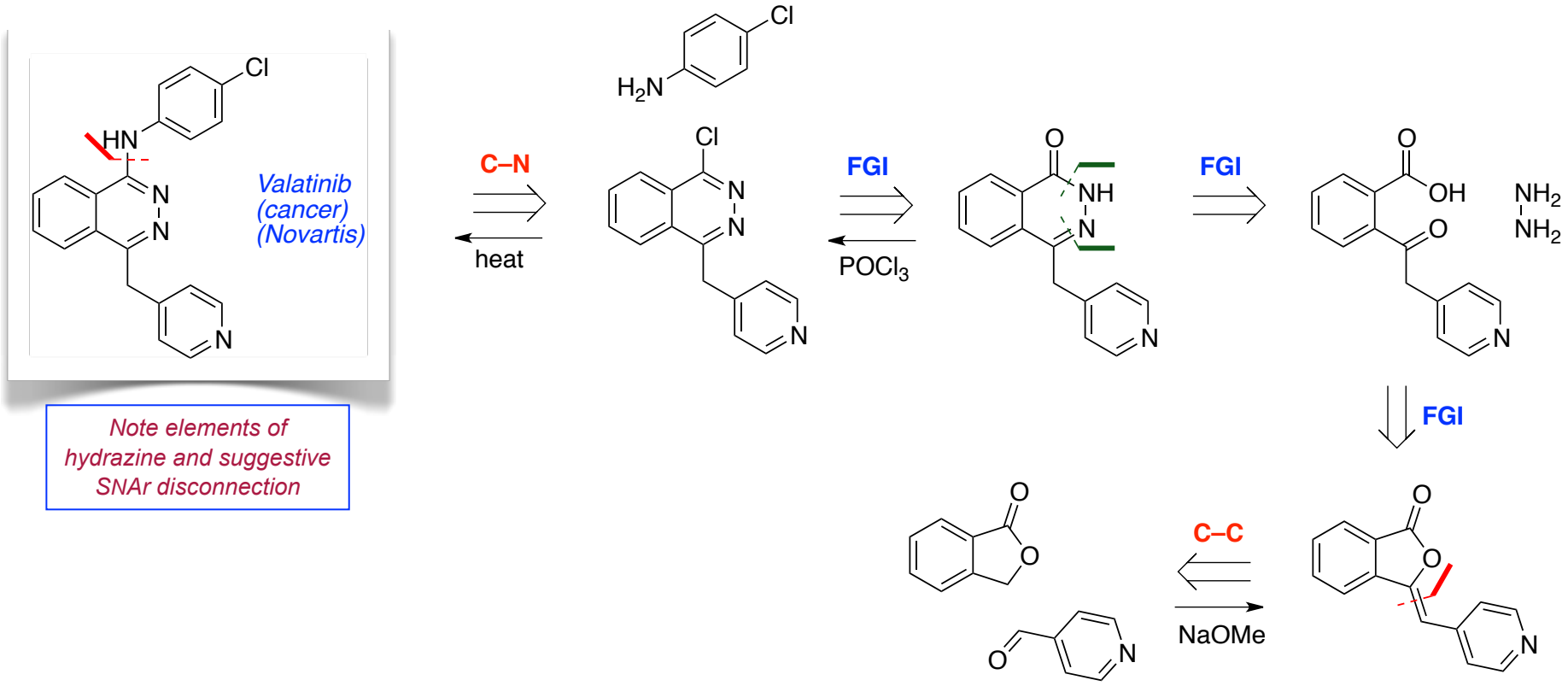
Propose a synthesis of the antimalarial agent amodiaquine



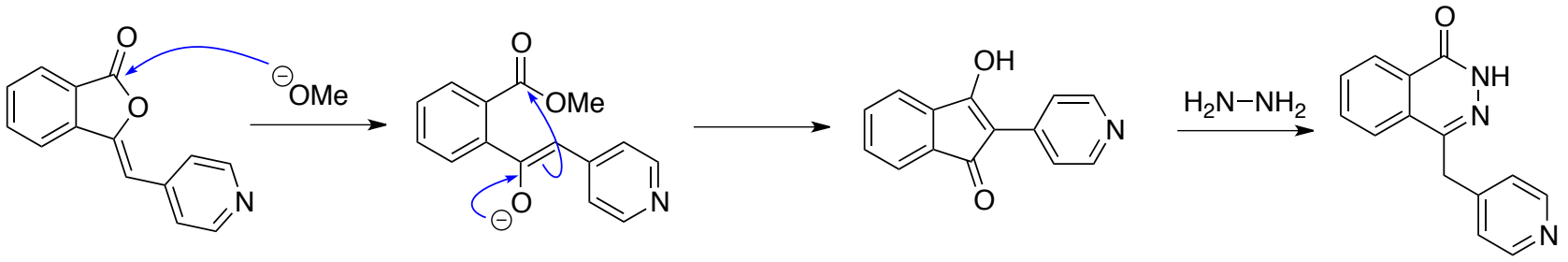


Exercise

Plan a synthesis of valatinib from starting materials of your choice



In reality, the condensation product rearranges...



J. Med. Chem. **2000**, *43*, 2310

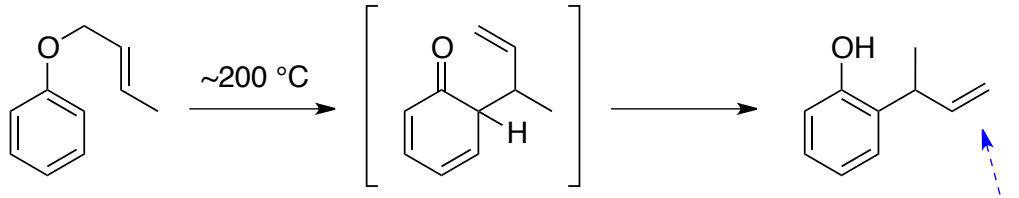
Revisiting arenes – advanced disconnections

A number of specific and reliable methods are available to functionalize arenes.

1. *ortho*-Functionalization. This is a very large topic. Some highlights are selected below.

a) Classical methods

i) *Claisen rearrangement* – a very convenient method to install an allyl group at the 2-position.

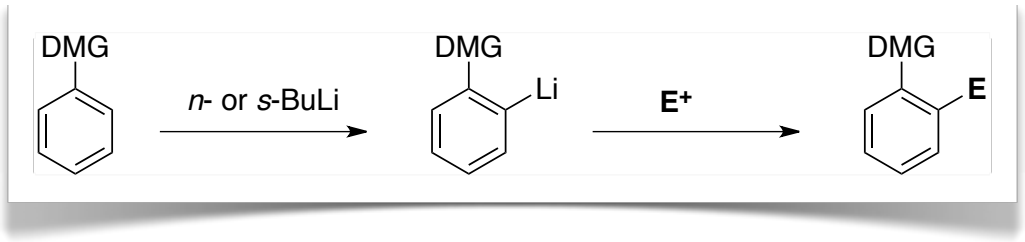


very versatile functionality for further manipulation!

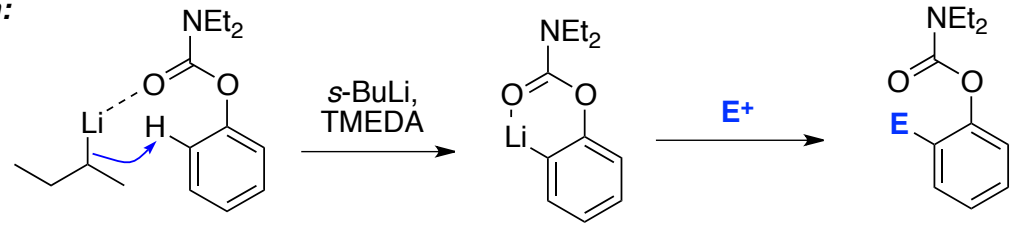
ii) *Fries rearrangement* – also generally quite selective for functionalization at the 2-position.

iii) Other ortho-selective classical reactions such as *Reimer-Teimann, Gattermann-Koch*, etc.

b) Directed *ortho*-Metallation.



Mechanism:



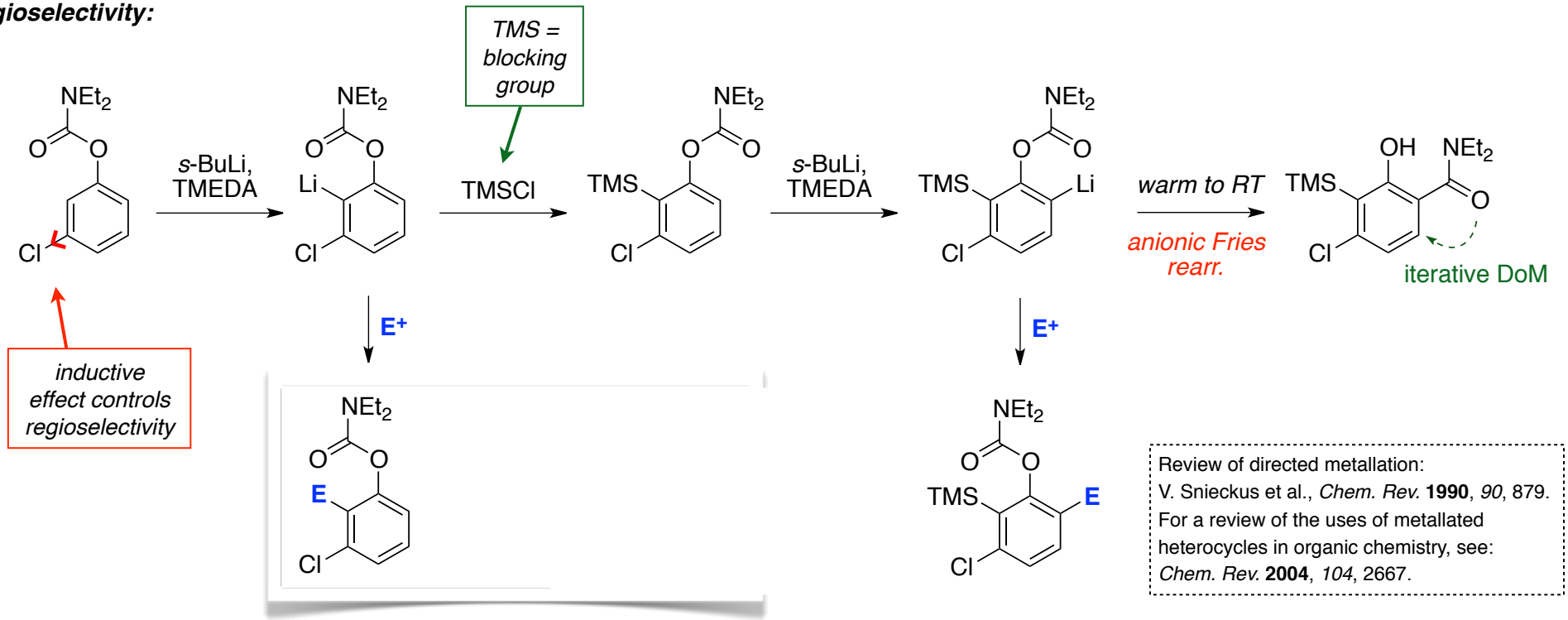
Good Directing groups: Amides, thioamides, carbamates, oxazoles, etc.

E = RCHO, R–I, X_2, TMSCl, $B(OMe)_3$ ....

Review of directed metallation: V. Snieckus et al., *Chem. Rev.* **1990**, *90*, 879.

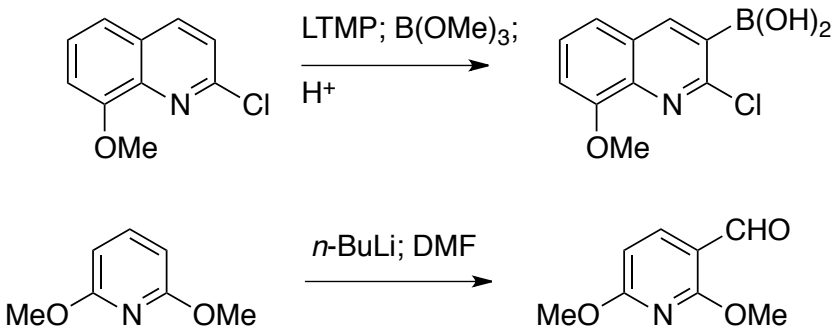
Revisiting arenes – advanced disconnections

Regioselectivity:



Review of directed metallation:
V. Snieckus et al., *Chem. Rev.* **1990**, *90*, 879.
For a review of the uses of metallated heterocycles in organic chemistry, see:
Chem. Rev. **2004**, *104*, 2667.

• ***Heteroaromatics****:* DoM can be useful in heteroaromatic systems, but often the anion can be unstable.



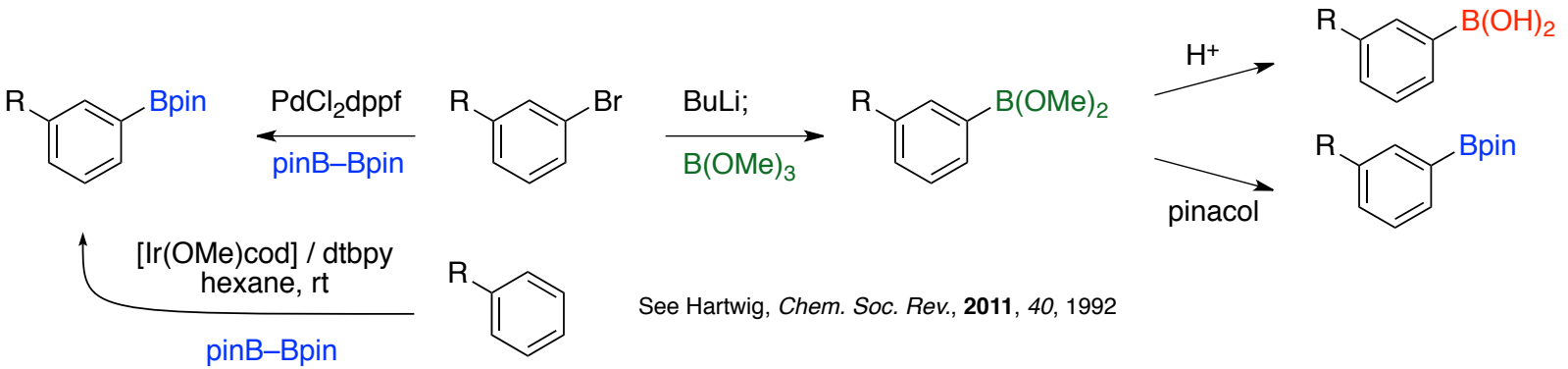
• Lithiation 'directed' by halogens and alkoxy groups is particularly effective

• Anions adjacent to N can be unstable (lp-lp repulsion?)

Reviews of heteroaromatic lithiation: *Tetrahedron* **2001**, *57*, 4059; *Tetrahedron* **2001**, *57*, 4489

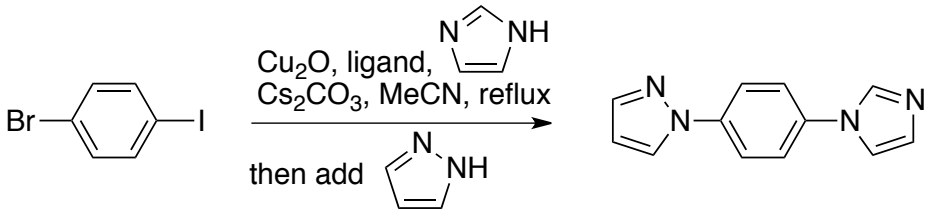
Revisiting arenes – advanced disconnections

2. Palladium / copper catalyzed cross-coupling: An obviously important strategy. The synthesis of boronic esters and acids is key to this chemistry; common methods include:



See Hartwig, *Chem. Soc. Rev.*, **2011**, *40*, 1992

Copper-catalyzed amination / amidation is a very attractive and cheap route into aryl amines etc.:



92%

See Beletskaya, *Organometallics* **2012**, *31*, 7753

3. C–H activation. A very large and rapidly expanding topic which we will not cover in detail!

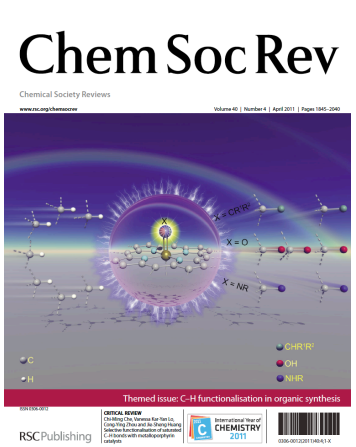
Reviews:

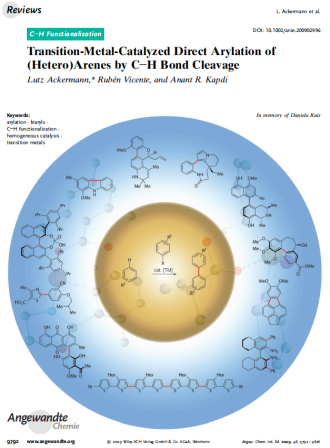
2 x C–H activation: *Chem. Rev.* **2011**, *111*, 1215

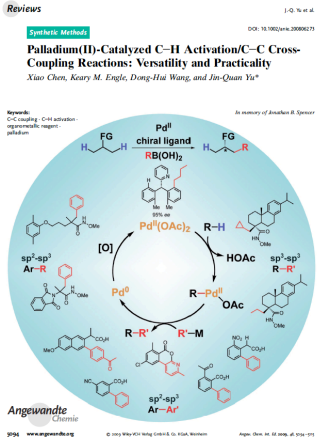
Arene arylation by C–H activation: *Angew. Chem. Int. Ed.* **2009**, *48*, 9792

Pd-cat C–H activation: *Angew. Chem. Int. Ed.* **2009**, *48*, 5094

Chem Soc Rev **2011** issue 4



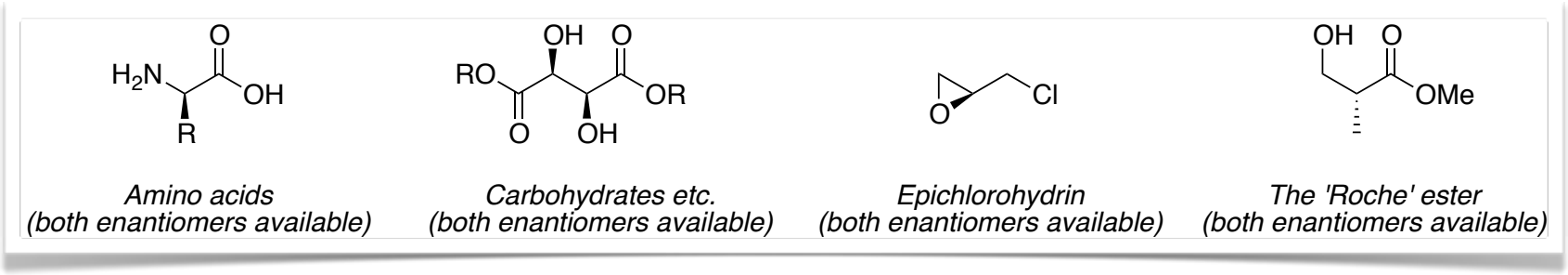




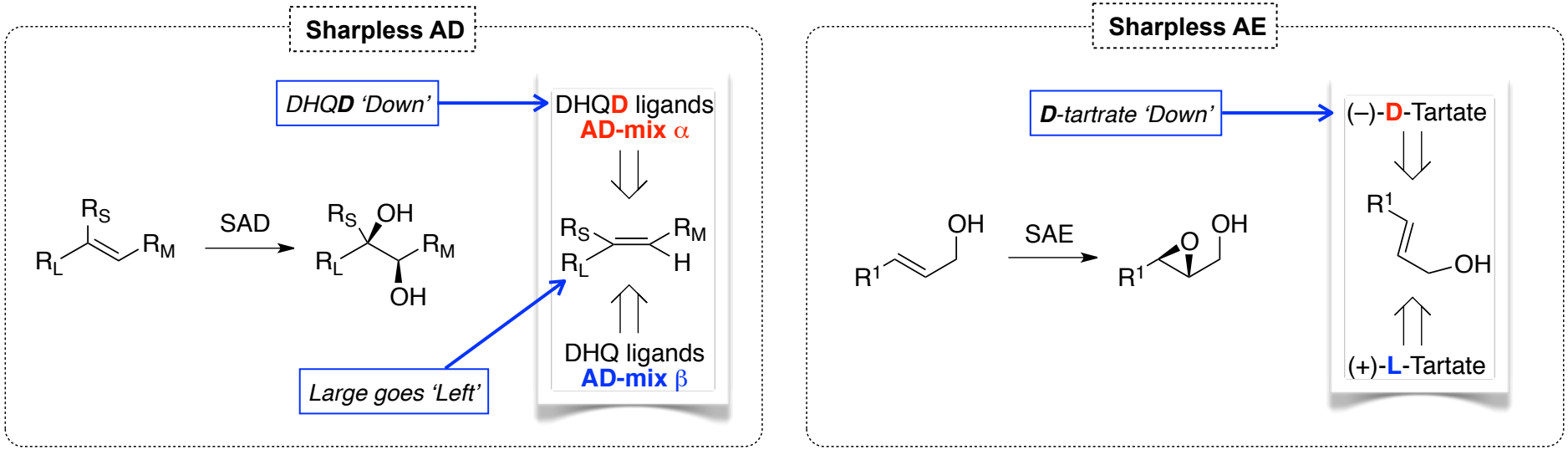
Asymmetric Synthesis

Due to the breadth of this area, we will not cover in detail! General strategies to bear in mind:

1. Look for available chiral sms, such as amino acids, sugars, epoxides (epichlorohydrin)



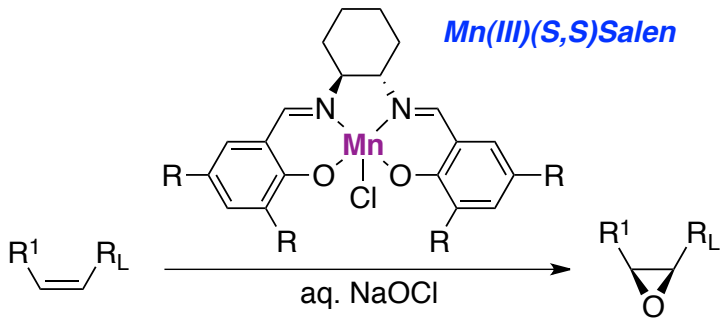
2. Look for 'high quality' catalytic asymmetric processes such as Sharpless AD and AE, Jacobsen epoxidation and hydrolytic kinetic resolution, Noyori hydrogenations, CBS reduction, organocatalysis (!)



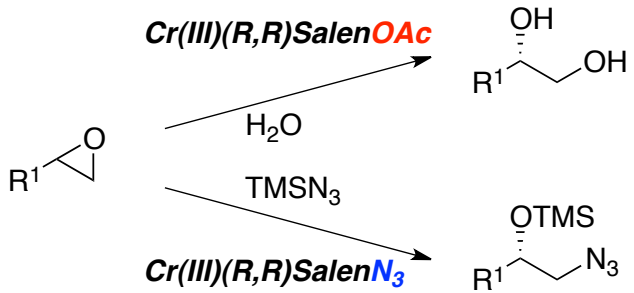
Asymmetric Synthesis

2. Look for 'high quality' catalytic asymmetric processes such as Sharpless AD and AE, Jacobsen epoxidation and hydrolytic kinetic resolution, Noyori hydrogenations, CBS reduction, organocatalysis (!)

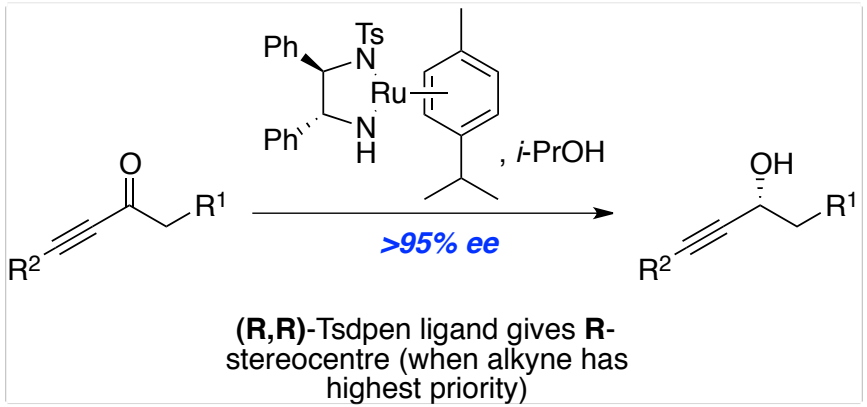
Jacobsen epoxidation



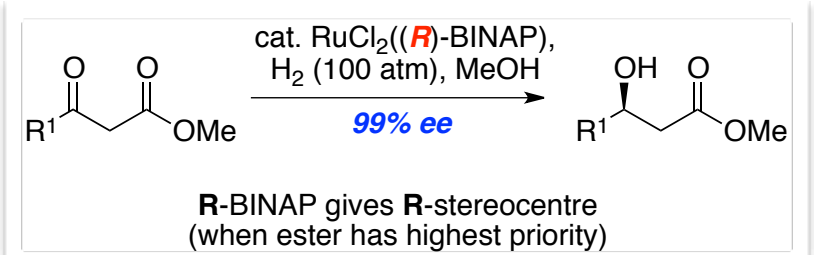
Jacobsen HKR



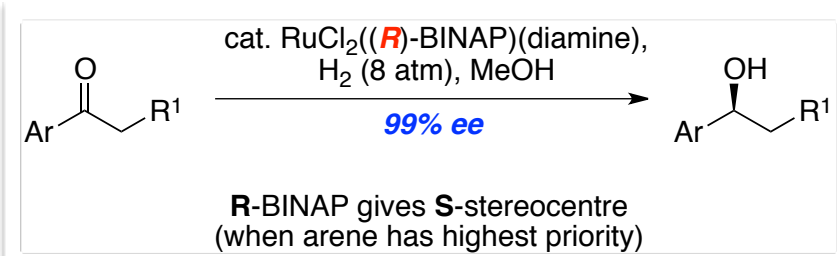
Various Noyori Hydrogenations:



(R,R)-Tsdpen ligand gives **R**-stereocentre (when alkyne has highest priority)



R-BINAP gives **R**-stereocentre (when ester has highest priority)

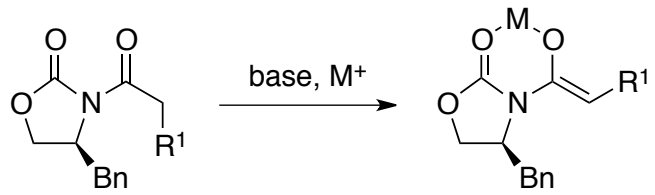


R-BINAP gives **S**-stereocentre (when arene has highest priority)

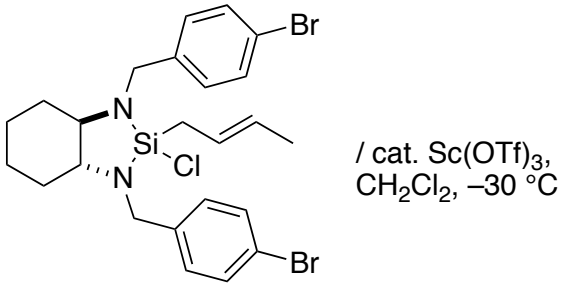
Asymmetric Synthesis

3. Look for 'high quality' chiral auxiliary / reagent approaches: Asymmetric allylation, Evans auxiliary, etc.

Evans auxiliary



Leighton allylation / crotylation

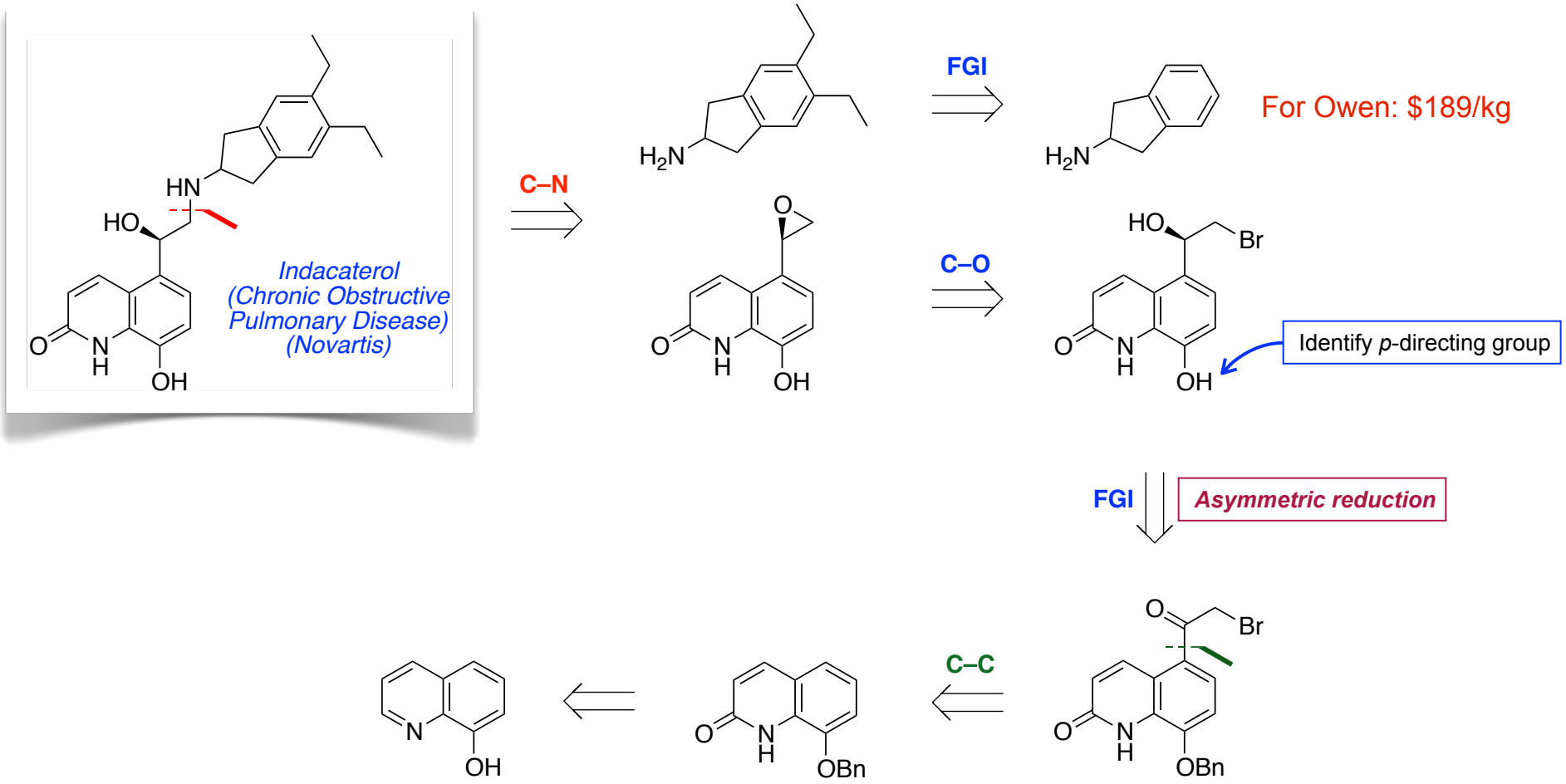


4. Look for high quality substrate stereocontrol, e.g. **Felkin-Anh, Allylic strain**, ring functionalisation (**stereoelectronics**), **steric effects** (less-hindered face approach in bicyclics), **stereospecific reactions** (e.g. epoxide opening with amines or azides to prepare aminoalcohols)

5. Use enzymatic or chemical resolution, which can work really well at an early stage of a synthesis

Case Study: Indacaterol

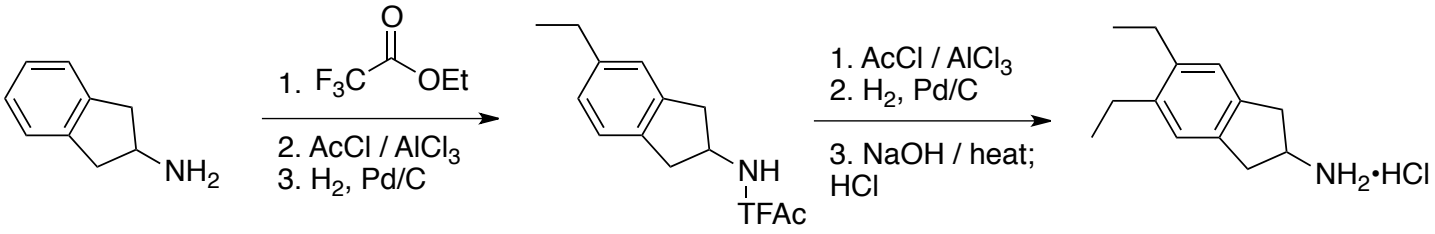
The synthesis of this drug requires the installation of a chiral benzylic alcohol adjacent to an amine. This could well suggest an epoxide strategy, albeit with regiocontrol issues in the ring-opening due to benzylic stabilisation of the S_N2 reaction.



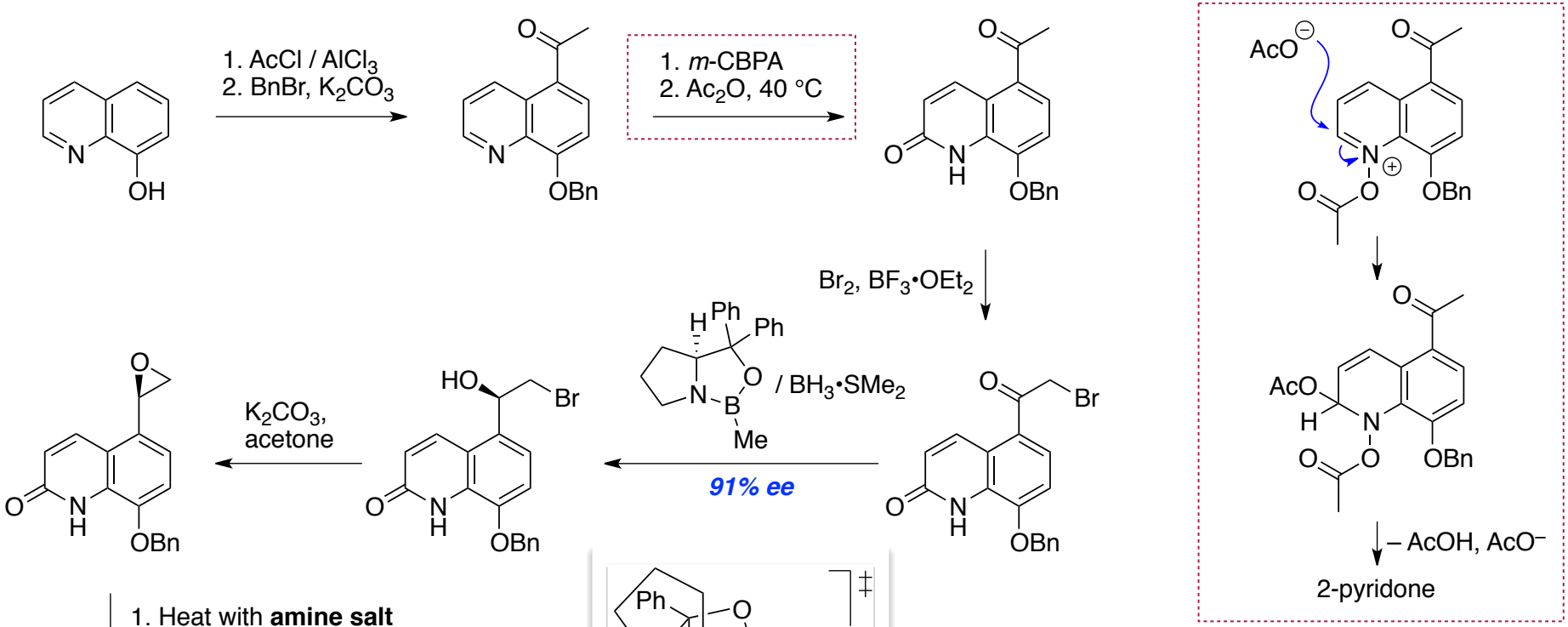
Org. Proc. Res. Dev. **2006**, *10*, 135.
See also: *Bioorg. Med. Chem.* **2011**, *19*, 1136.

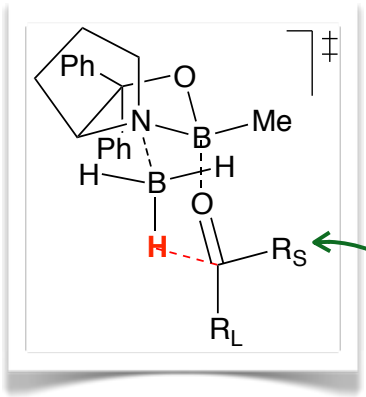
Case Study: Indacaterol

Synthesis:



Recognise symmetry





'Small' group positioned here to minimise 1,3-allylic strain
Interestingly R_L is the CH_2Br

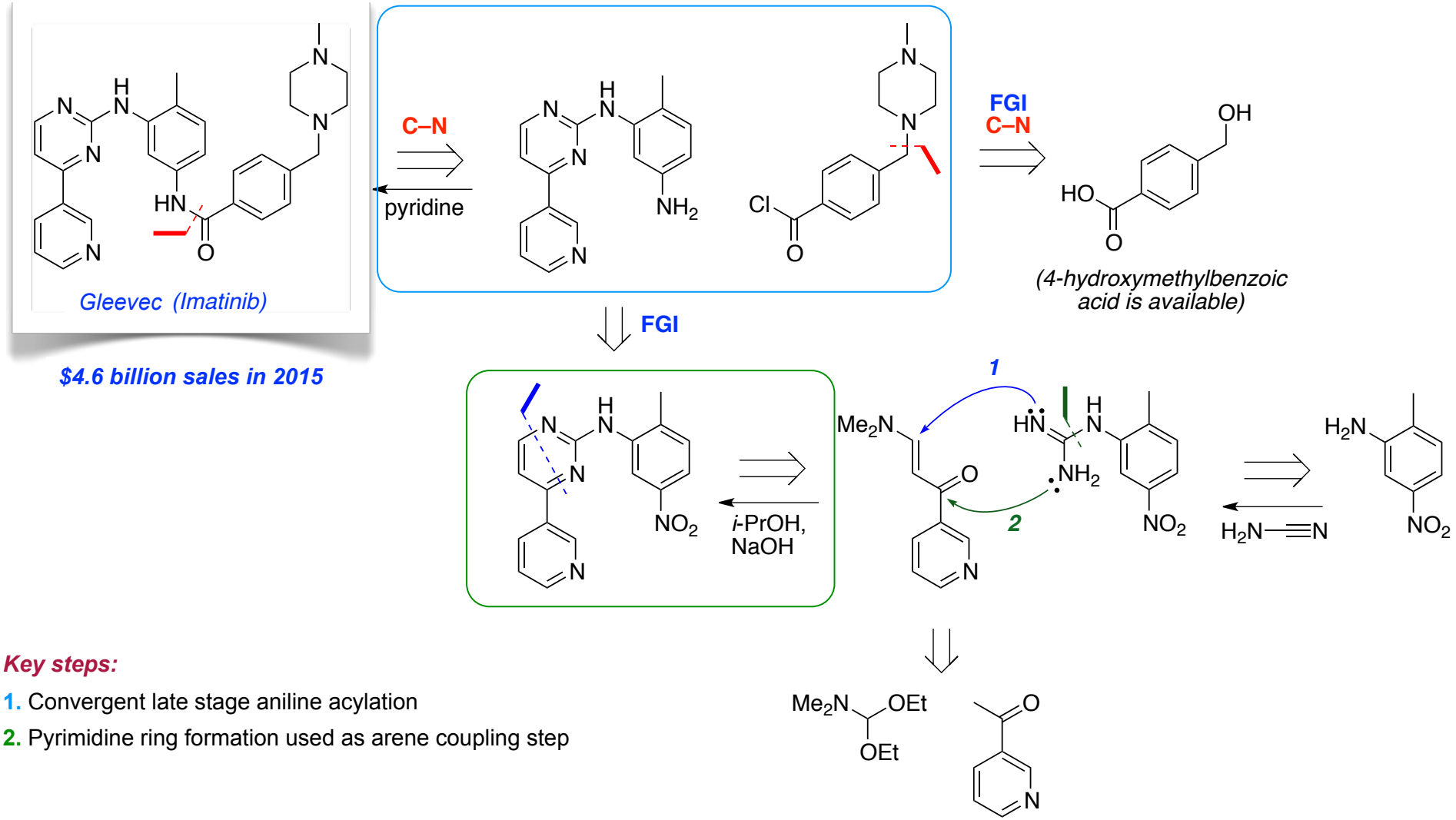
Org. Proc. Res. Dev. **2006**, *10*, 135.
See also: *Bioorg. Med. Chem.* **2011**, *19*, 1136.

Case study: Gleevec

Gleevac (Novartis) – Tyrosine kinase inhibitor used against gastrointestinal tumours.

Process synthesis developed ca.1996.; several reports on improved syntheses including OPRD paper in 2008, and flow synthesis in 2010.

• Original process route (Zimmermann)



$4.6 billion sales in 2015

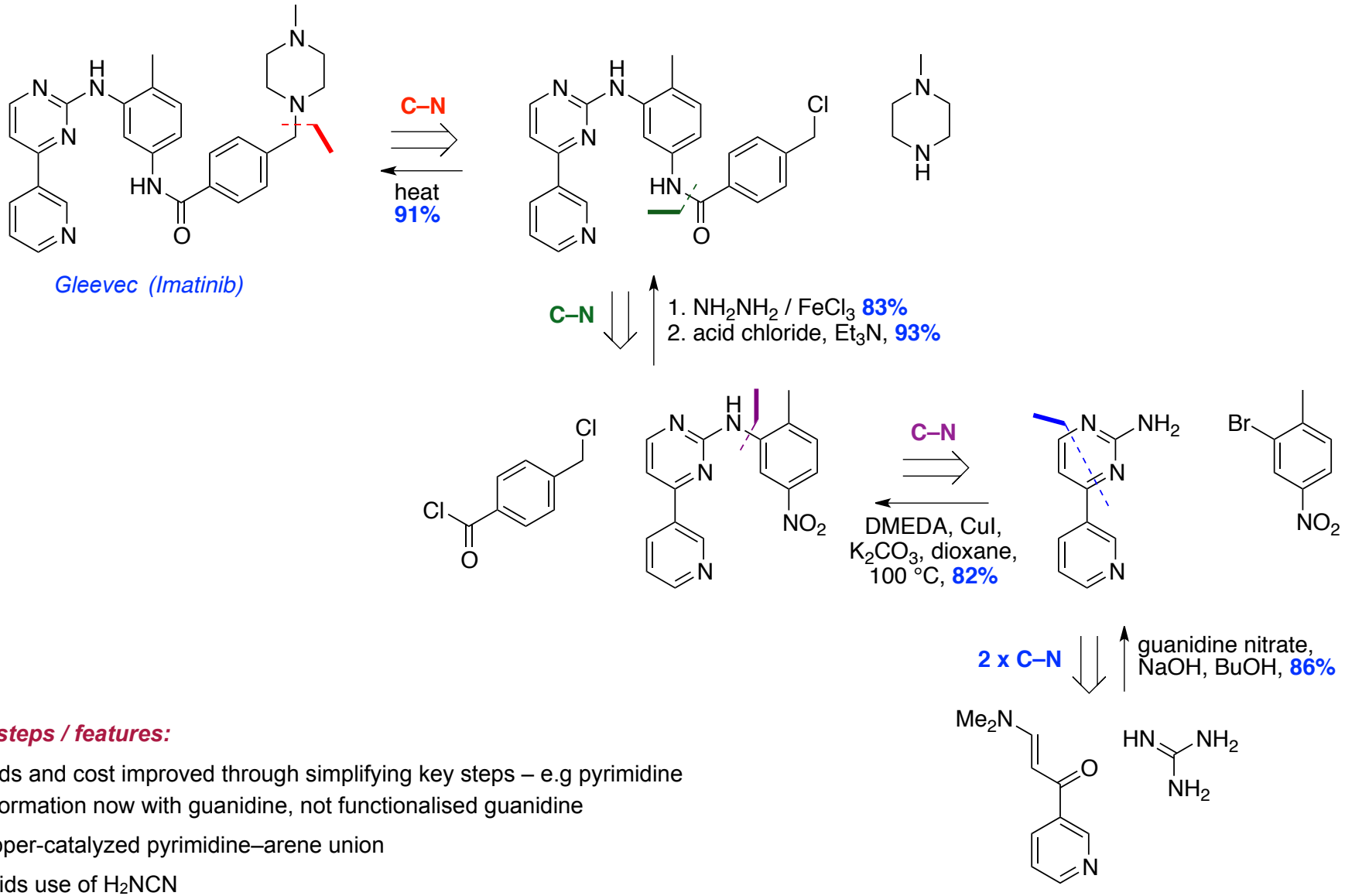
Key steps:

1. Convergent late stage aniline acylation
2. Pyrimidine ring formation used as arene coupling step

Bioorg MCL **1996**, *6*,1221

Case study: Gleevec

- Improved 'process' route (Wang, 2008)

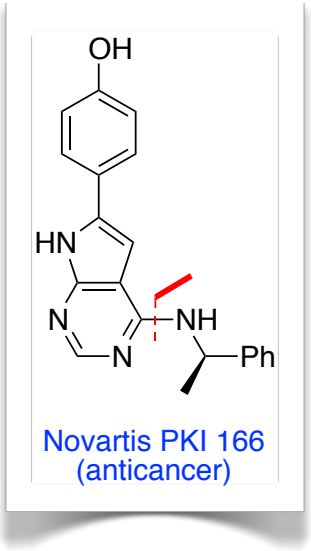


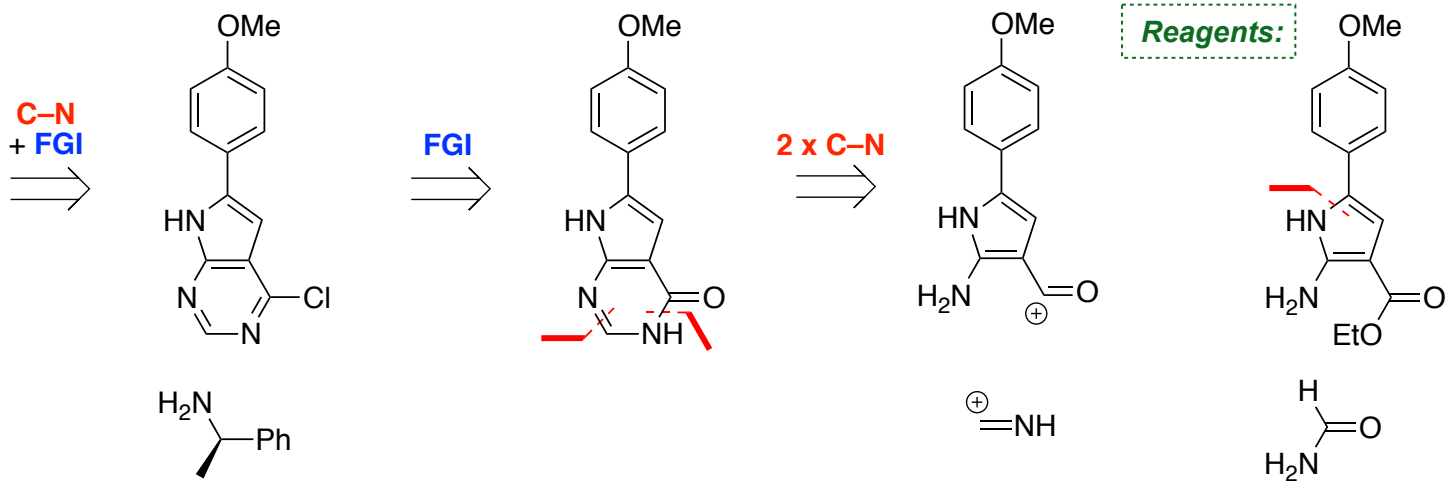
Key steps / features:

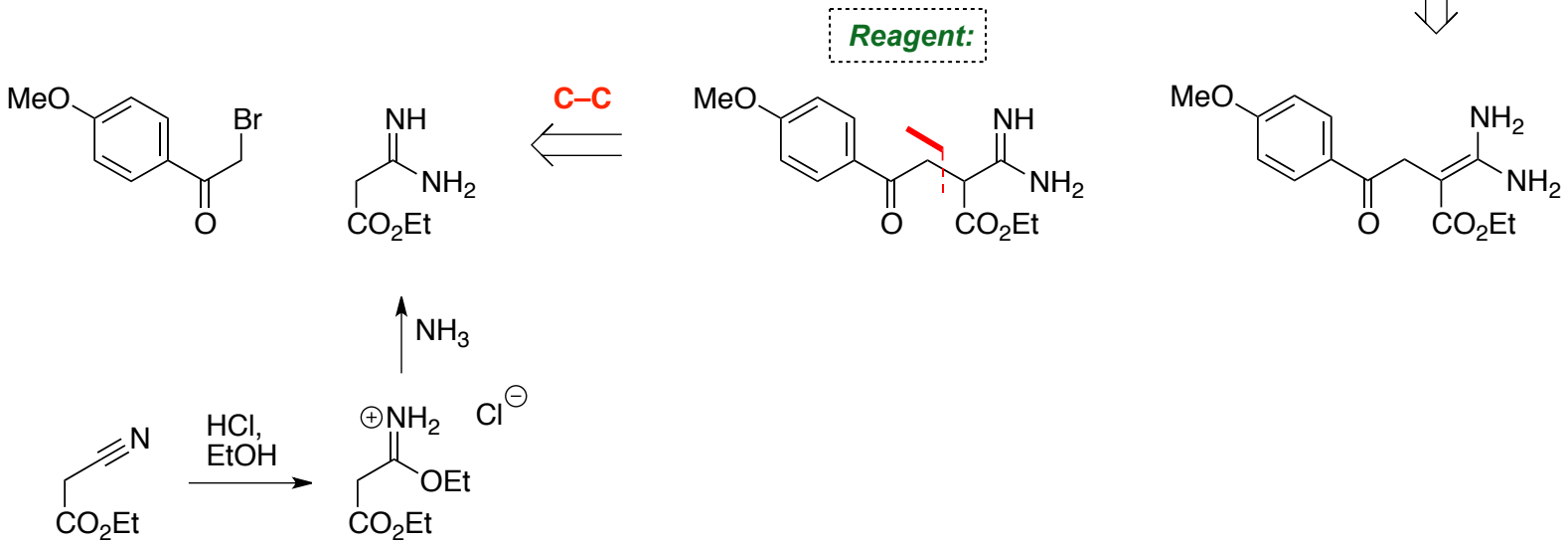
- Yields and cost improved through simplifying key steps – e.g pyrimidine ring formation now with guanidine, not functionalised guanidine
- Copper-catalyzed pyrimidine–arene union
- Avoids use of H_2NCN

OPRD **2008**, *12*, 490

Case study: PKI 166

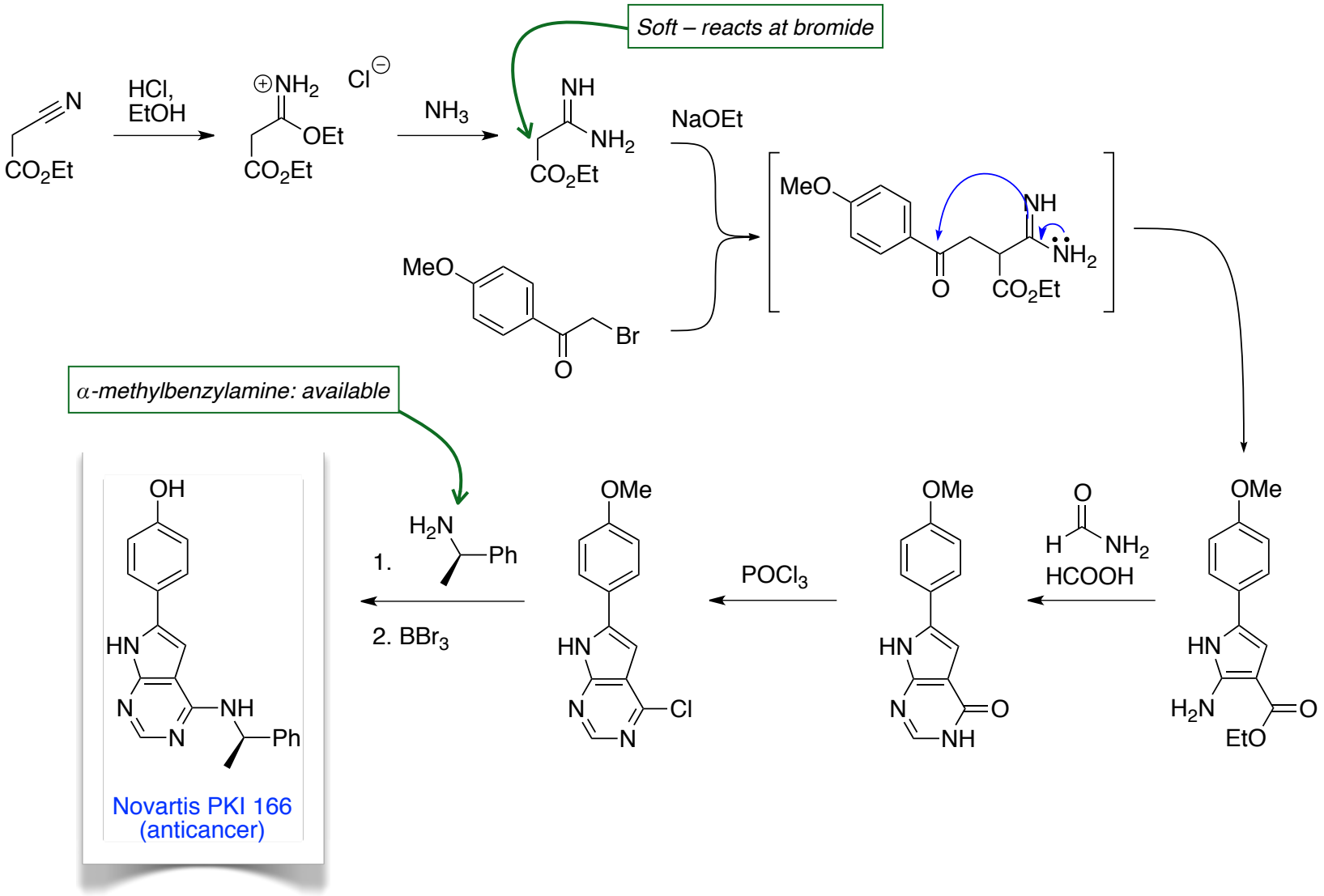






Case study: PKI 166

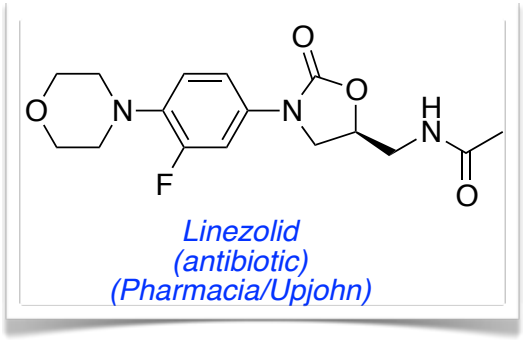
Synthesis:



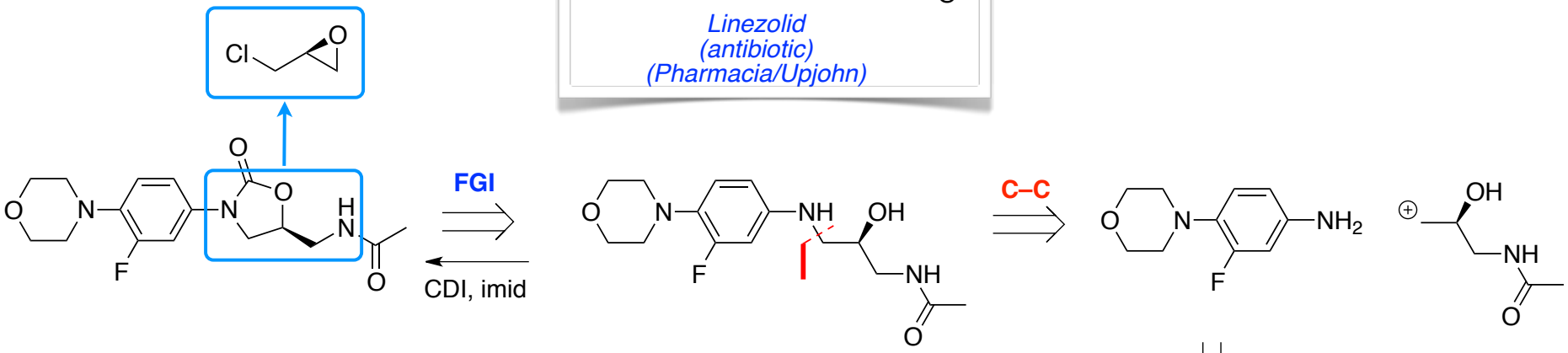
Synthesis: http://www.chem24h.com/drug/synthesis/ykkjfgvlg.html

Traxler, P.; Bold, G.; Brill, W.K.-D.; Frei, J. (Novartis AG); Pyrrolopyrimidines and processes for the preparation thereof. EP 0836605; JP 1999508570; US 6140332; WO 9702266 .

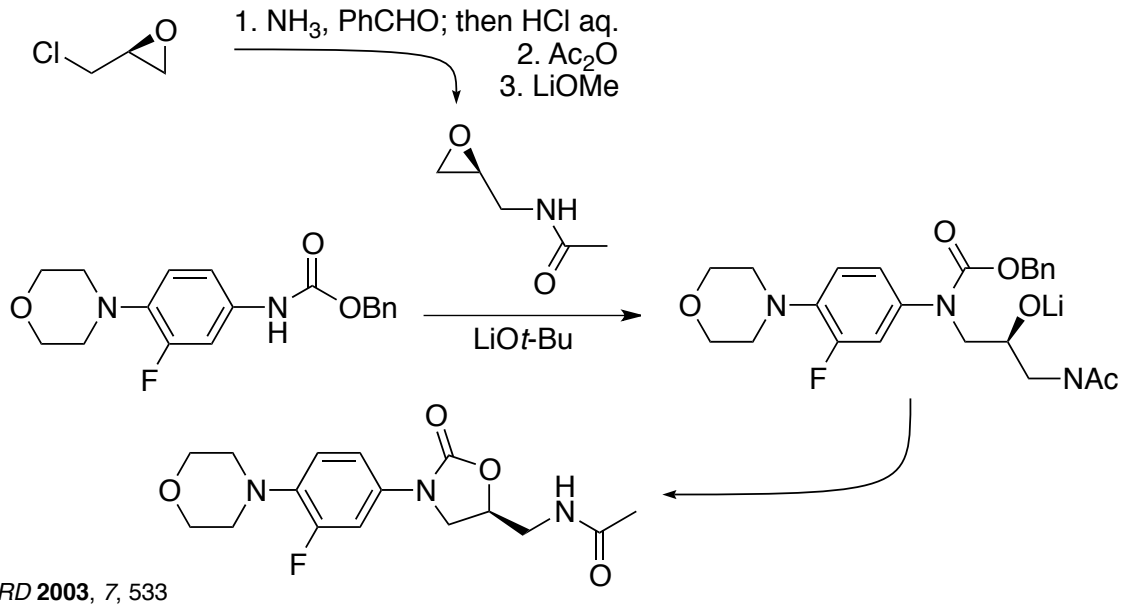
Case Study: Linezolid



$1.3 billion sales in 2013

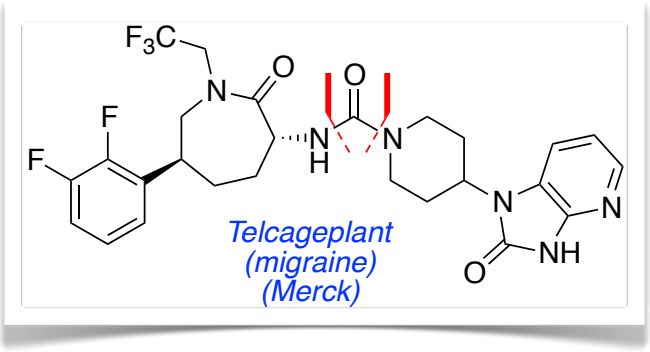


Actual process synthesis: key step:

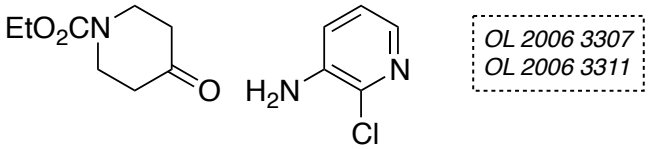


OPRD **2003**, *7*, 533
J. Med. Chem. **1996**, *39*, 673

Case Study: Telcagepant



The azepane in this Merck migraine drug features two remote stereocentres. These were installed using an **organocatalytic** asymmetric conjugate addition reaction:



OL 2006 3307
OL 2006 3311

C–N
C–N

1. $NaBH_3CN$, TFA
2. ClO_2S–N=O then H_2O

2 x C–N (CDI)

C–N

$Pd(OAc)_2$ (1 mol%)
dppb (2 mol%)
aq. *i*-PrOH, 83 °C
99%

C–N asymmetric conjugate addn

FGI

C–N

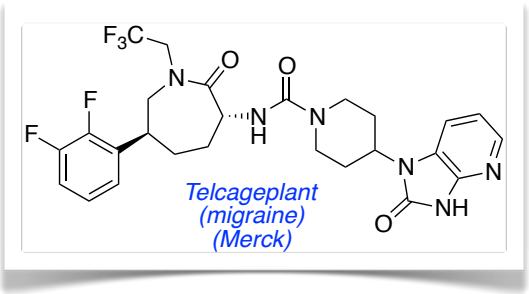
FGI

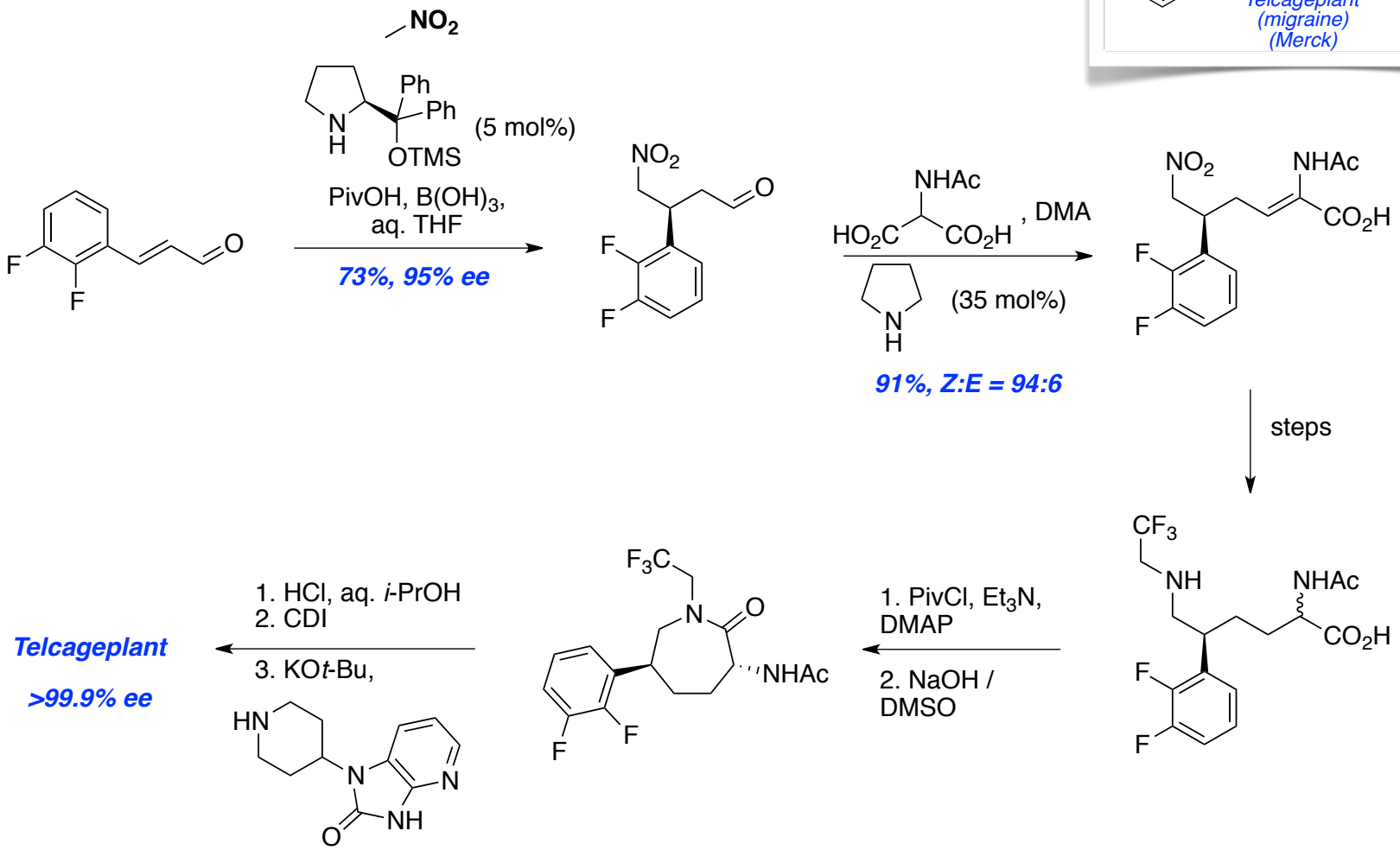
C=C

JOC **2010**, *75*, 7829
Review: Chem. Soc. Rev., **2013**, *42*, 774

Case Study: Telcagepant

Synthesis highlights:





JOC **2010**, *75*, 7829
Review: *Chem. Soc. Rev.*, **2013**, *42*, 774

Excellent reviews of recent / key methods to prepare important pharmaceuticals, and very readable!

Beilstein Journal of Organic Chemistry

An overview of the key routes to the best selling 5-membered ring heterocyclic pharmaceuticals

Marcus Baumann*, Ian R. Baxendale*, Steven V. Ley* and Nikzad Nikbin*

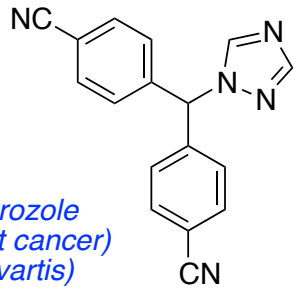
Beilstein J. Org. Chem. **2011,** *7,* 442–495.
doi:10.3762/bjoc.7.57

An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles

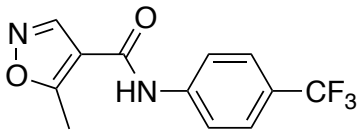
Marcus Baumann* and Ian R. Baxendale*

Beilstein J. Org. Chem. **2013,** *9,* 2265–2319.
doi:10.3762/bjoc.9.265

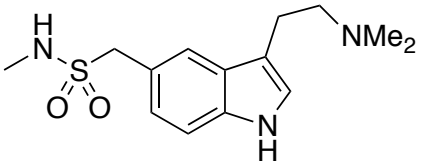
Problem Session 2



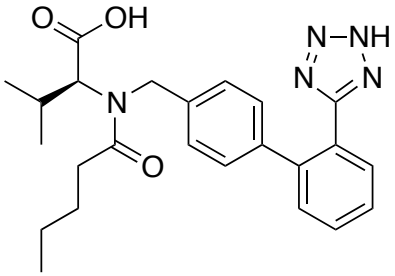
Lestrozole
(Breast cancer)
(Novartis)



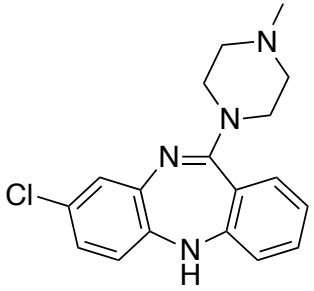
Leflunomide
(Arthritis)
(Sanofi-Aventis)



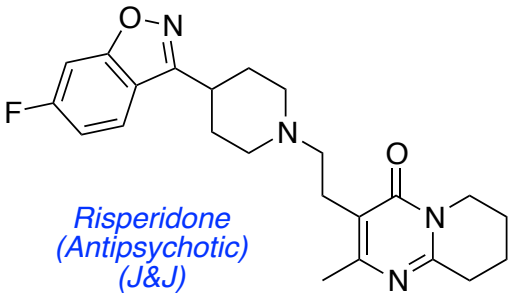
Sumatriptan
(Migraine)



Valsartan
(Blood pressure)
(Novartis)

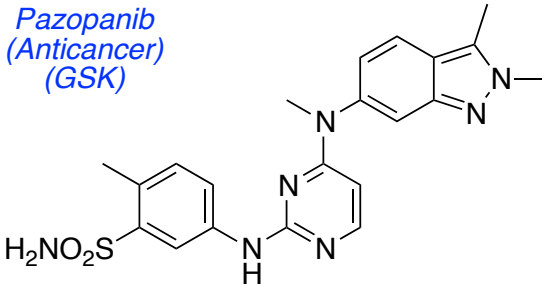


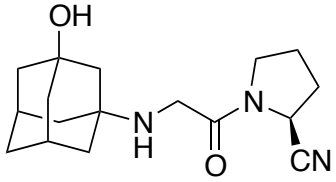
Clozapine
(Bipolar disorder)
(Novartis)



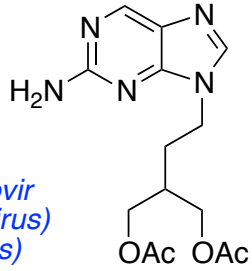
Risperidone
(Antipsychotic)
(J&J)

Pazopanib
(Anticancer)
(GSK)



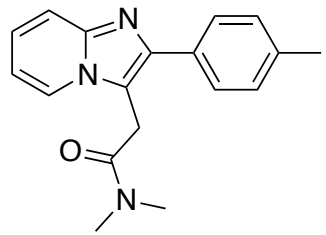


Vildagliptin
(Anti-diabetic)
(Novartis)

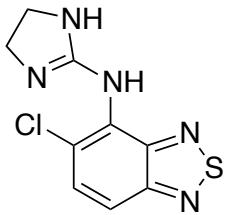


Famciclovir
(Herpes virus)
(Novartis)

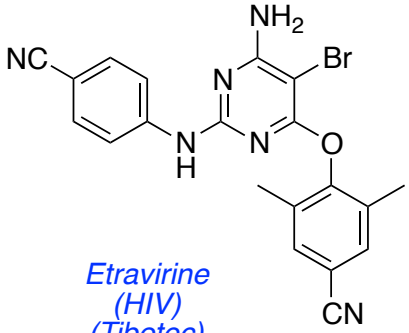
Problem Session 2



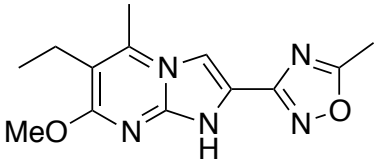
Zolpidem
(Insomnia)
(Sanofi-Aventis)



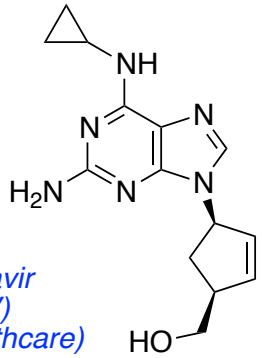
Tizanidine
(Muscle relaxant)
(Novartis)



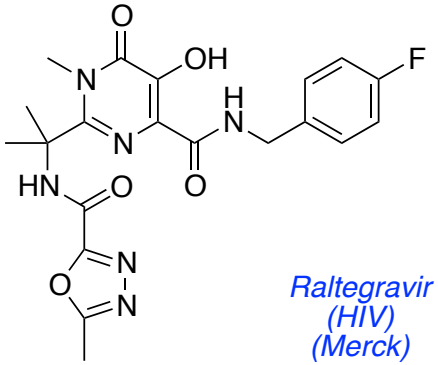
Etravirine
(HIV)
(Tibotec)



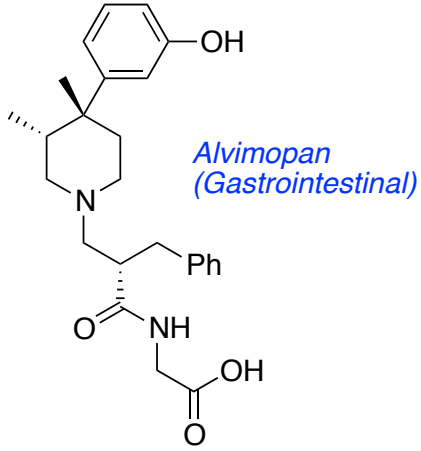
Fasiplon
(Anxiolytic)
(Roussel Ucla)



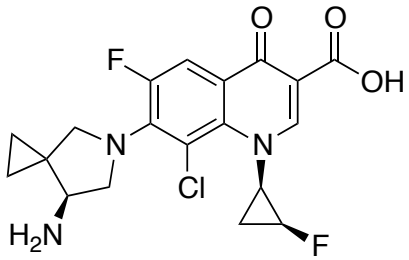
Abacavir
(HIV)
(ViiV healthcare)



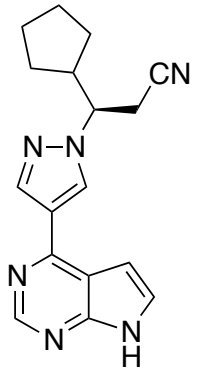
Raltegravir
(HIV)
(Merck)



Alvimopan
(Gastrointestinal)



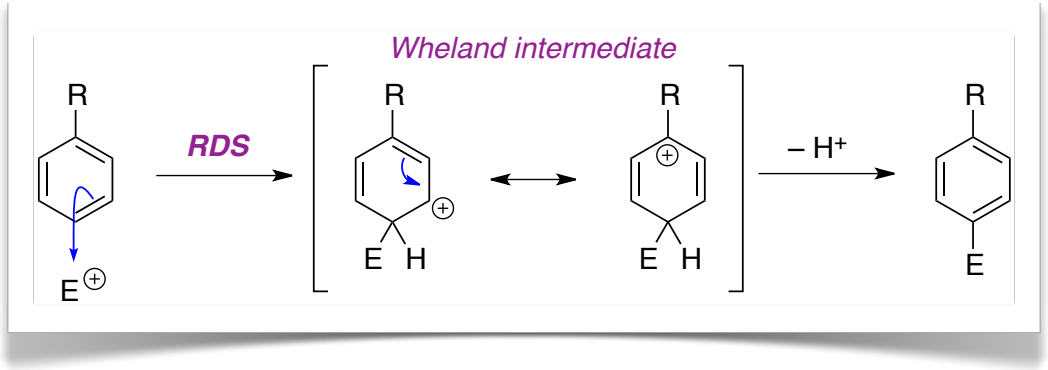
Sitafloxacin
(Ulcer)
(Daiichi Sankyo)



Ruxolitinib
(Cancer)
(Novartis)

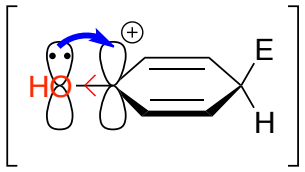
Appendix: Selectivity in Electrophilic aromatic substitution (S_EAr)

Directing effects are crucial for arene functionalization:

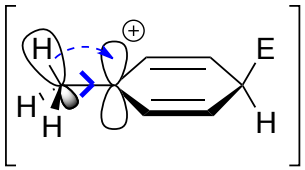


- Electron-donating groups (R) stabilize this intermediate so favour *ortho*- and *para*-substitution
- Electron-withdrawing groups destabilize this intermediate so favour *meta*-substitution where the Wheland intermediate is less destabilized

• Activating electron-donating groups:

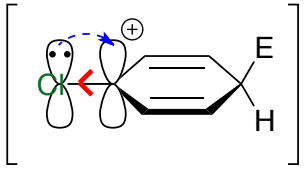


π-donors: groups with lone pairs are *o*-, *p*- directing
e.g. **OR, OC(O)R, NR_2, NHAc, RS**



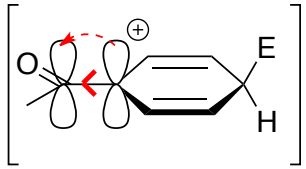
σ-donors: **alkyl** groups (inductive effect I+ and σ-conjugation) are *o*-, *p*- directing

• Deactivating electron-donating groups: Cl, Br, I, F



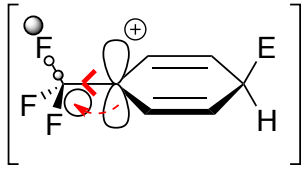
weak π-donor so still *o*-, *p*- directing but strong I– deactivates

• Electron-withdrawing groups:



π-acceptors: groups with low-lying π* orbitals are *m*- directing
e.g. **CO_2R, NO_2, COR, $CONH_2$, SO_2R**, etc.

These intermediates are disfavoured

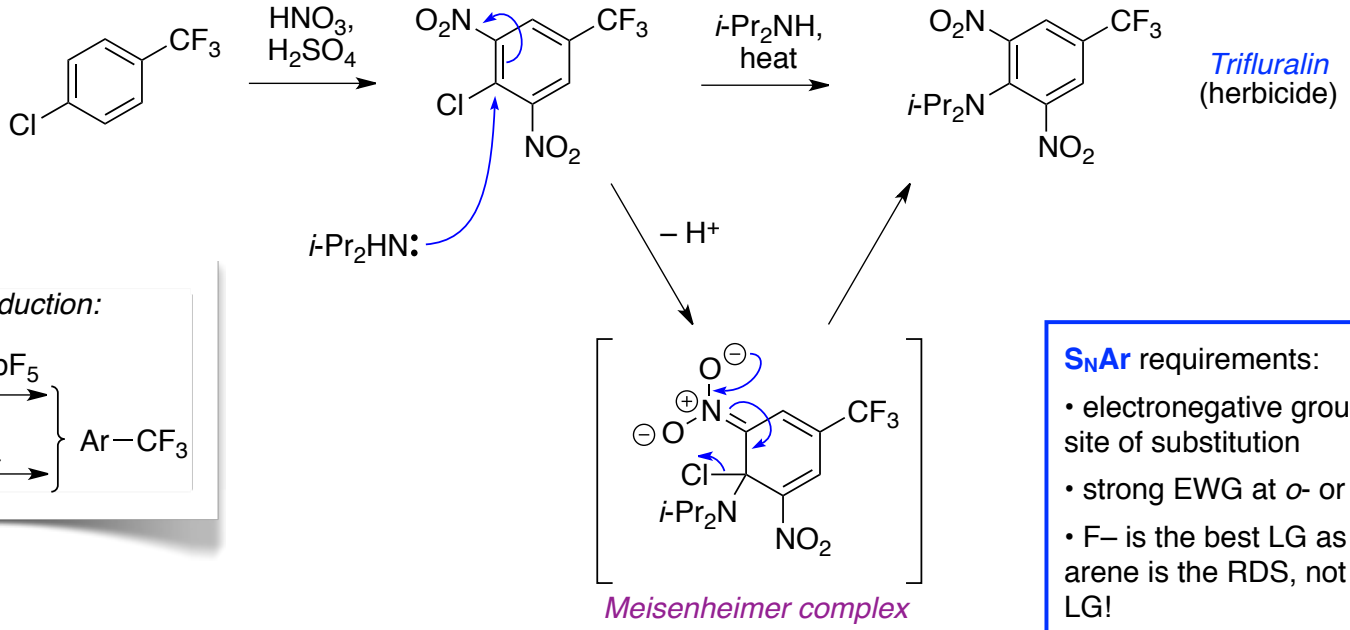


σ-acceptors: groups with low-lying σ* orbitals are *m*- directing
e.g. **CF_3**

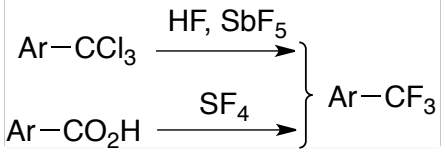
partial positive charge on EWG also destabilizes these intermediates.

Appendix: Selectivity in Nucleophilic aromatic substitution (S_NAr)

We can also effect nucleophilic substitution in specific arene systems:



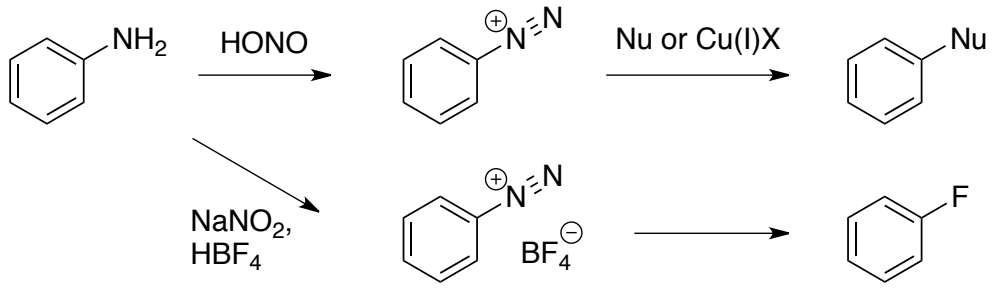
Note: CF_3 introduction:



S_NAr requirements:

- electronegative group (Cl, F) at site of substitution
- strong EWG at *o*- or *p*- position
- F– is the best LG as attack on the arene is the RDS, not ejection of the LG!

Classical aromatic S_N1 is particularly useful for the synthesis of aryl iodides, phenols, nitriles



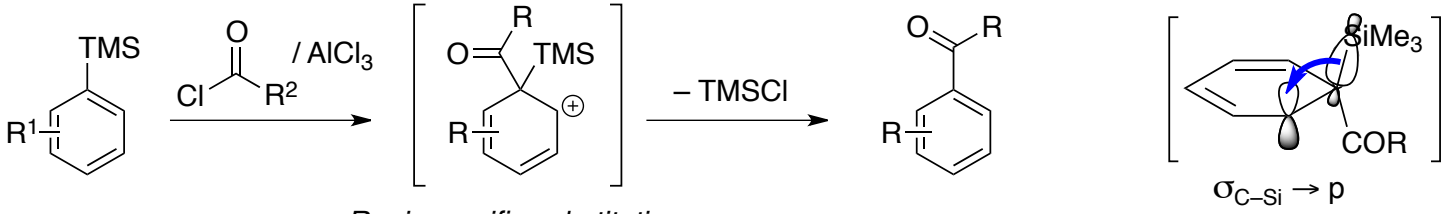
Particularly useful for Nu:

H_2O, ROH
Cu(I)X (Cl, Br, **CN**)
K**I**

Appendix: Arenes – other disconnections

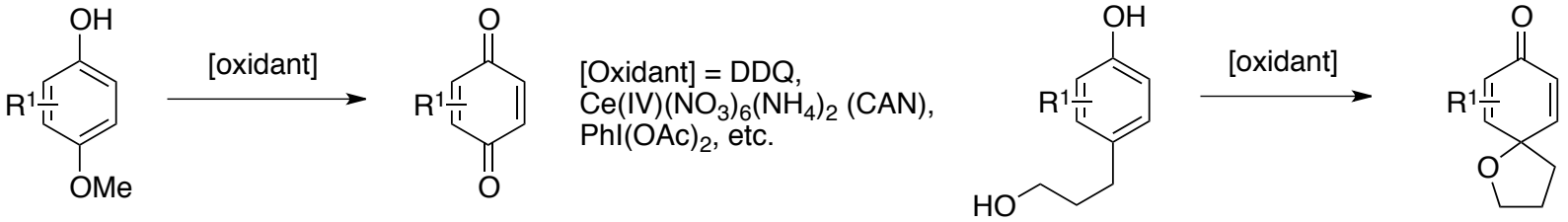
4. Miscellaneous transformations

a) ipso-substitution



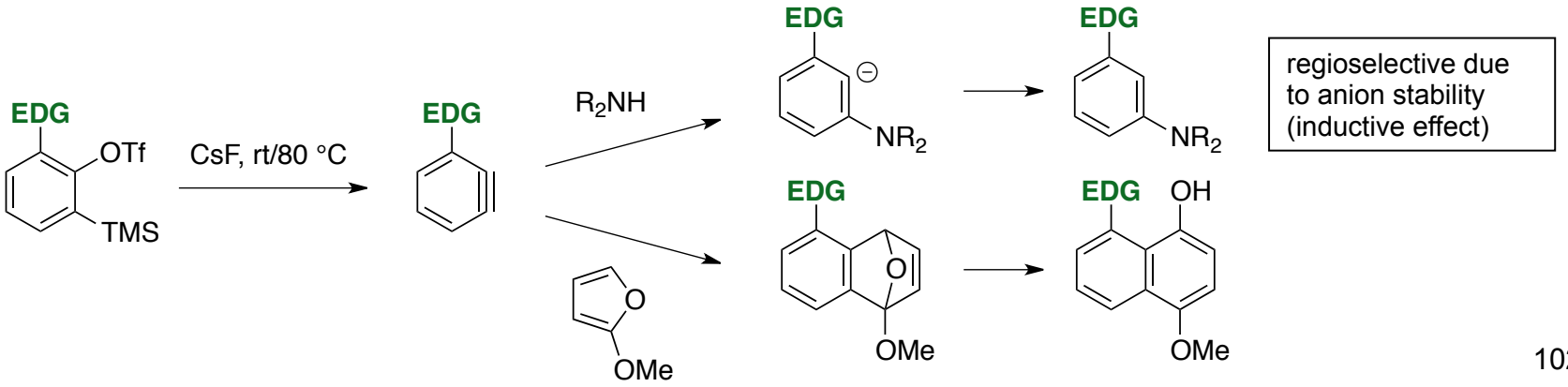
Regiospecific substitution

b) oxidative dearomatisation



c) reductive dearomatisation (Birch)

d) arynes

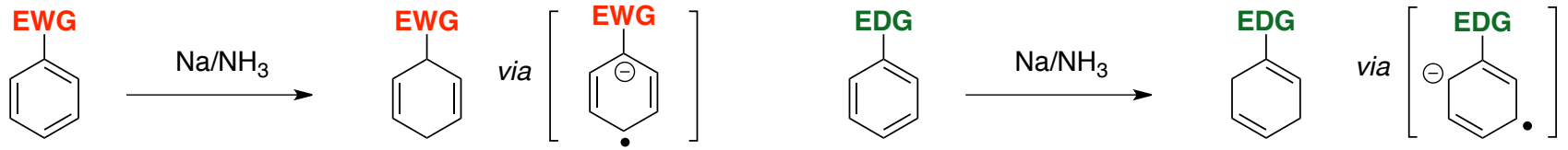


regioselective due to anion stability (inductive effect)

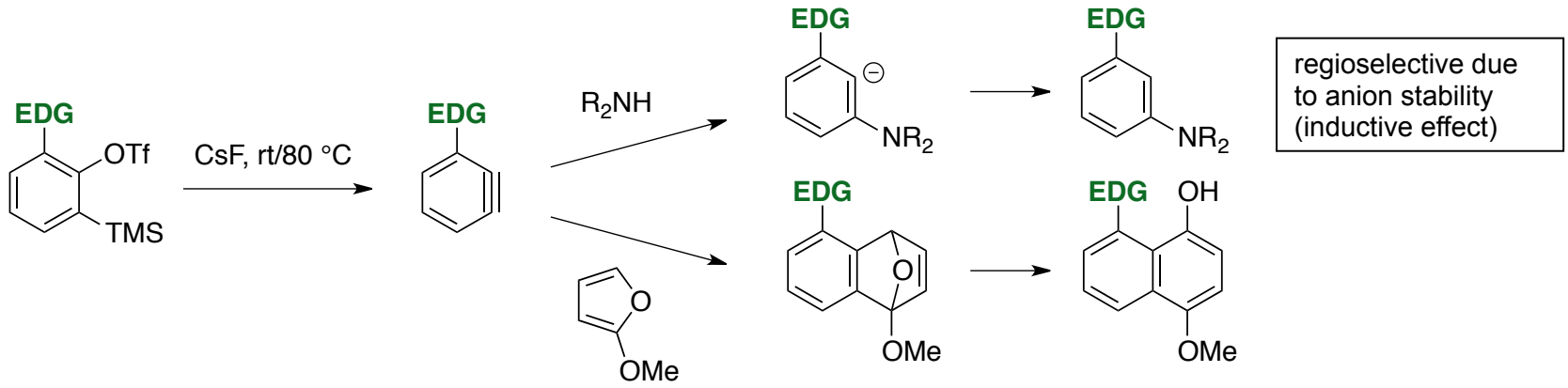
Revisiting arenes – advanced disconnections

4. Miscellaneous transformations

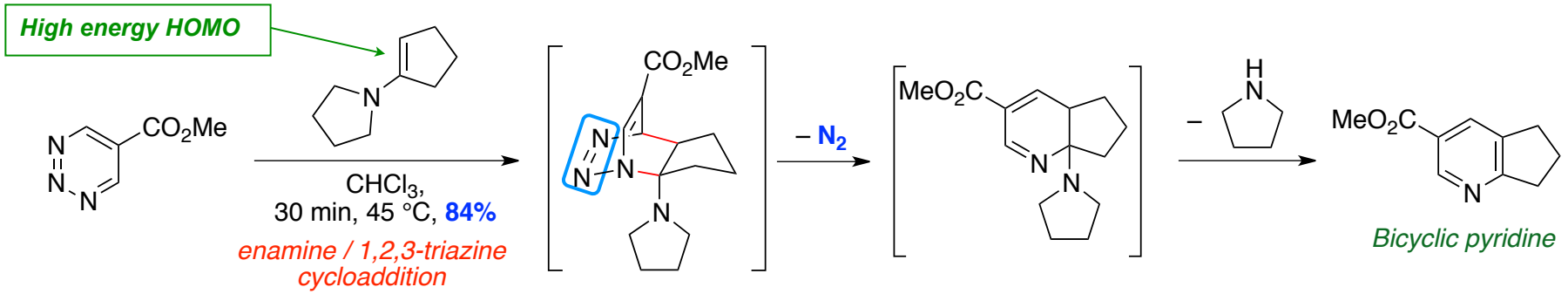
a) reductive dearomatisation (Birch)



b) arynes

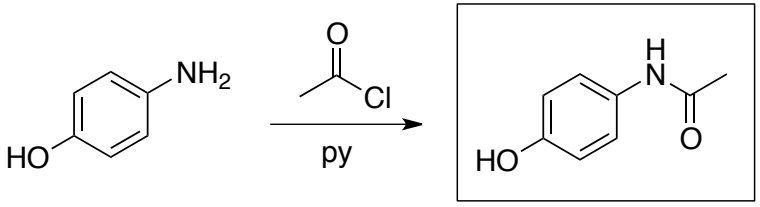


c) Inverse electron-demand Diels-Alder sequences

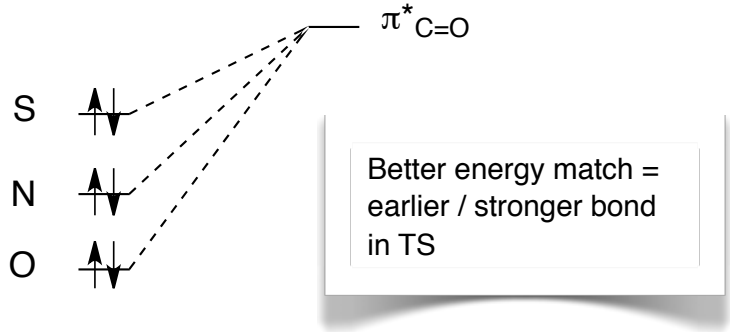


Recap: Chemoselectivity based on stereoelectronics

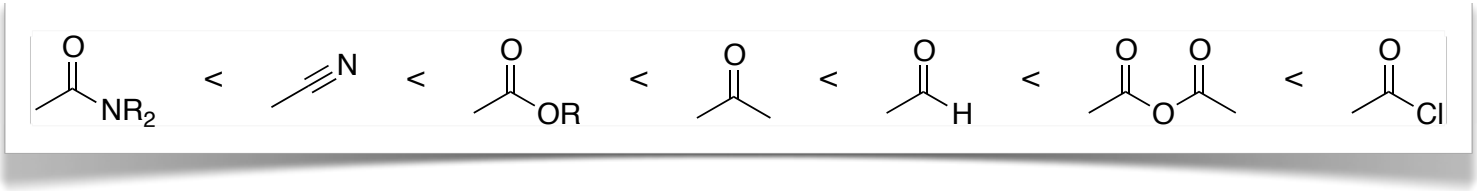
Nucleophile selectivity: In the absence of steric effects, nucleophile selectivity is based on the relative energies of the lone pairs – the higher the HOMO energy, the better the nucleophile...

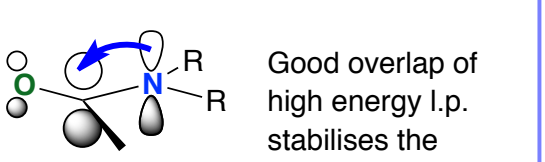


The amine is more nucleophilic than the alcohol...



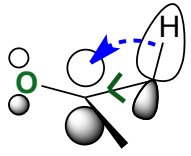
Electrophile selectivity: Electrophile selectivity is based on sterics, electrostatics, and the relative energies of the acceptor orbitals – the lower the LUMO energy, the better the electrophile. Another way of looking at this is to consider the degree of stabilisation of the carbonyl, which will be lost on nucleophilic addition.





$n_N \rightarrow \pi^*_{C=O}$

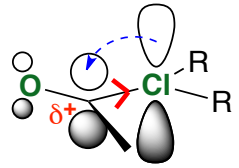
Good overlap of high energy l.p. stabilises the amide and raises the π* energy



$\sigma_{C-H} \rightarrow \pi^*_{C=O}$

+I effect

Lower energy donor orbital – less stabilisation. Positive inductive effect.



$n_{Cl} \rightarrow \pi^*_{C=O}$

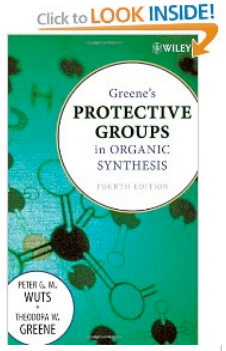
–I effect

Poor overlap of Cl l.p. (3p). Negative inductive effect increases electrophilicity

Appendix: Protecting groups

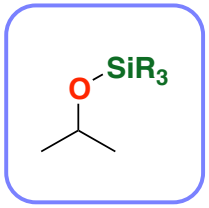
Protecting groups provide an obvious way to protect reactive functionality and achieve chemoselectivity. The cost is at least one additional step in a synthesis, usually two.

- Sometimes the deprotection of protecting groups can be the most challenging step in a synthesis!
- Protecting group-free synthesis preferred – and may be achieved using a careful ordering of steps...



1. Protection for alcohols

• Silyl ethers



Protection

all alcohols: R_3SiCl, imidazole, cat. DMAP, **DMF** (concentrated)

R_3SiOTf, 2,6-lutidine or Et_3N, CH_2Cl_2

1° alcohol: R_3SiCl, imidazole, **CH_2Cl_2**

Deprotection

TBAF, HF•py, HF(aq.)

H^+ / MeOH (e.g. CSA, PPTS, HCl aq.)

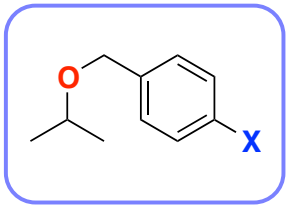
AcOH / THF / H_2O (3:1:1)

1° alcohol: PPTS, MeOH/CH_2Cl_2 (<1:1)

Order of stability (towards acid): TMS < TES < TBS (TBDMS) < TPS (TBDPS) < TIPS

- *The TBDPS group is somewhat more base labile than expected – Ar–Si is more electrophilic.*

• Benzyl ethers

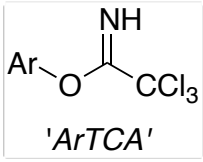


Protection

BnBr or PMBCl, NaH, THF or DMF

PMBTCA / cat. mild H^+ (PPTS, CSA), or $Sc(OTf)_3$

BnTCA / cat. TfOH



'ArTCA'

Deprotection

Bn: H_2, Pd/C; Raney Ni; etc.

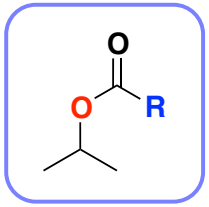
Single electron transfer agents (e.g. Na/NH_3, Li naphthalenide)

PMB: $Ce(IV)(NH_4)_2(NO_3)_6$ (***CAN***)
DDQ; SET-agents.
BBr_3 or BCl_3

Selective deprotection of silyl ethers: R. D. Crouch, *Tetrahedron* **2013**, *69*, 2383.

Appendix: Protecting groups

- **Esters / carbonates**



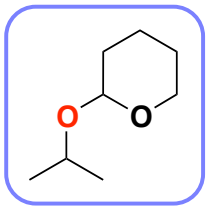
Protection

Esters: RCOCl or $(RCO)_2O$, py, DMAP, CH_2Cl_2
Particular favourites: R = Me, Ph, CCl_3
Carbonates: ROCOCl, py, DMAP,
Particular favourites: R = Me, Allyl, Bn, CH_2CCl_3

Deprotection

NaOH (aq.), DIBALH. Others are case specific...
Halogenated: Use Zn
Allyl: Use Pd(0) (generates pi-allyl)
Benzyl: Use H_2, Pd/C

- **Acetals**



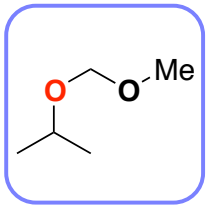
Protection

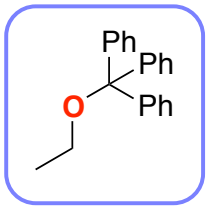
THP: Dihydropyran / PPTS

Deprotection

Mild acid (aq. or methanolic) (e.g. PPTS or AcOH)

- **Other ethers**





Protection

MOMCl, Hunig's base, CH_2Cl_2
MOMCl, NaH, THF

Trityl chloride, DMAP, DMF (selective for 1° OH)
$Ph_3C\ BF_4$

Deprotection

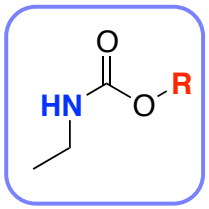
HCl (aq.) (fairly concentrated!)
TFA, CH_2Cl_2
Boron-based Lewis acids

very mild acid! (e.g. a column!)

Appendix: Protecting groups

2. Protection for amines

• Carbamates



Protection

R$OCOCl$ or $(ROCO)_2O$, py, CH_2Cl_2

Particular favourites:

R = Bn (Cbz)

R = *t*-Bu (Boc)

R = Allyl (Alloc)

R = Fluorenyl (Fmoc)

R = CH_2TMS (Teoc)

Deprotection

The following conditions are particularly useful as they are orthogonal to other PGs:

Cbz: H_2, Pd/C

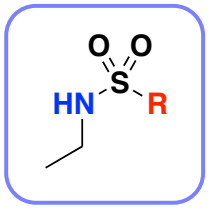
Boc: TFA / CH_2Cl_2

Alloc: Pd(0), dimedone

Fmoc: Et_3N

Teoc: TBAF

• Sulfonamides



Protection

RSO_2Cl, py, CH_2Cl_2

Particular favourites:

R = *p*-toluene (Ts)

R = *p*-nitrophenyl (Ns)

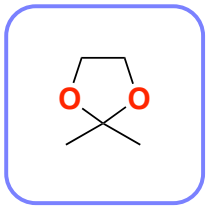
Deprotection

Ts: Mg / MeOH, sonication.
or Na/Hg *or* other single electron reductants (e.g. Na naphthalenide) *or* strong base

Ns: PhSH / K_2CO_3

3. Protection for carbonyls (and diols!)

• Acetals



Protection

For carbonyl:

$HOCH_2CH_2OH$, PPTS or TsOH

For alcohol:

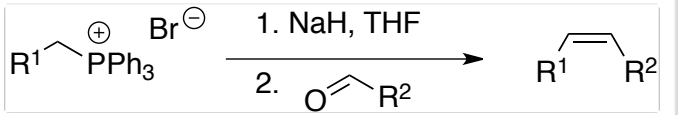
ketone / aldehyde / dimethyl acetal, PPTS or TsOH

Deprotection

MeOH, H_2O, PPTS or HCl

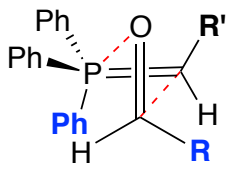
Appendix: Alkene synthesis : Wittig Mechanisms

Mechanistic focus: Wittig reaction



Non-stabilized ylid:
(*Z*)-selective

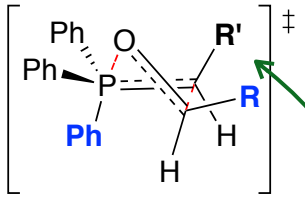
Approach of reagents



Sterically favoured

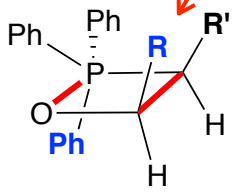
[2+2]

Transition state



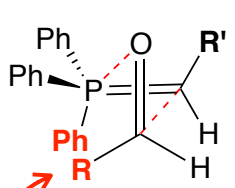
Puckered EARLY TS *minimises sterics between R and R'*

Sterically disfavoured *but it's TOO LATE!!*



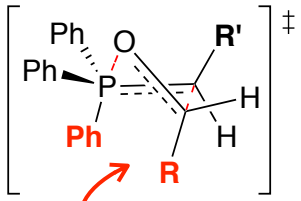
retro [2+2]

Z

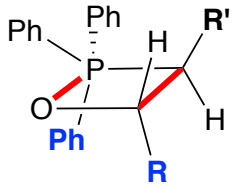


Sterically disfavoured

[2+2]



Sterically disfavoured *in the transition state*



retro [2+2]

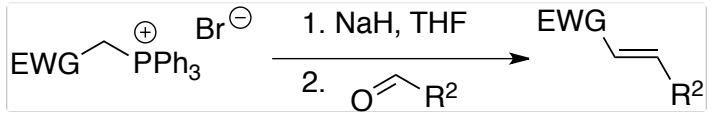
E

- Reaction is irreversible, i.e. under kinetic control.
- Mechanism is a concerted [2+2] cycloaddition

Recent literature: Gilheany et al., *JACS,* **2012**, *134*, 9255. Aggarwal et al., *JACS,* **2006**, *128*, 2394.

Appendix: Alkene synthesis : Wittig Mechanisms

Mechanistic focus: Wittig reaction



Stabilized ylid:
(*E*)-selective

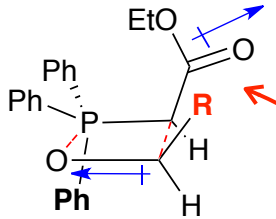
Note: This reaction is NOT under thermodynamic control

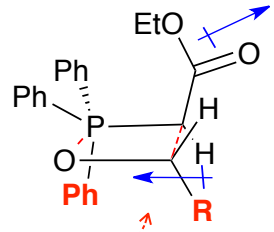
• The initial [2+2] is irreversible, and the geometry of the transition state is believed to be controlled by **sterics** and **favourable dipole alignment:**

cis-Transition states

trans- Transition states

***Planar** Transition states*

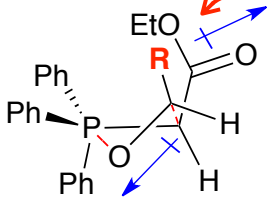


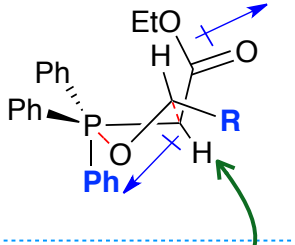


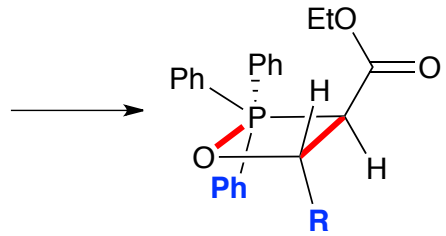
All structures benefit from favourable opposed dipole alignment

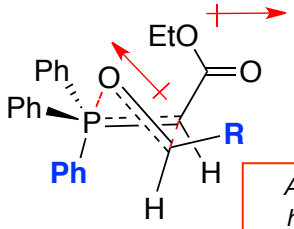
Sterically disfavoured

***Puckered** Transition states*









***Puckered LATE TS** minimises sterics between R and Ph*

Alternative Puckered-cis TS has less favourable dipoles

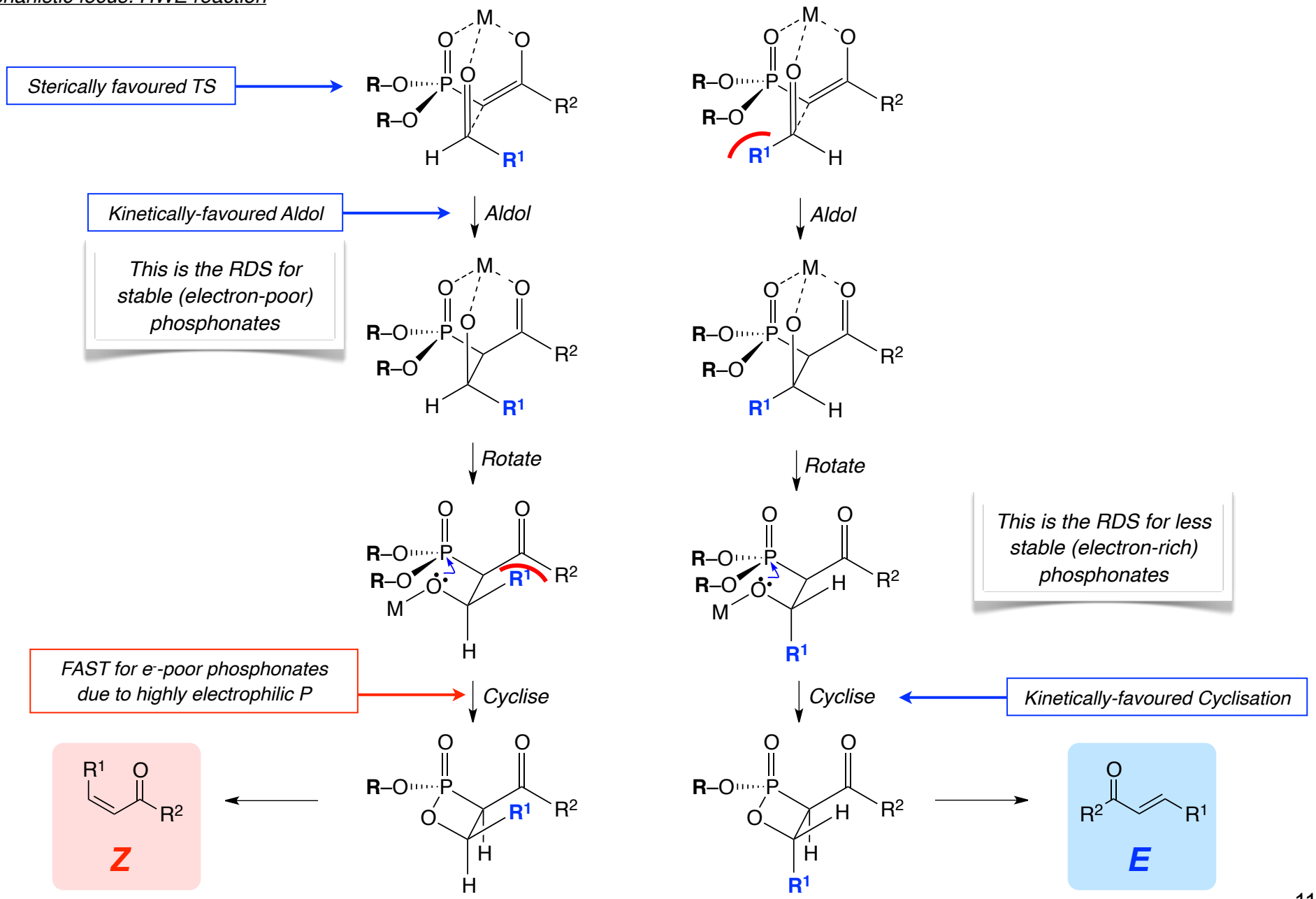
• Reaction is irreversible, i.e. under kinetic control.

• Late TS due to more stable ylid being used

Recent literature: Gilheany et al., *JACS,* **2012**, *134*, 9255. Aggarwal et al., *JACS,* **2006**, *128*, 2394.

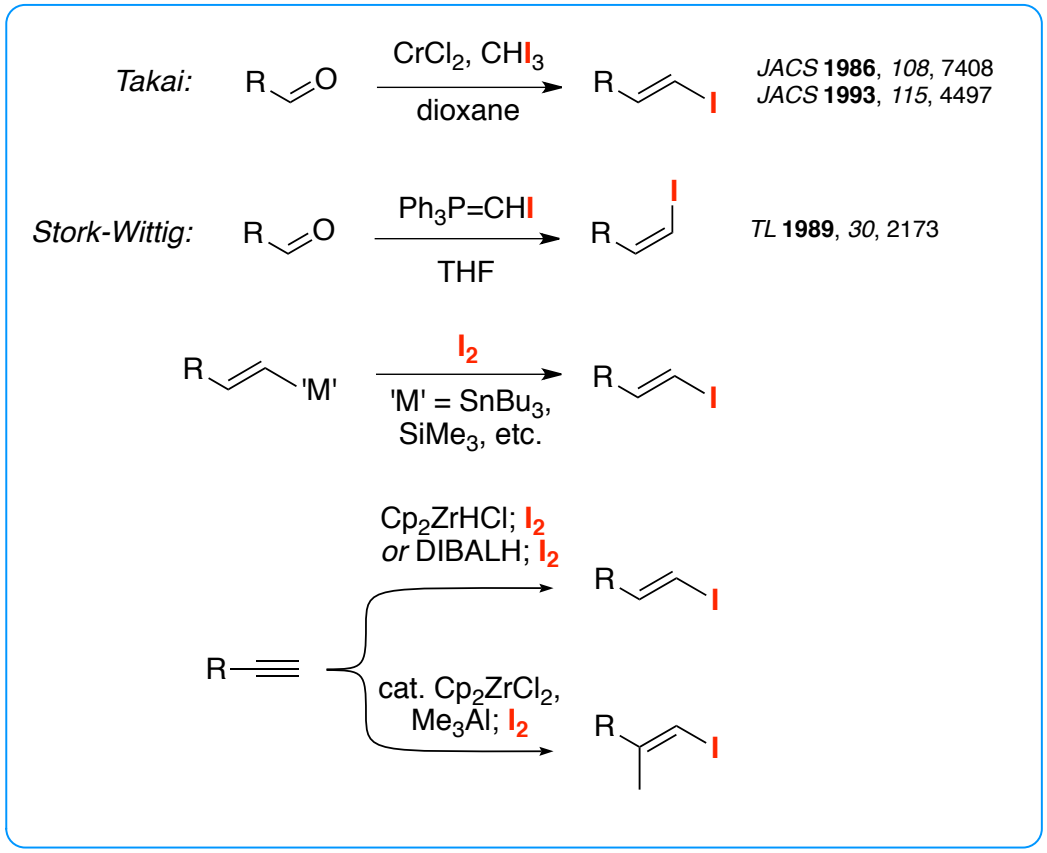
Appendix: Alkene synthesis : HWE-type Mechanisms

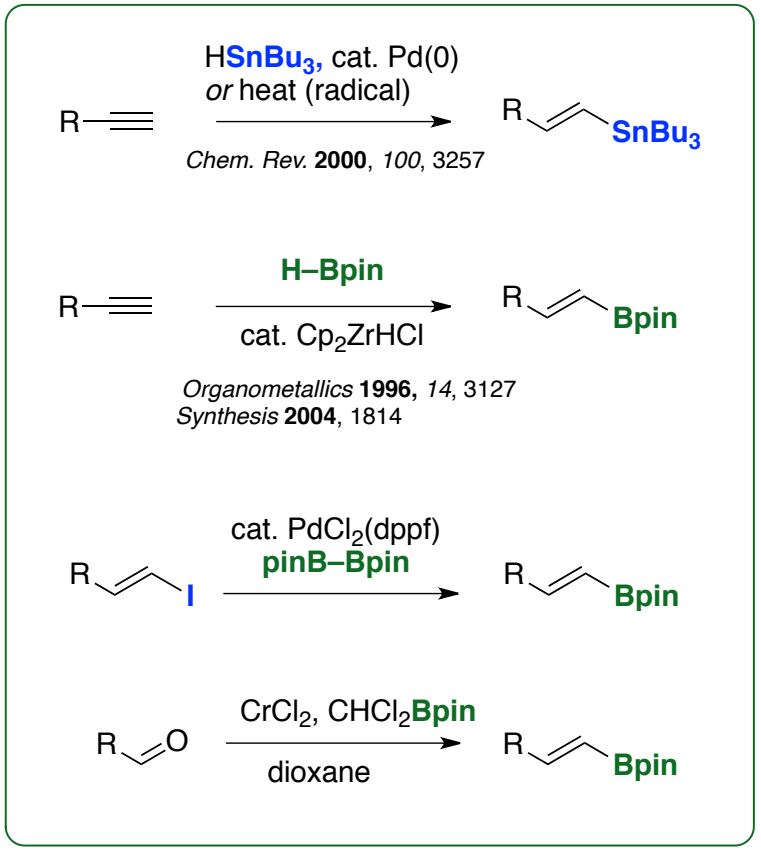
Mechanistic focus: HWE reaction



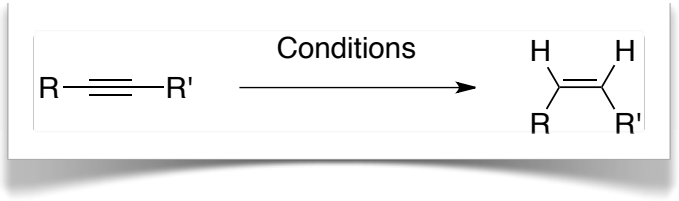
Appendix: Methods for the synthesis of alkenyl halides and metals

Synthesis of alkenyl halides and alkenylorganometallics:





Other methods for cis-reduction:

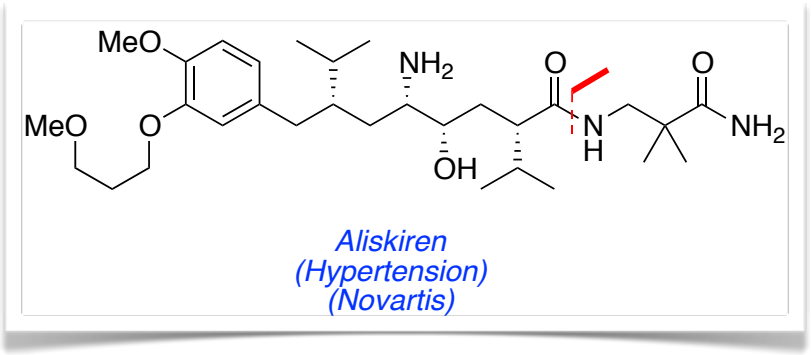


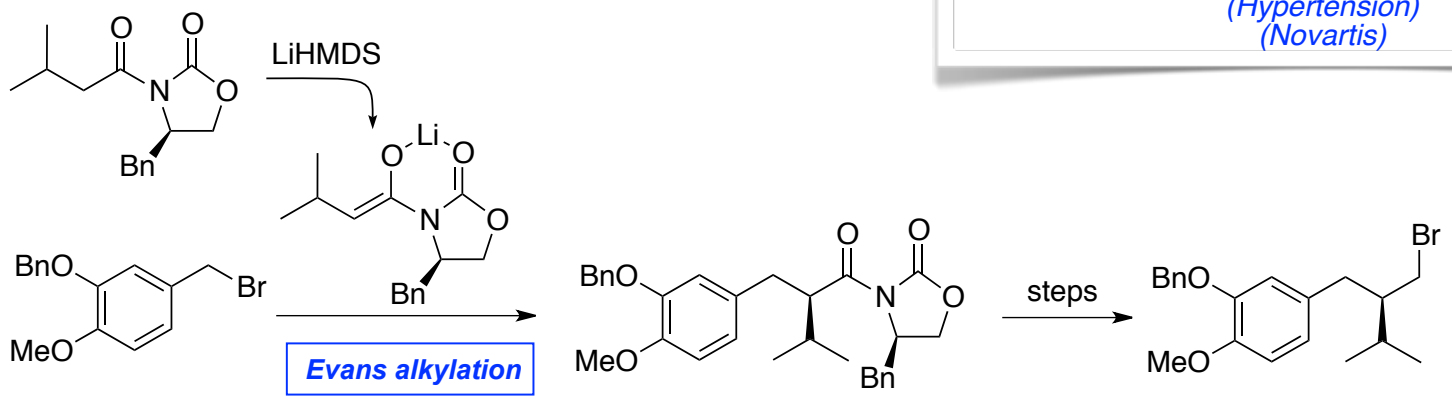
- *Diimide and equivalents:* $KO_2CN{=}NCO_2K$; $TsNHNH_2$ / base; NBSH = nitrobenzenesulfonyl azide
- *hydrometallation / protodemetallation:* BH_3; HOAc

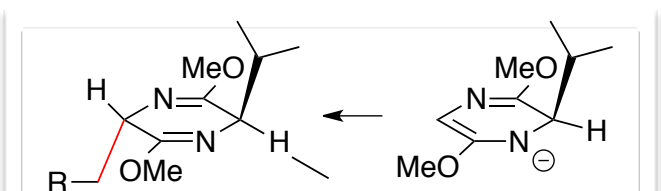
Case Study: Aliskiren

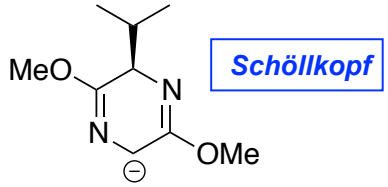
The aminoalcohol / diisopropyl core of this drug poses a significant chemical challenge. Compare chiral auxiliary approaches (including those used by Novartis) with a superior recent development that recognises symmetry.

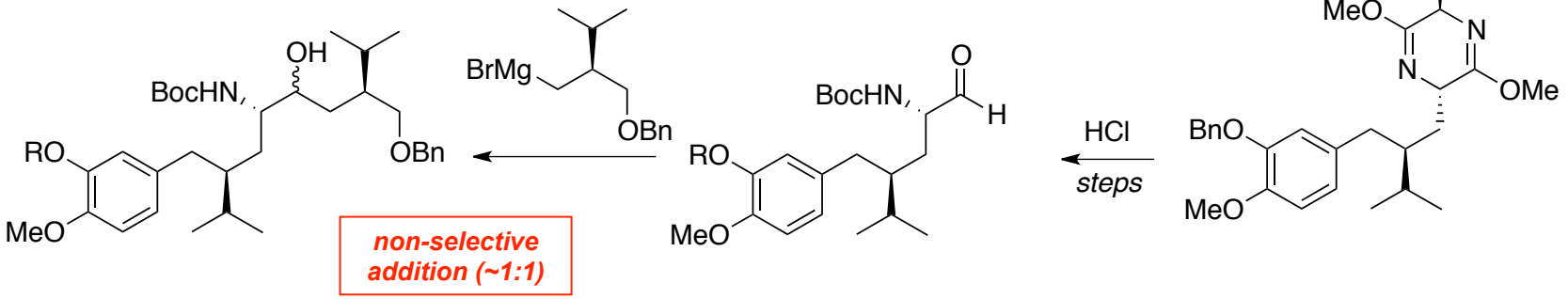
• **Approach 1: Novartis** *J. Med. Chem.* **1997**, *50*, 4818 and 4832.











Case Study: Aliskiren

The aminoalcohol / diisopropyl core of this drug poses a significant chemical challenge. Compare chiral auxiliary approaches (including those used by Novartis) with a superior recent development that recognises symmetry.

• **Approach 2: S. Y. Ko** *Helv. Chim. Acta.* **2012**, *95*, 1937