



University of
Nottingham

UK | CHINA | MALAYSIA

CHEM3065 Synthesis and Reactive Intermediates

O'Duill lecture 1

miriam.oduill@nottingham.ac.uk



How is the course structured?

Lectures

- Tue, 2 pm + Friday, 2 pm
- Weeks 2–6: Miriam O'Duill
Weeks 7–11: Rob Stockman
- Attendance recorded via SEAtS app (QR code)
- Lecture recordings and slides provided on Moodle
- Don't fall behind!

Tutorials

- Tutorials are important exam prep.
- The question sheets have been designed for you to practice (and get personalised feedback on) exam-style questions.
- Using ChatGPT / AI to complete them wastes this opportunity.

Please scan the QR code in your SEAtS app to record your attendance.



Expectations

What I expect of you

- **You can't get good at a sport by watching it on TV! The same thing applies to chemistry.**
- Attend lectures and tutorials.
- **Self-study:**
A 10-credit course requires on average **100 hours of study.**
 - go over lecture notes;
 - attempt practice questions;
 - recommended reading:

Clayden, Organic Chemistry: free ebook

Oxford Primers:

Organometallics and Catalysis,

Organometallic Reagents in Synthesis

What you can expect of me

- Lecture material provided on Moodle in a timely fashion.
- Short practice questions + model answers throughout to consolidate material and prepare you for exams.
- University can be hard, so don't be afraid to ask for support!



Course Overview

Part 1: Stoichiometric Organometallic Chemistry (Clayden, Chapter 9)

1. Introduction to organometallic reagents: structure, stability, synthesis and reactivity
2. Synthesis of organometallic reagents by Li–Hal exchange and transmetallation
3. Synthesis of organometallic reagents by deprotonation
4. Organocuprate chemistry

Part 2: Transition Metal Catalysis (Clayden, Chapter 40)

Important:

- We will be building on foundations laid in 1st and 2nd year – you need to be familiar with your fundamental organic chemistry!



Learning outcomes

In this lecture course, you will learn to:

- Identify organometallic reagents, describe their structure, synthesis and reactivity.
- Identify the features that affect the stability of organometallic reagents.
- Explain the difference in reactivity of hard and soft organometallic reagents.
- Describe the effect of oxidation state, valence electron count and ligands on stability and reactivity of palladium catalysts.
- Draw catalytic cycles and describe the fundamental reaction steps for Suzuki, Heck, and Buchwald-Hartwig cross-coupling reactions.



Lecture 1: Introduction to organometallic reagents

Structure, synthesis, stability and reactivity of organometallic reagents (R–M)

Learning outcomes

In this lecture, you will learn to:

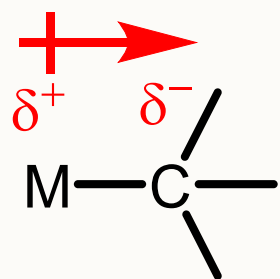
- Identify organometallic reagents;
- Describe their structure and reactivity with electrophiles and proton sources;
- Synthesise organometallic reagents by oxidative addition;
- Identify the features that affect the stability of organometallic reagents.

Recommended Reading: Clayden, Organic Chemistry, Chapter 9



Structure of organometallic reagents

- Organometallic compounds contain a carbon–metal bond.
- Carbon is more electronegative than the metal, so the bond is **polarised towards carbon**, making the carbon **nucleophilic**.
- The more electropositive the metal, the more ionic the bond:

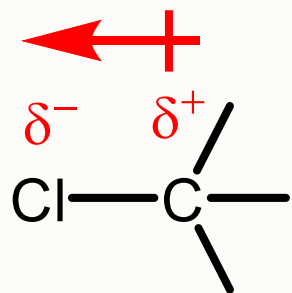


MeK

almost completely ionic
only stable in solution, will catch fire in air
not stable to water

MeMgBr

Fairly covalent
highly reactive, stable in solution
not stable to water



Me₄Sn

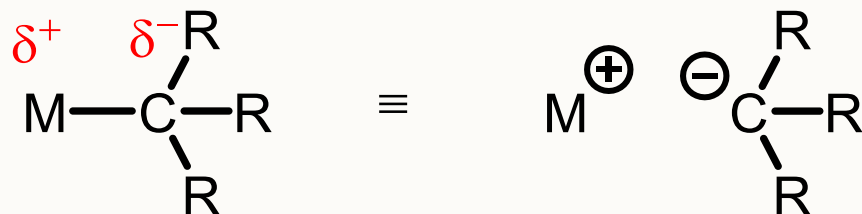
completely covalent
very stable, can be purified and isolate
doesn't react with water

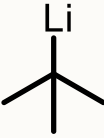
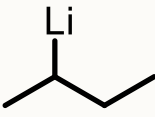
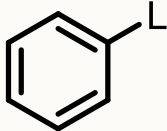
You have seen this in second year: Grignard reagents (more on these later!)



Stability of organometallic compounds

- Organometallics are highly reactive, but some are more stable (i.e. slightly less reactive) than others.
- When thinking about the stability of an organometallic compound, we need to think about the stability of the negative charge on carbon.
- pK_{aH} (basicity) can be used as a guide to reactivity/stability: The lower the pK_{aH} , the more stable the organometallic.

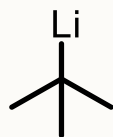


	pK_{aH}	increasing reactivity
	tBuLi 50	 
	sBuLi 45	
	nBuLi 40	
	PhLi 37	
	25	
		increasing stability



Question

Which of these organometallic compounds is more stable? Why?





Factors affecting the stability of organometallics

- The metal (see previous slide): More electropositive metal: more ionic C–M bond: less stable organometallic
- The nature of the carbon:



Increasing stability

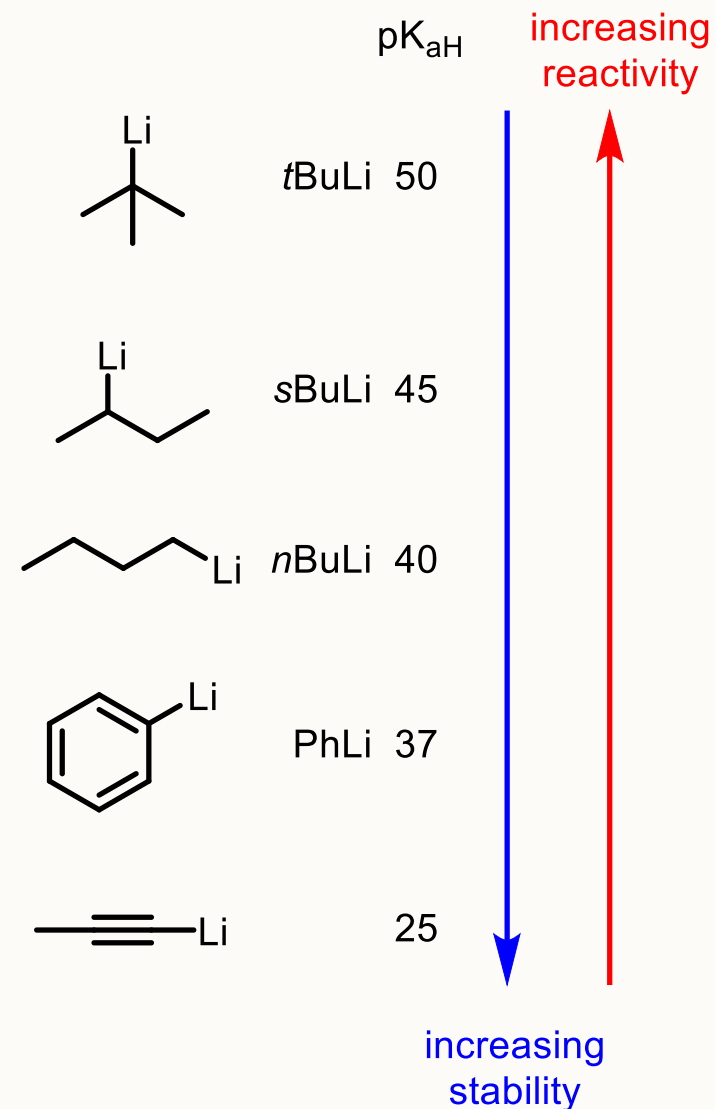
(The negative charge on C is more stabilised in orbitals with higher s character: closer to nucleus)

- For sp^3 carbons:



Increasing stability

(Inductively electron-donating alkyl groups destabilise the negative charge on C)





Reactivity of organometallic reagents

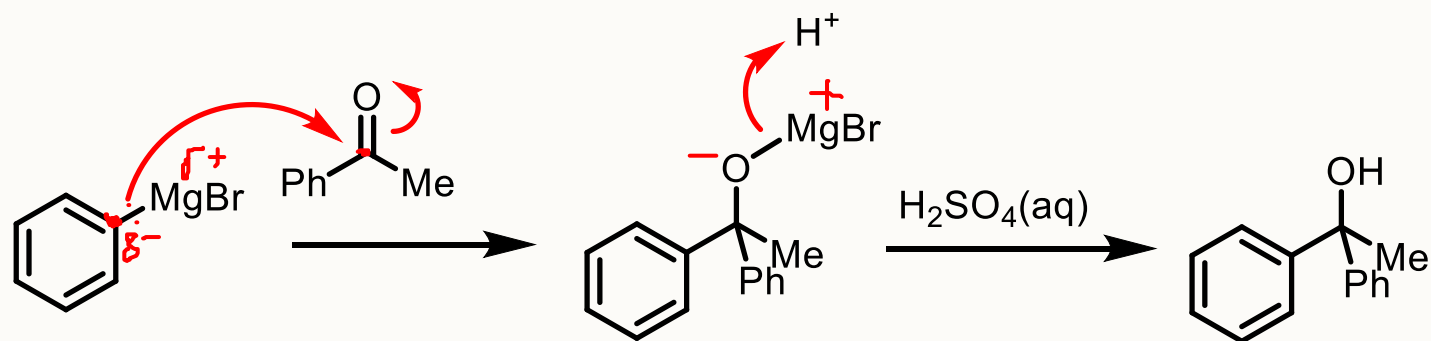
- Organometallics are highly reactive (very unstable).
- Practical considerations: Organometallics
 - are nucleophilic and basic: need to use aprotic solvents (e.g. THF, Et₂O, Hex)
 - react with O₂: need to use an inert dry atmosphere such as N₂ or Ar.
 - react rapidly and violently with H₂O: need to be kept absolutely free of moisture.





Reactivity of organometallic reagents

- When we take the necessary precautions, organometallics are very useful reagents: they are **nucleophilic** on carbon and react with a variety of electrophiles.
- Revision: reactivity of Grignard reagents:

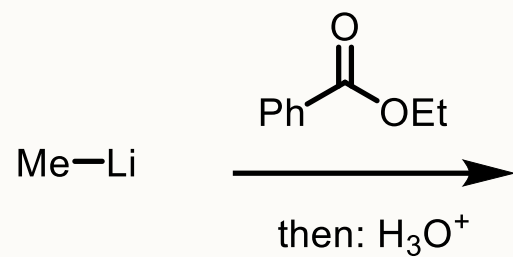


Organometallic compounds
are **nucleophiles**.



Question

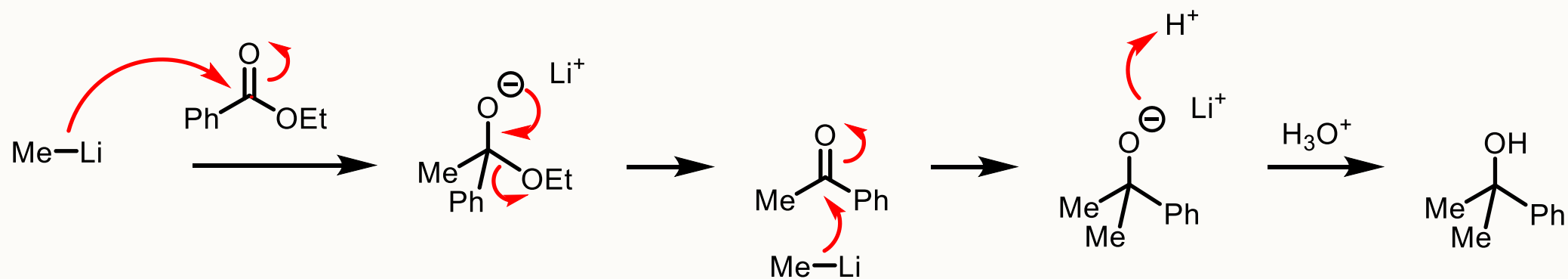
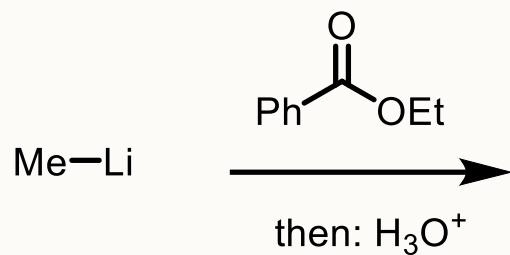
Draw the product of this organometallic reaction:





Question

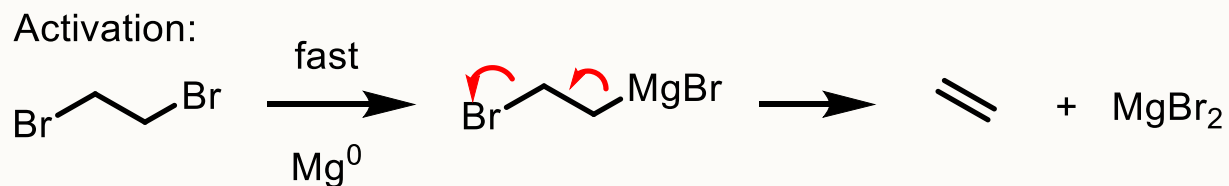
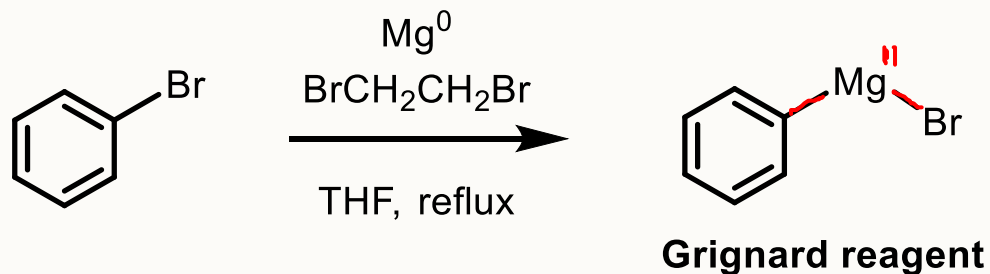
Draw the product of this organometallic reaction:





Synthesis of organometallics: Grignard reagents

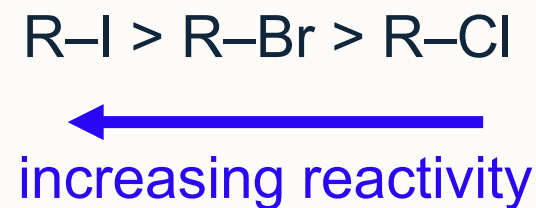
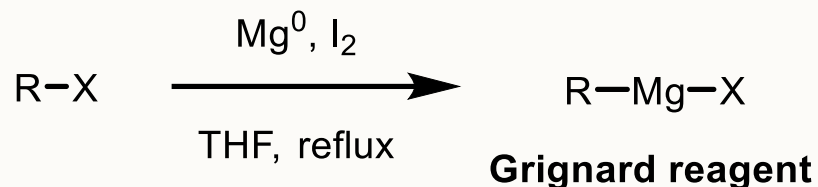
- Grignard reagents are made by oxidative addition of Mg^0 into a C–halogen bond.
- These reactions are fairly slow and often require heating.
- If the surface of the Mg^0 turnings is partially oxidized, the Grignard reaction can be slow to initiate. To help activate the reaction, we can add I_2 or 1,2-dibromoethane:



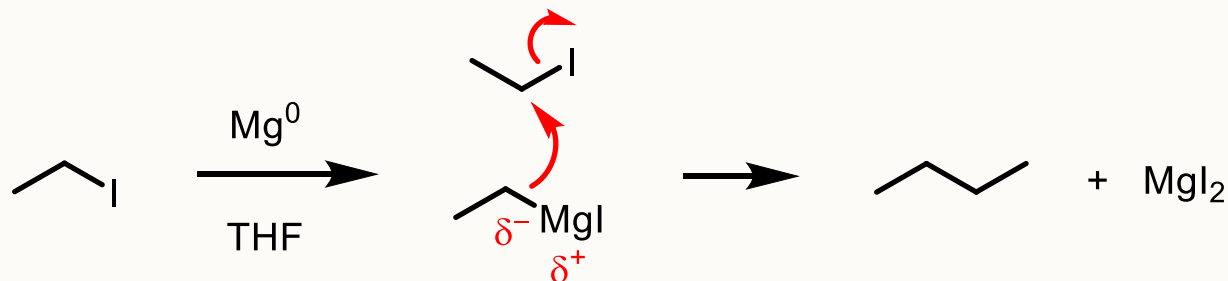


Synthesis of organometallics: Grignard reagents

- Order of reactivity towards oxidative addition:



- But: chlorides (R-Cl) are often cheap, and the by-product (MgCl_2) is insoluble and therefore easy to remove.
- Alkyl iodides sometimes undergo an unwanted side-reaction (Wurtz coupling):

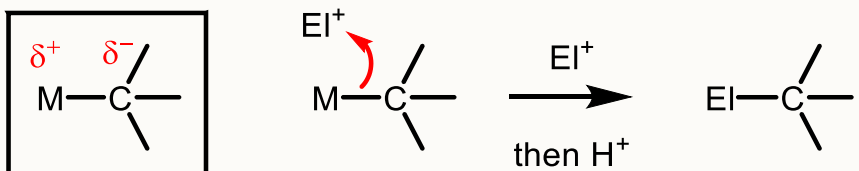




Summary

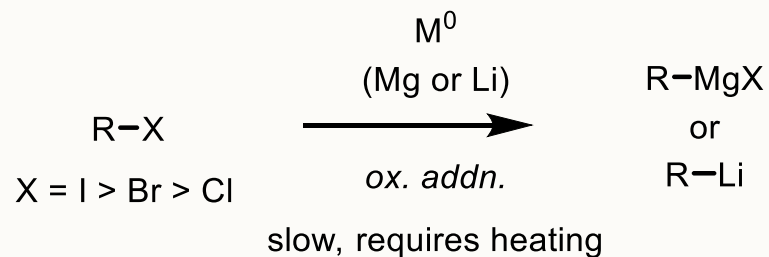
In this lecture, you learnt

- what organometallic reagents are and how they react;



- **nucleophilic** on carbon: react with electrophiles
- strong bases: easily destroyed by very weak acids

- how to make them by oxidative addition;



- the factors that affect their stability.

The negative charge on carbon is stabilised by:

- $sp > sp^2 > sp^3$
- sp^3 : $1^\circ > 2^\circ > 3^\circ$
- conjugation, coordinating heteroatoms, α -heteroatoms

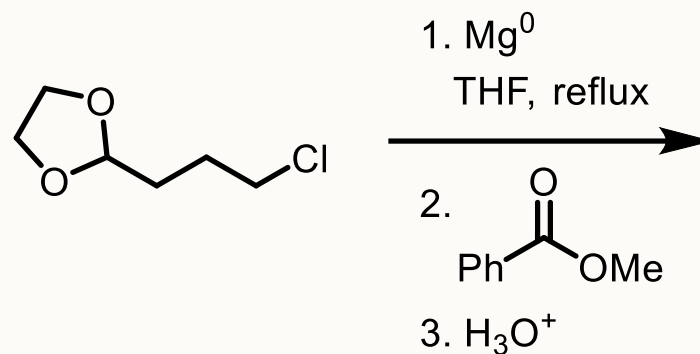


Practice questions

1. Which of the following solvents are suitable for organometallic reactions, and which are not?

ethyl acetate, acetonitrile, THF, hexane, methanol, Et_2O

2. Draw a curly arrow reaction mechanism and product for the following reaction:





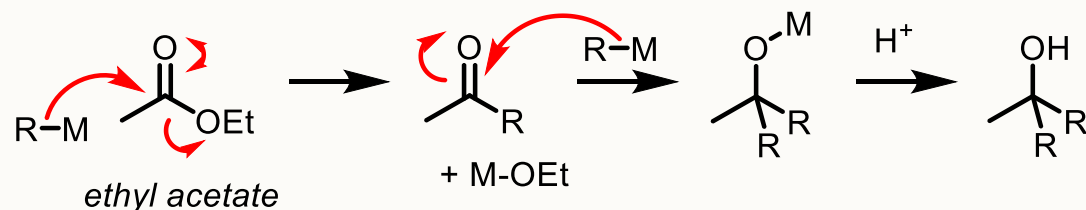
Lecture 1 practice questions – answers

1. Which of the following solvents are suitable for organometallic reactions, and which are not? Why? acetonitrile, THF, hexane, methanol, Et₂O

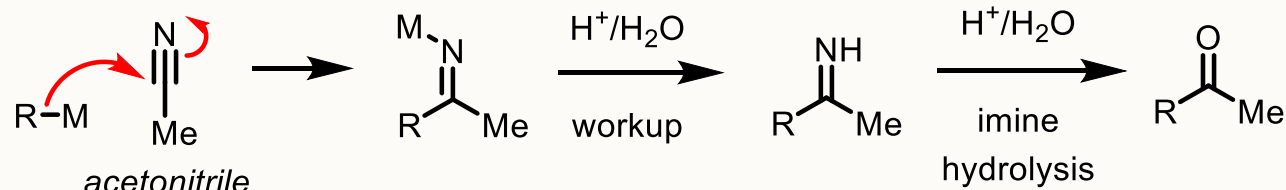
Suitable: THF, hexane and Et₂O: aprotic solvents, compatible with organometallics.

Not suitable:

- ethyl acetate: organometallic reagents react with esters:



- acetonitrile: organometallic reagents react with nitriles:



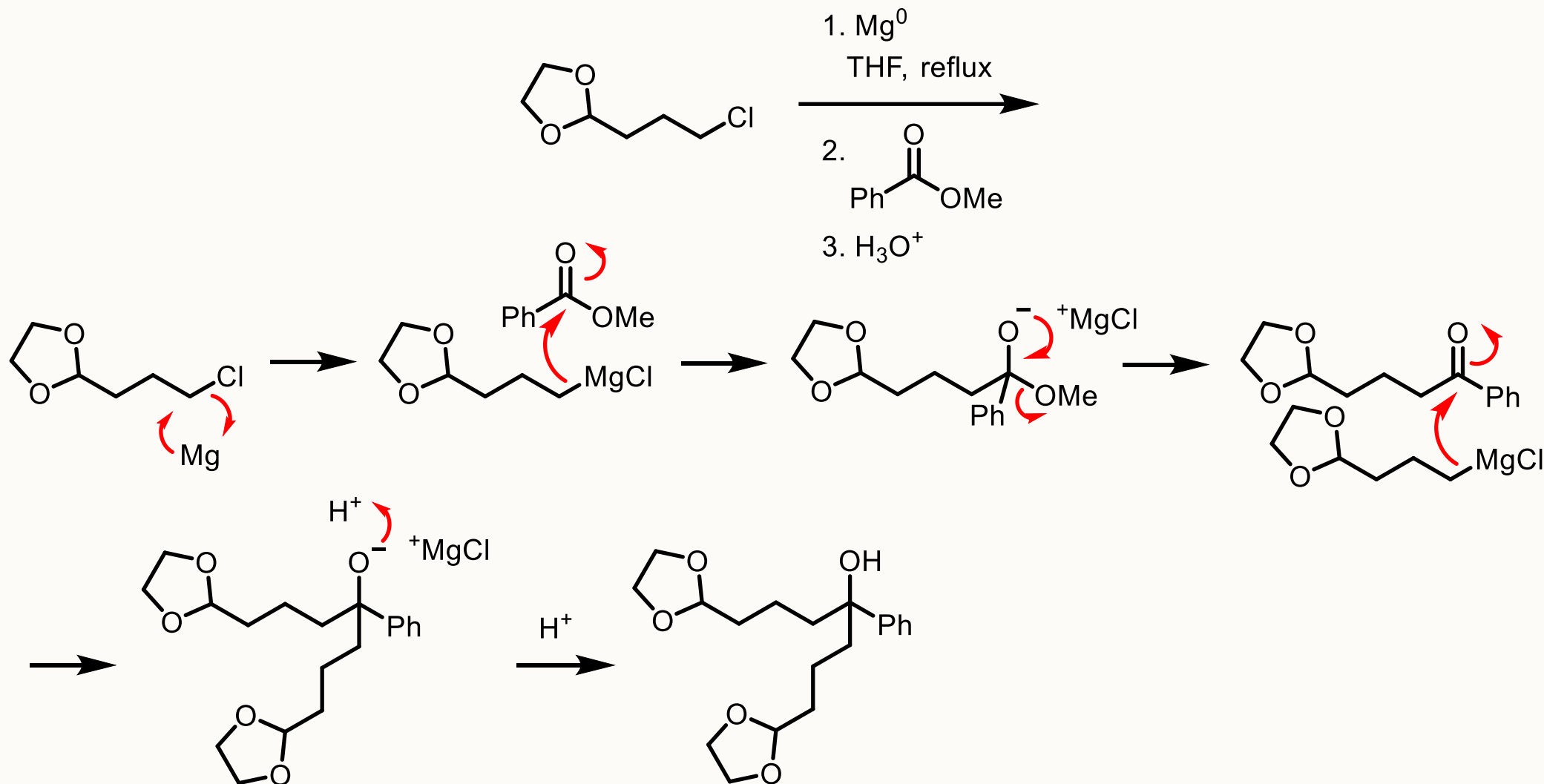
- methanol is a protic solvent and rapidly decomposes (protonates) organometallics:





Lecture 1 practice questions – answers

2. Draw a curly arrow reaction mechanism and product for the following reaction:





University of
Nottingham

UK | CHINA | MALAYSIA

CHEM3065 Synthesis and Reactive Intermediates

O'Duill lecture 2

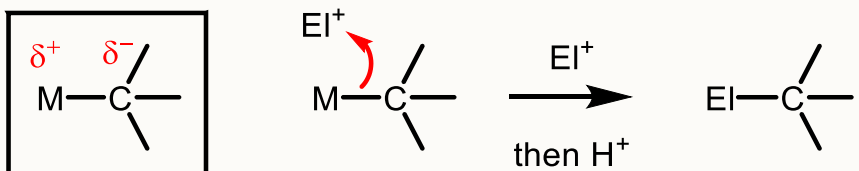
miriam.oduill@nottingham.ac.uk



Recap lecture 1

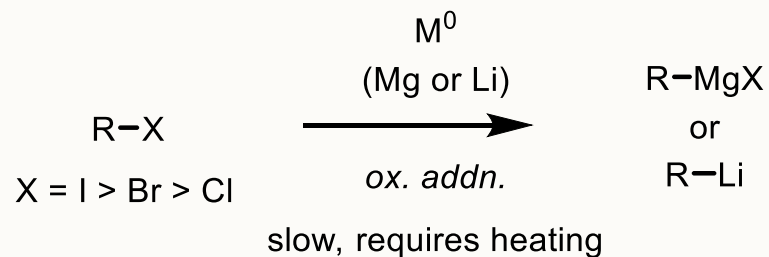
In the last lecture, you learnt :

- what organometallic reagents are and how they react;



- **nucleophilic** on carbon: react with electrophiles
- strong bases: easily destroyed by very weak acids

- how to make them by oxidative addition;



- the factors that affect their stability.

The negative charge on carbon is stabilised by:

- $sp > sp^2 > sp^3$
- sp^3 : $1^\circ > 2^\circ > 3^\circ$
- conjugation, coordinating heteroatoms, α -heteroatoms



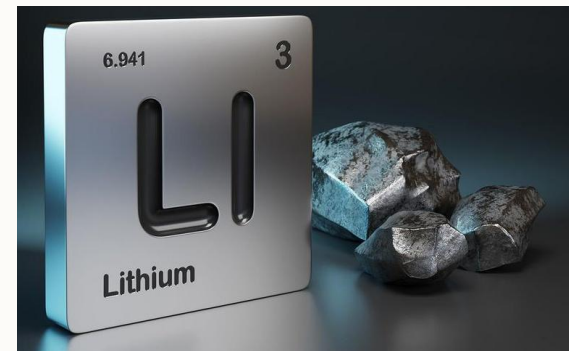
Lecture 2: Synthesis of organolithium reagents

Halogen–Lithium exchange, *ortho*-lithiation

Learning outcomes

In this lecture, you will learn:

- how to synthesise organolithium reagents by halogen-lithium exchange
- how to synthesise organolithium reagents by transmetallation
- how to synthesise organolithium reagents by deprotonation of acidic C–H bonds (*ortho*-lithiation).



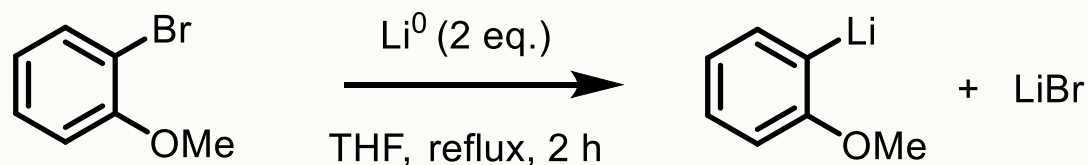
Recommended Reading: Clayden, Organic Chemistry, Chapter 9



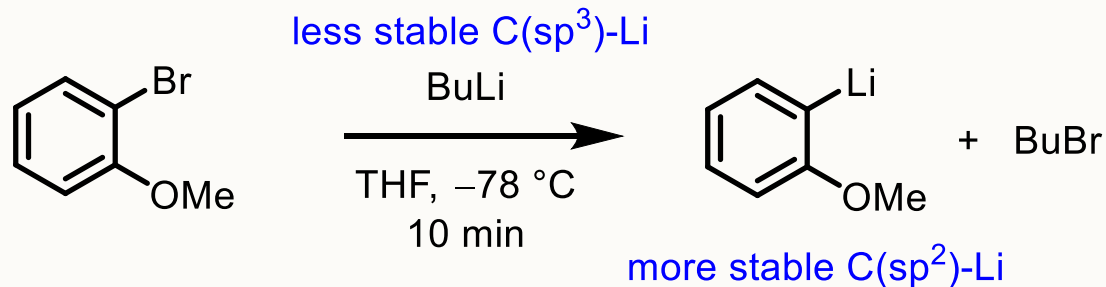
Synthesis of Organometallics: Halogen-Lithium exchange

- Organolithium compounds can be made by oxidative insertion of Li^0 into a C–halogen bond. These reactions are slow and require heating.
- They can also be made by halogen-lithium exchange, where a C–Hal bond exchanges with a C–Li (if it generates a more stable C–Li species). These reactions are fast and occur at low temperatures:

Oxidative insertion



Halogen-lithium exchange



Driving force: formation of a more stable C–Li from a less stable C–Li compound.

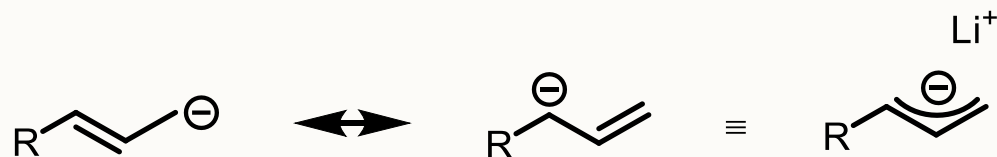


Factors affecting Hal–Li exchange

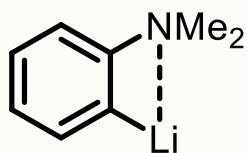
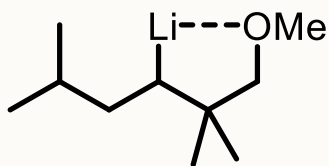
To understand if a Hal–Li exchange is possible, we need to know the stability of the product C–Li :

- $sp > sp^2 > sp^3$
- $sp^3 : 1^\circ > 2^\circ > 3^\circ$

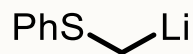
- Conjugation increases stability:



- Internal heteroatom co-ordination increases stability:



- α -heteroatom stabilization:

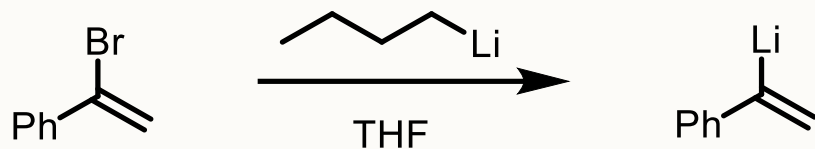




Question

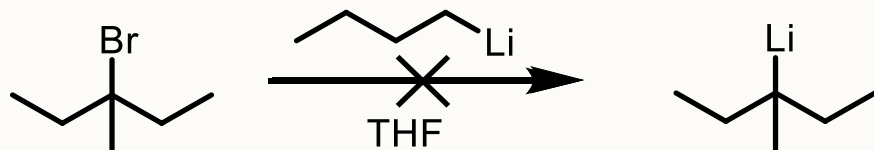
Predict whether the following transformations will proceed:

1)



To answer this question, compare the relative stability of the organolithium reagents (carbanions).

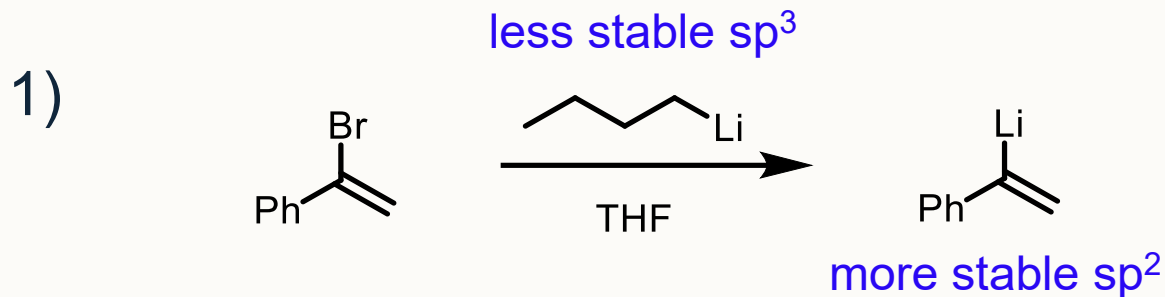
2)





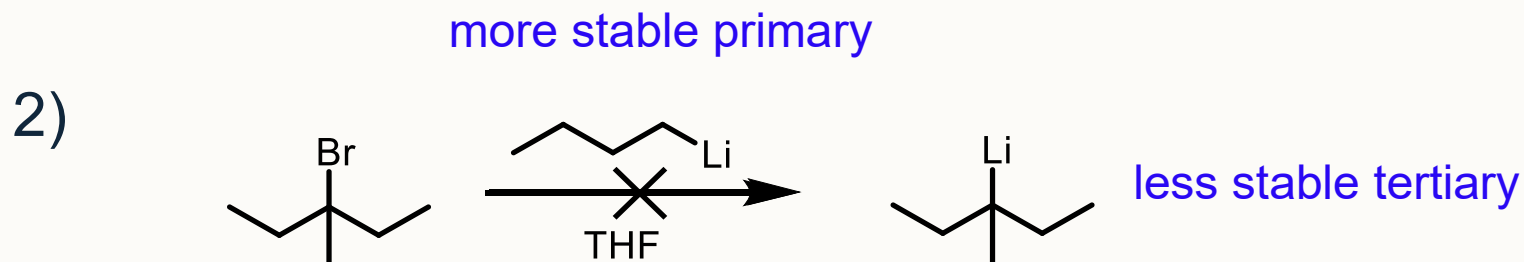
Question

Predict whether the following transformations will proceed:



To answer this question, compare the relative stability of the organolithium reagents (carbanions).

This reaction proceeds, because vinyl (sp^2) carbanions are more stable than saturated (sp^3) carbanions: the increased s-character stabilises the carbanion / C–Li bond.

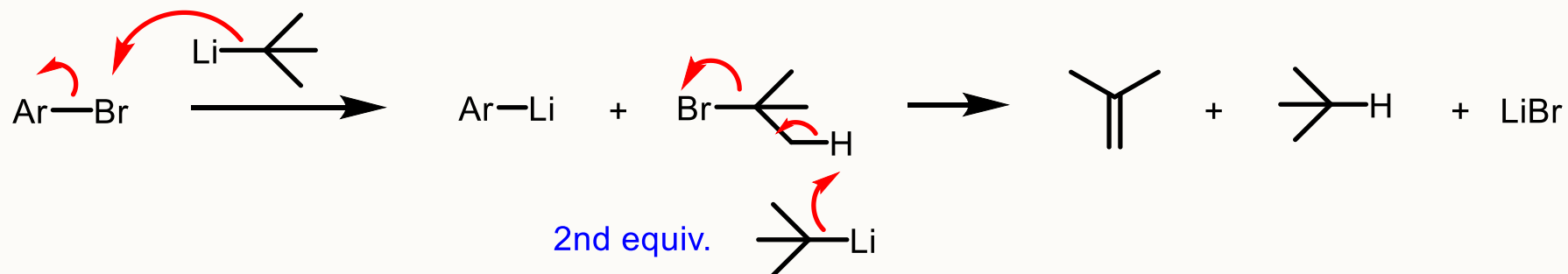


This reaction does not proceed, because tertiary carbanions are less stable than primary carbanions: electron-donating alkyl groups destabilise the carbanion / C–Li bond.



How much BuLi is necessary?

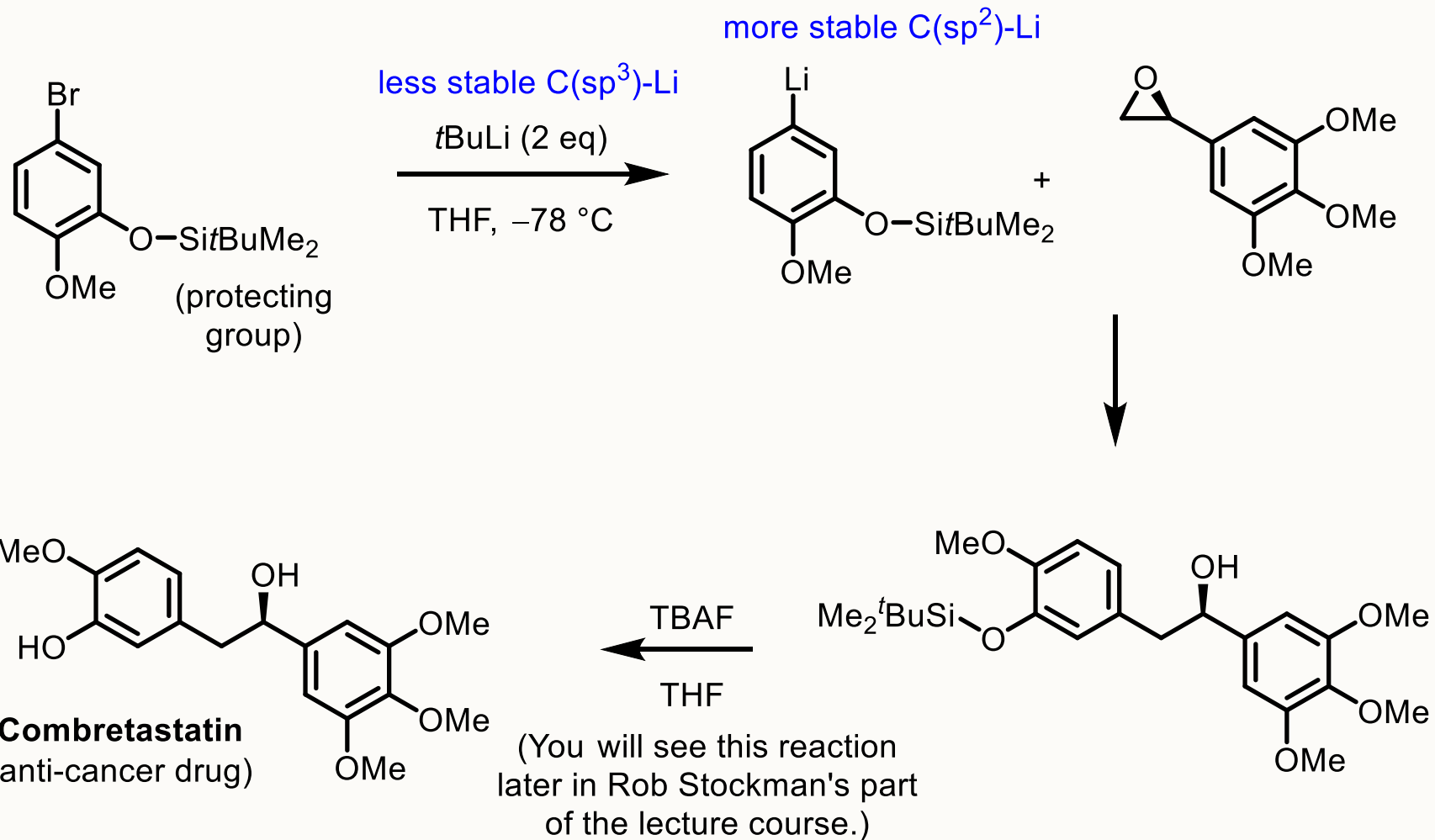
With *t*BuLi, we can get a secondary process happening, and thus we use 2 equivalents to overcome this.



ArLi is basic: it can react with *t*BuBr.
We use a second equivalent of *t*BuLi (more reactive than ArLi) to eliminate HBr and prevent the decomposition of ArLi.



An example from the pharmaceutical world



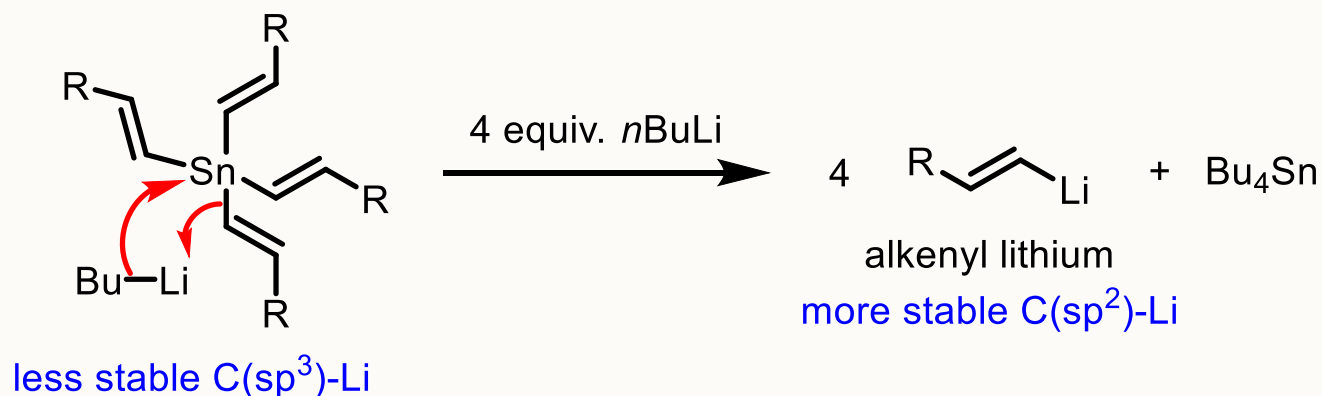


Transmetalation: Tin–Lithium exchange

- Instead of halogen–lithium exchange (i.e. exchanging C–Hal and C–Li bonds), organometallics can also be made by **transmetalation** (i.e. exchanging C–MgX or C–Li with a less electropositive metal, e.g. C–Cu, C–Sn, etc. bonds).
- This gives us less reactive organometallics that are easier to control.

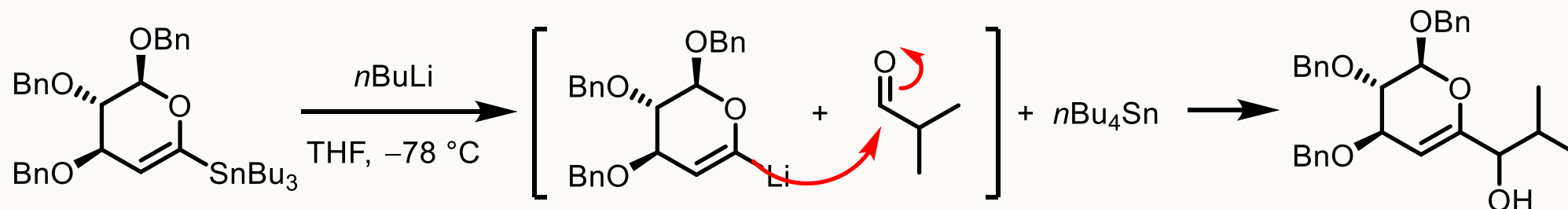
Tin-Lithium Exchange

- Like for Hal–Li exchange, the driving force for this reaction is the formation of a more stable C–Li from a less stable / more reactive C–Li:





Advantages and disadvantages of tin compounds



Advantages of tin compounds

- Available via several routes (e.g. hydrostannylation)
- Sn compounds are stable: can be easily purified, stored, etc.
- Sn to Li exchange is rapid and high yielding

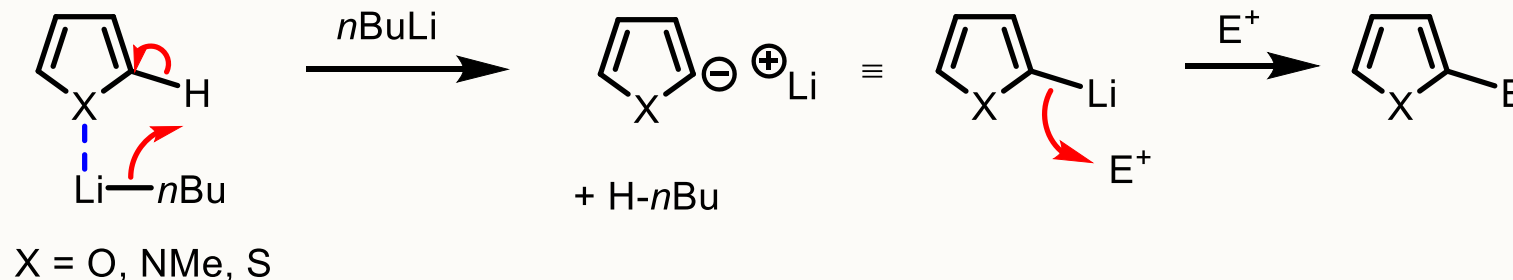
Disadvantages of tin compounds

- Tin compounds are very toxic
- By-products can be difficult to remove
- Indirect route compared to other methods (often made from R-Br to R-Li to R-Sn)
- In lecture 4, we will see a less toxic alternative (copper)



Ortho-lithiation (deprotonation) of aryl rings

- We can also make organolithium reagents by deprotonation of C–H bonds: strong bases (e.g. *n*BuLi or LDA) can deprotonate aromatic compounds.
- In 5-membered heteroaromatics, lithiation occurs next to the heteroatom:

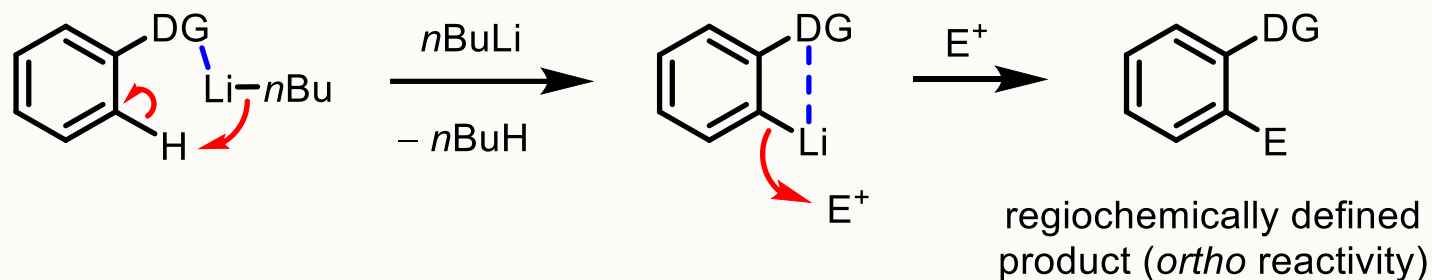


You have already seen this in second year (CHEM2010)



Ortho-lithiation (deprotonation) of aryl rings

- Even benzene derivatives can be lithiated *ortho* to certain substituents (DG = directing groups) that can help coordinate the lithium:

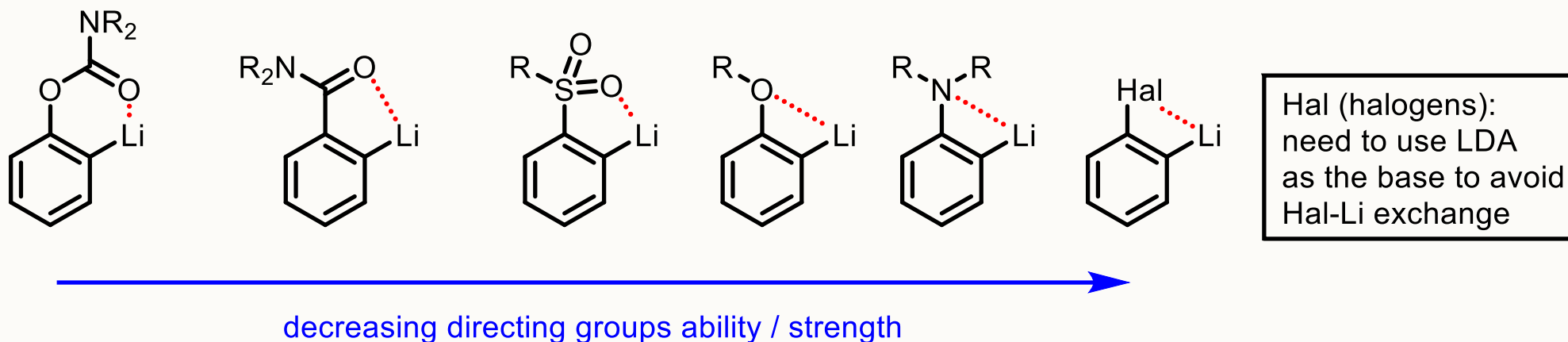


You have already seen this in second year (CHEM2010)



Ortho-lithiation (deprotonation) of aryl rings

- Directing groups for *ortho*-lithiation have heteroatoms that can coordinate to lithium:

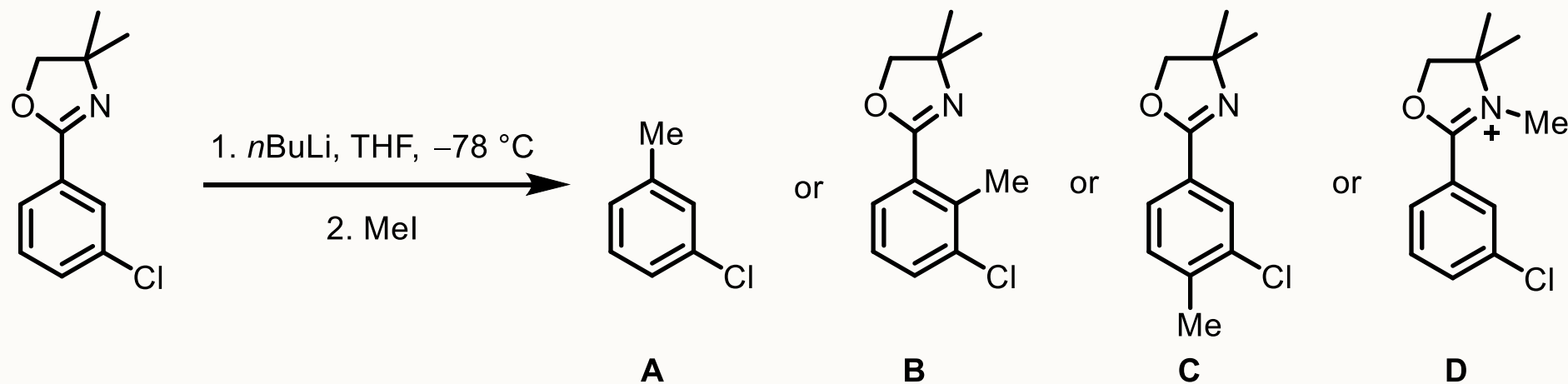


- Factors that govern directing group strength: electronics, geometry
- We cannot use functional groups that would react with BuLi (esters, ketones, etc.)



Question

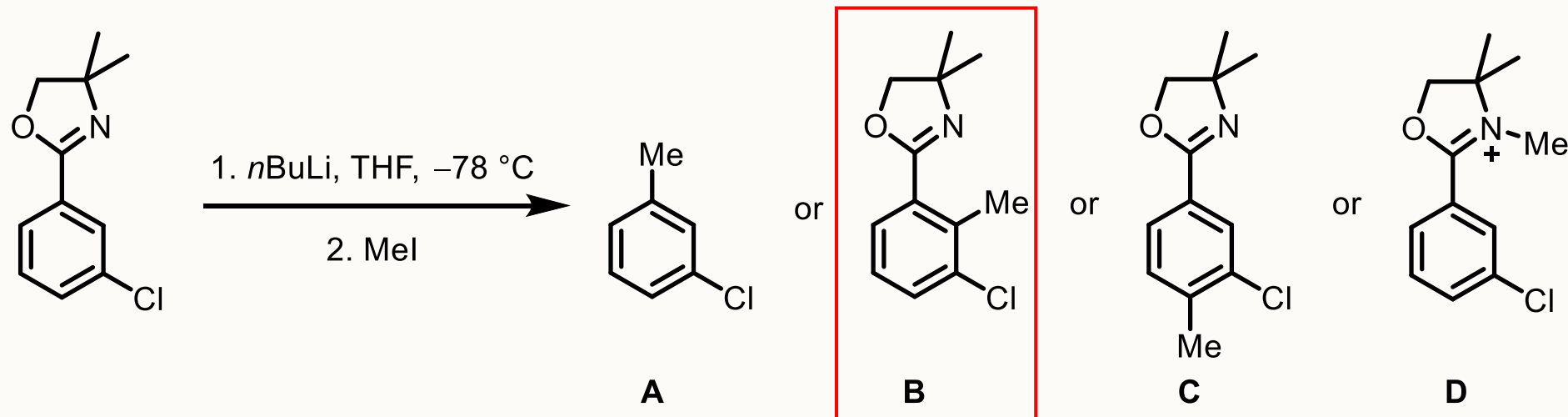
Which product is formed in the following reaction?





Question

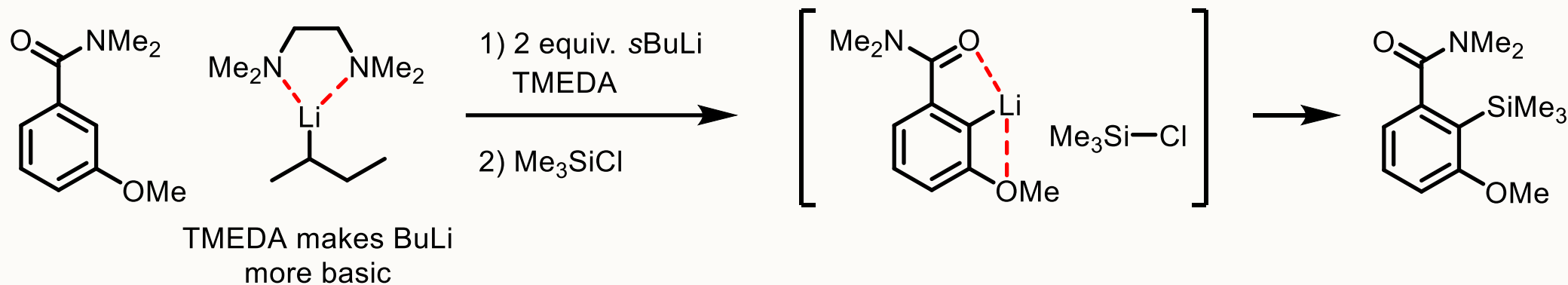
Which product is formed in the following reaction?



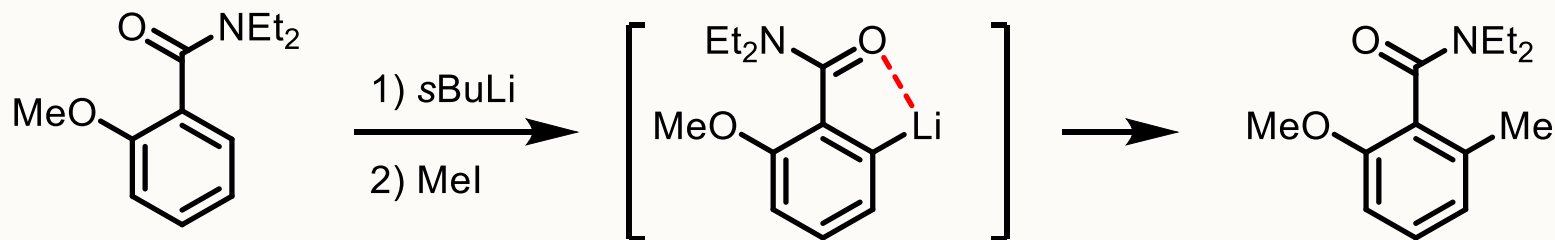


Two directing groups in *ortho*-lithiation

- Reinforcing: both groups direct to the same position



- Competing: the stronger directing group 'wins'

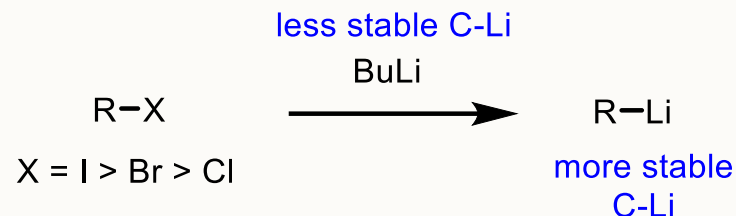




Summary

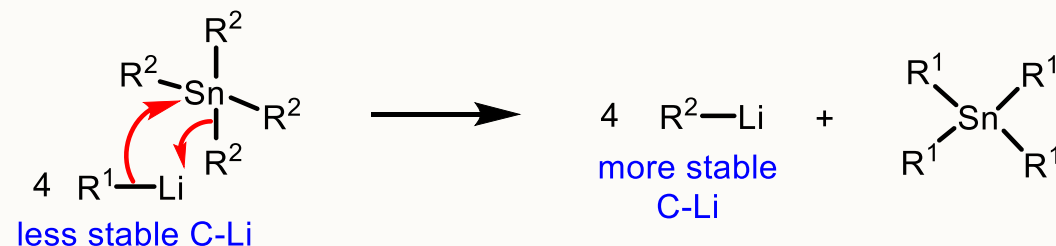
In this lecture, you learnt how to synthesise organolithium reagents:

- by Hal–Li exchange

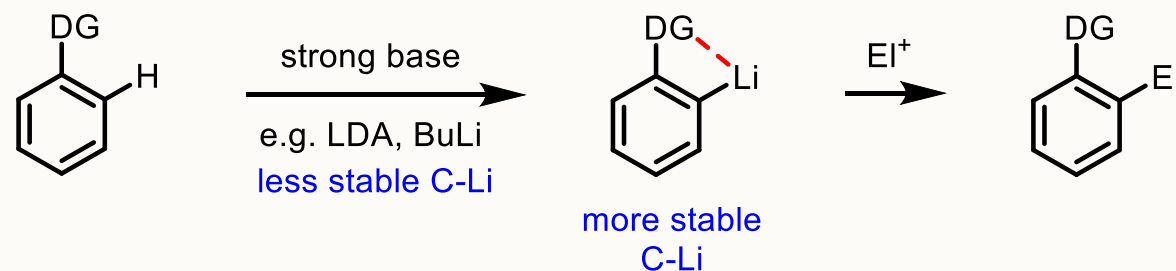


Driving force: formation of a more stable C–Li species from a less stable C–Li species.

- by transmetallation (metal–metal exchange);



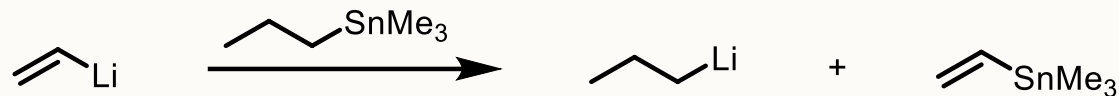
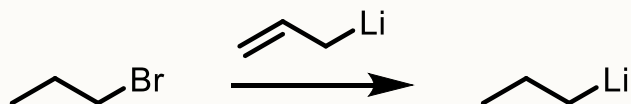
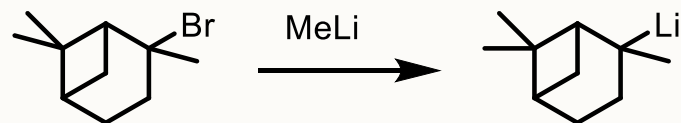
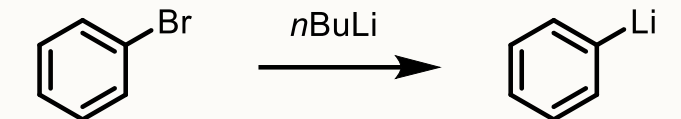
- by deprotonation of aromatic C–H bonds (*ortho*-lithiation).



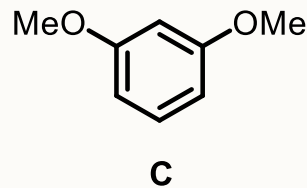
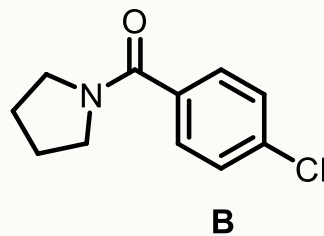
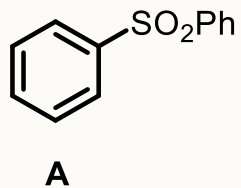


Lecture 2: Practice questions

1. Predict whether the following transformations will proceed:



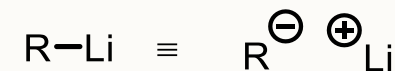
2. Predict the products of the reactions of **A**, **B** and **C** with BuLi and CO₂:





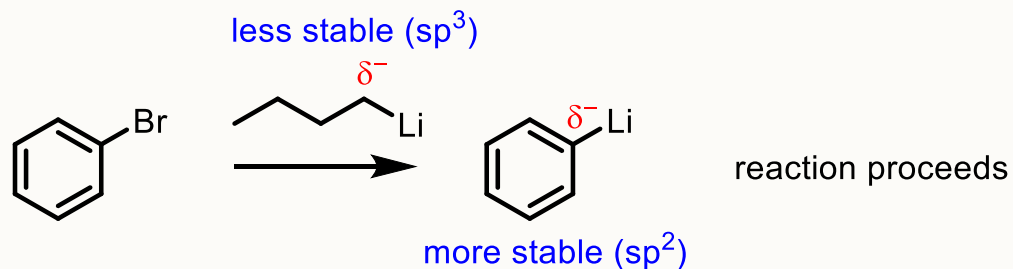
Lecture 2 practice questions – answers

1. Predict whether the following transformations will proceed:

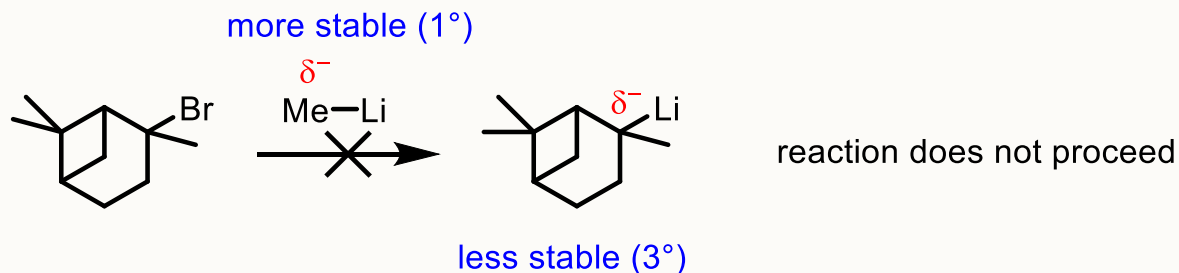


The first part of this question is about Li-Hal exchange.

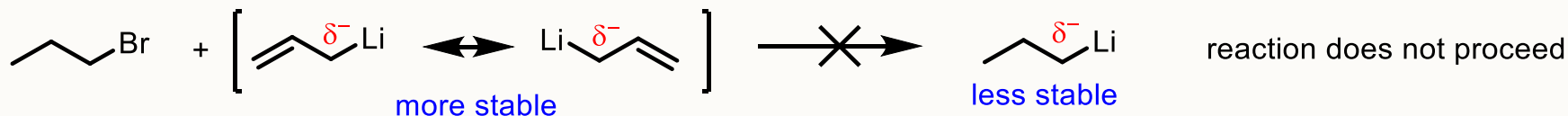
Driving force: formation of a more stable C-Li species from a less stable C-Li species:



sp^2 orbitals have more s-character, i.e. they experience the positive charge of the nucleus more, which stabilises the negative charge on the organolithium carbon.



Electron-donating alkyl groups destabilise the negative charge on the organolithium carbon.



Conjugation stabilised the negative charge on the organolithium carbon.

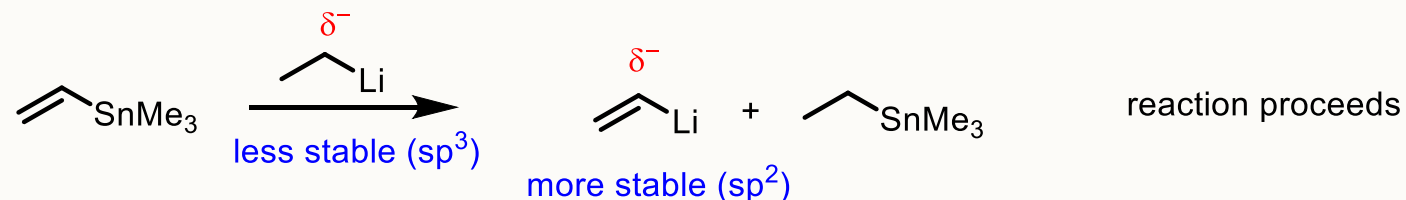
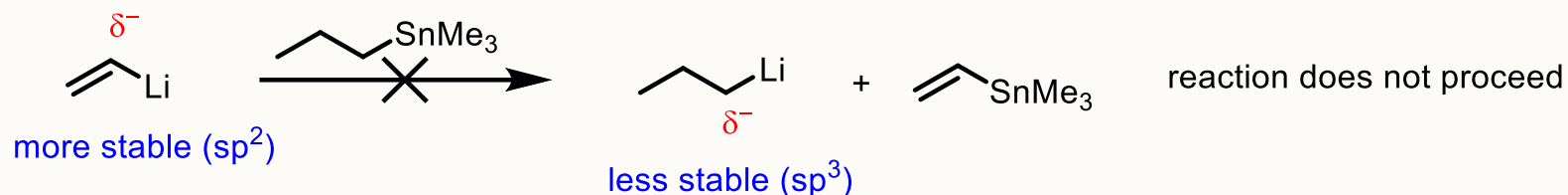


Lecture 2 practice questions – answers

1. Predict whether the following transformations will proceed:

The second part of this questions is about transmetalation.

Consider the stability of the organometallics containing the more electropositive metal (in this case: Li).



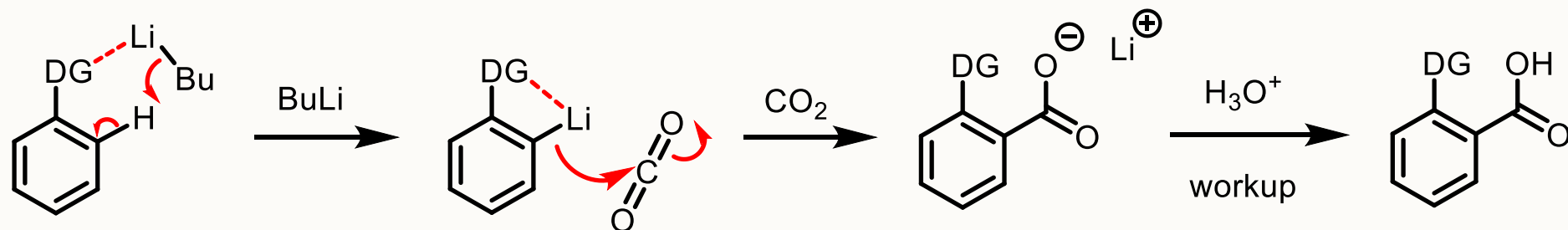
sp^2 orbitals have more s-character, i.e. they experience the positive charge of the nucleus more, which stabilises the negative charge on the organolithium carbon.



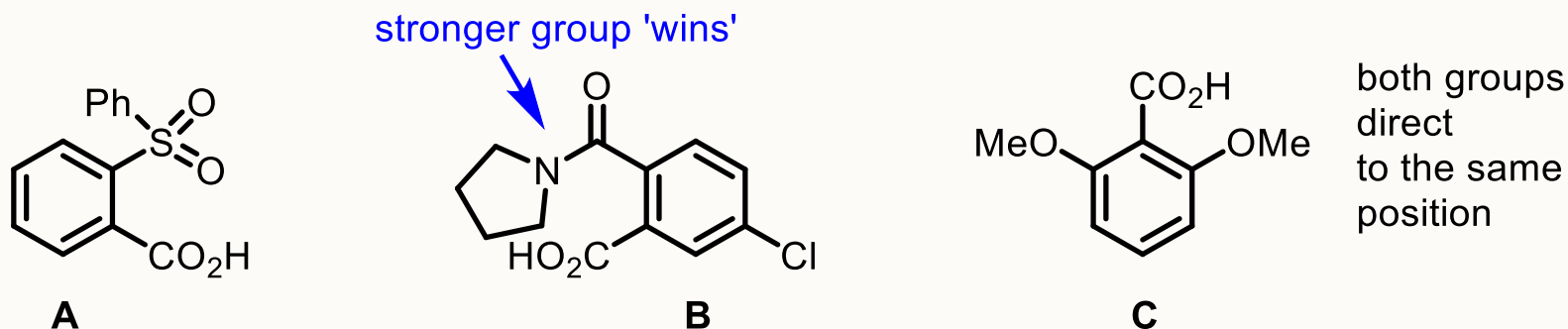
Lecture 2 practice questions – answers

2. Predict the products of the reactions of **A**, **B** and **C** with BuLi and CO₂:

This question is about *ortho*-lithiation:



To predict the products, consider the strength of the directing groups:





University of
Nottingham

UK | CHINA | MALAYSIA

CHEM3065 Synthesis and Reactive Intermediates

O'Duill lecture 3

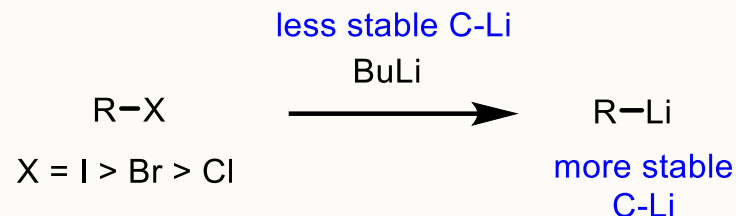
miriam.oduill@nottingham.ac.uk



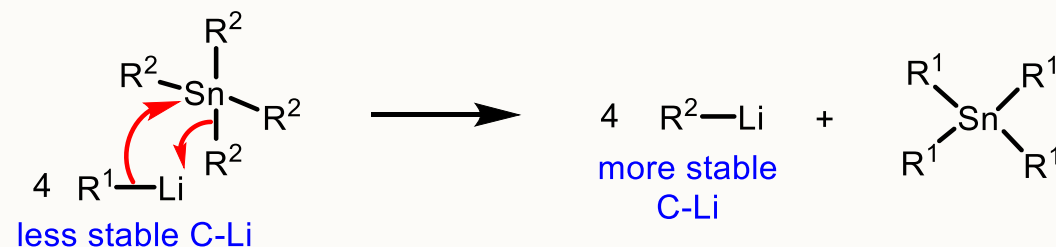
Recap Lecture 2

In lecture 2, you learnt how to synthesise organolithium reagents:

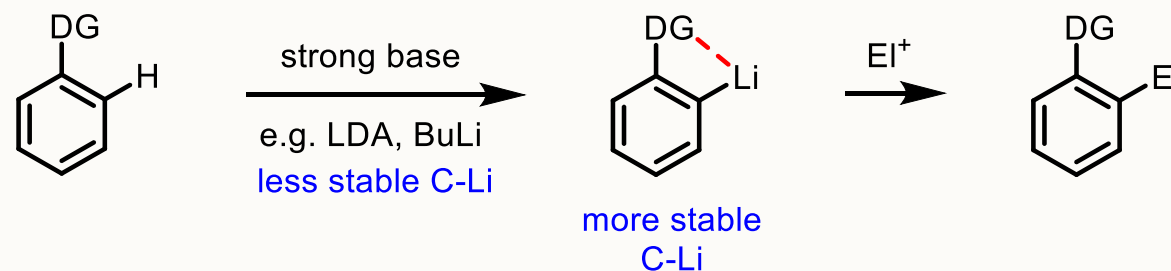
- by Hal–Li exchange



- by transmetallation (metal–metal exchange);



- by deprotonation of aromatic C–H bonds (*ortho*-lithiation).



Driving force: formation of a more stable C–Li species from a less stable C–Li species.



Lecture 3: Synthesis of organolithium reagents II

Organolithium synthesis by deprotonation (part 2)

Learning outcomes

In this lecture, you will learn:

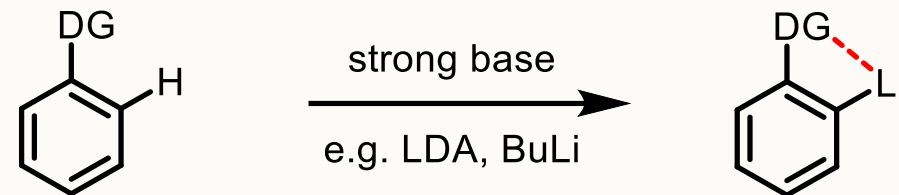
- how to make organolithiums by deprotonating acidic protons (*e.g. alpha* to heteroatoms, enolates),
- how to generate “superbases” for the deprotonation of weakly acidic protons.

Recommended Reading: Clayden, Organic Chemistry

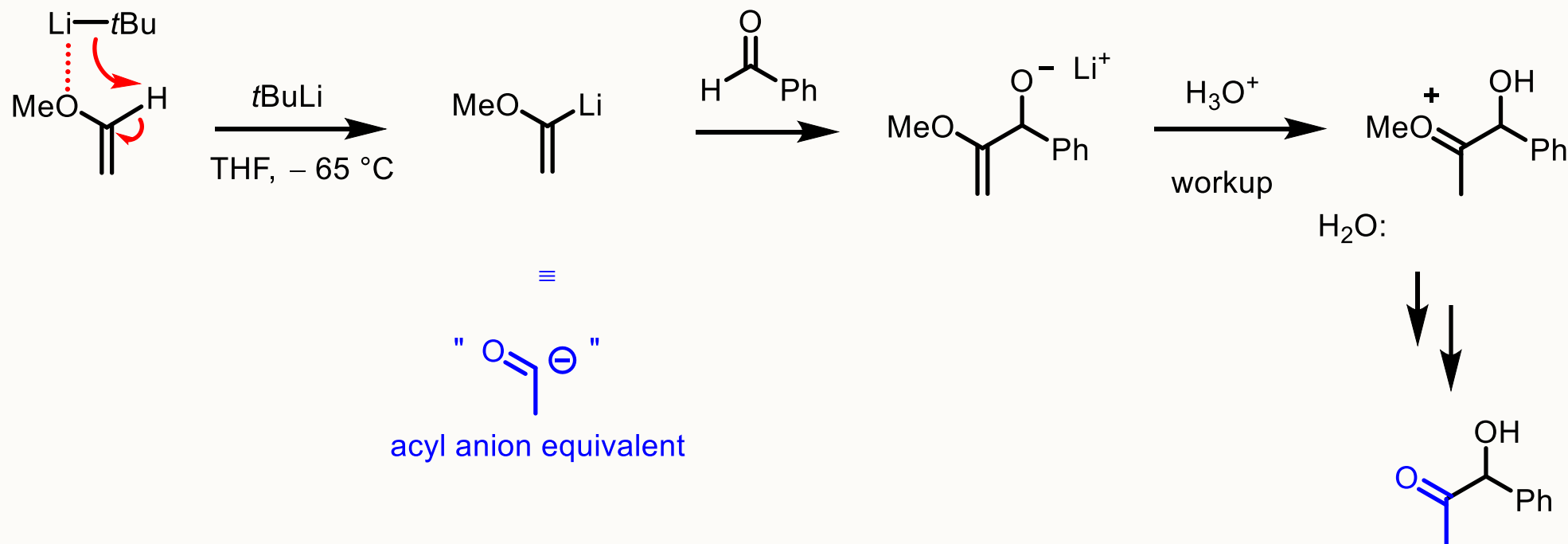


Lithiation α to Heteroatoms: Oxygen

- We have seen directed lithiation of aromatics:



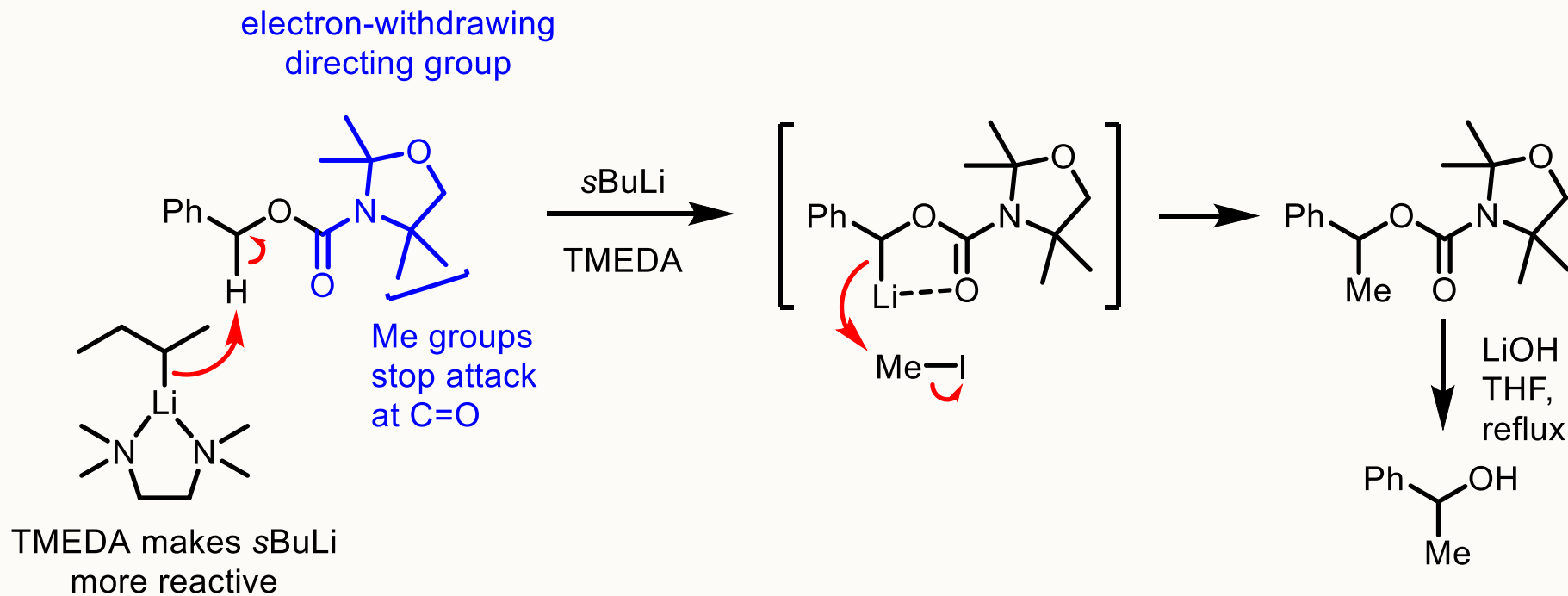
- Similar reactivity can be observed at other $C(sp^2)$ –H bonds, e.g. alkenes:





Lithiation α to Heteroatoms: Hoppe Lithiation

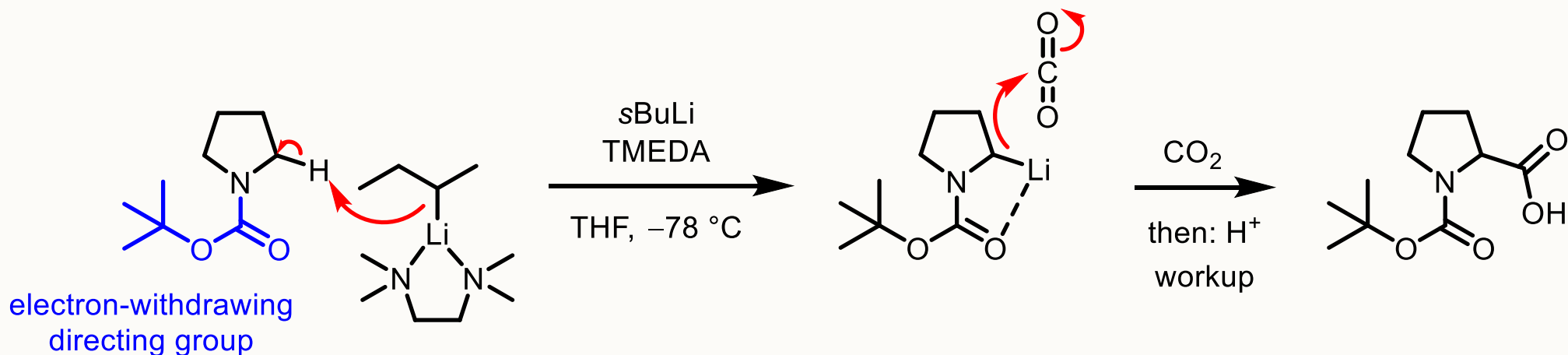
- sp^3 C–H bonds are less acidic than sp^2 C–H bonds.
- But we can even deprotonate an sp^3 C–H if it is next to a strong directing group:
- E.g.* deprotonation alpha to oxygen:





Lithiation α to Heteroatoms: Nitrogen

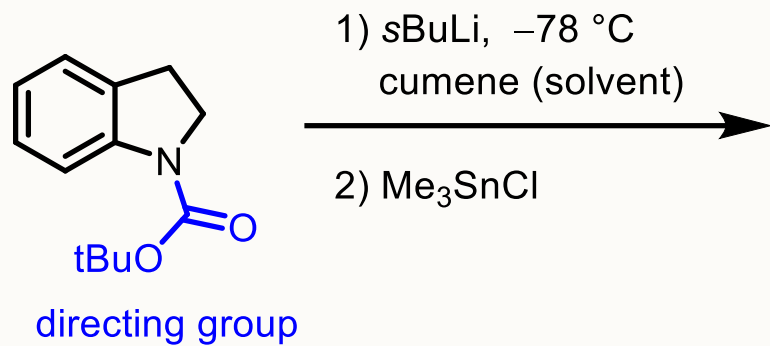
- We can also deprotonate sp^3 C–H *alpha* to nitrogen if there is an electron-withdrawing group on the nitrogen.
- The *N*-Boc protecting / directing group works well:





Question

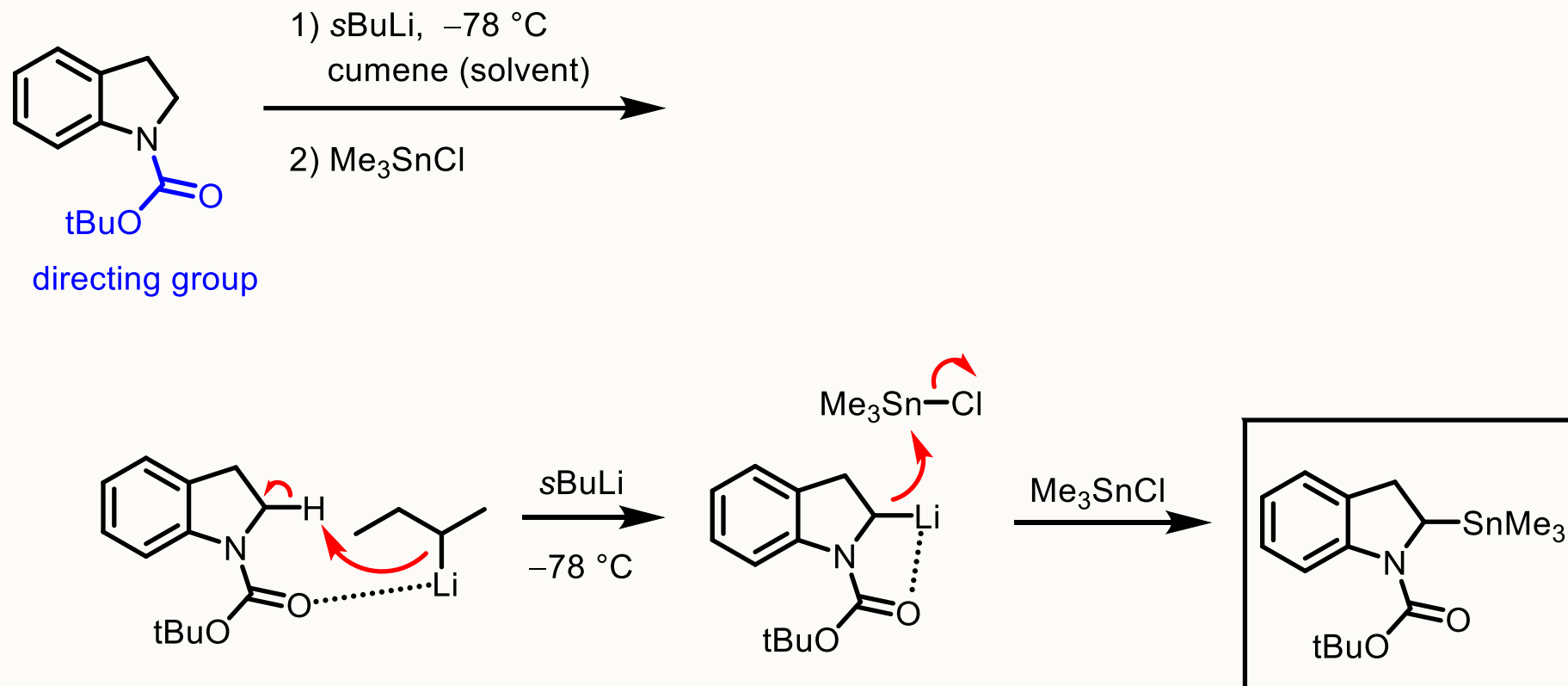
Draw the structure of the product formed in this directed lithiation:





Question

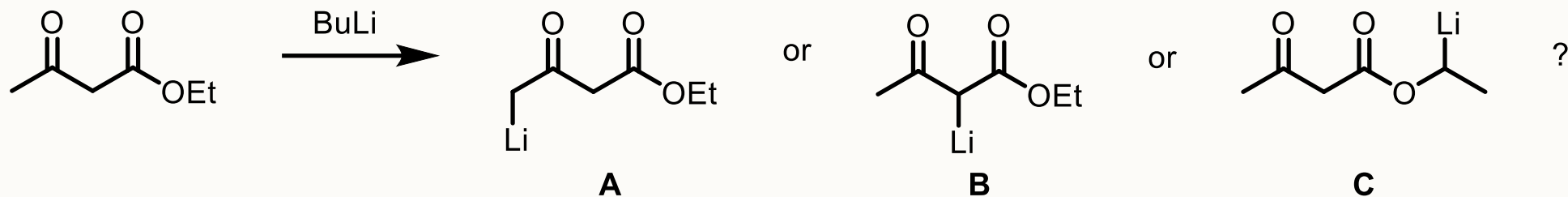
Draw the structure of the product formed in this directed lithiation:





Revision: Enolate formation

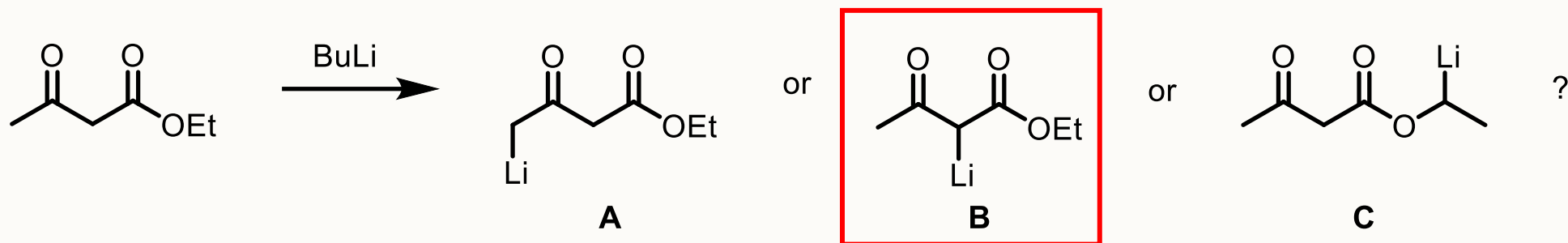
- Enolate formation with strong, unhindered bases (e.g. BuLi) occurs at the most acidic proton.
- Can you identify the most acidity proton in this molecules: Where would you expect deprotonation / organolithium formation to occur?





Revision: Enolate formation

- Enolate formation with strong, unhindered bases (e.g. BuLi) occurs at the most acidic proton.
- Can you identify the most acidity proton in this molecules: Where would you expect deprotonation / organolithium formation to occur?

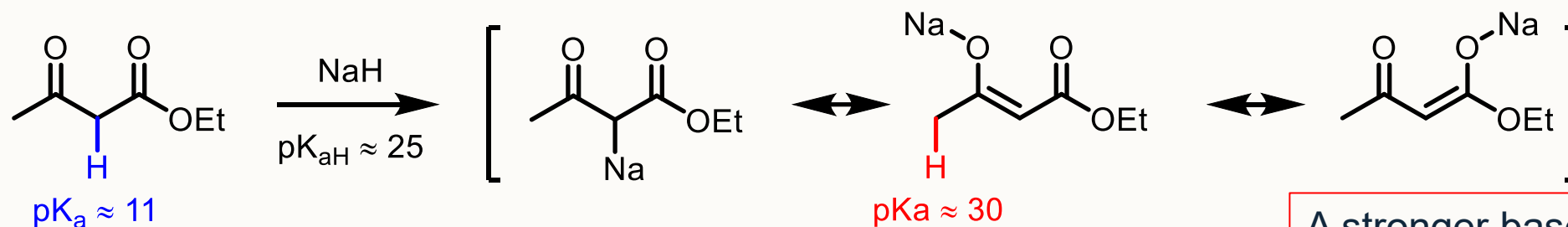


- Deprotonation occurs at the most acidic proton: the negative charge in **B** can be delocalised into two carbonyl groups.



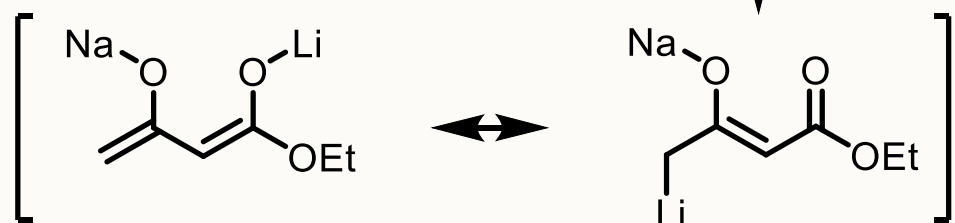
Dienolates

- If we want to functionalise the less acidic position, we can form a dienolate using two different strong bases:

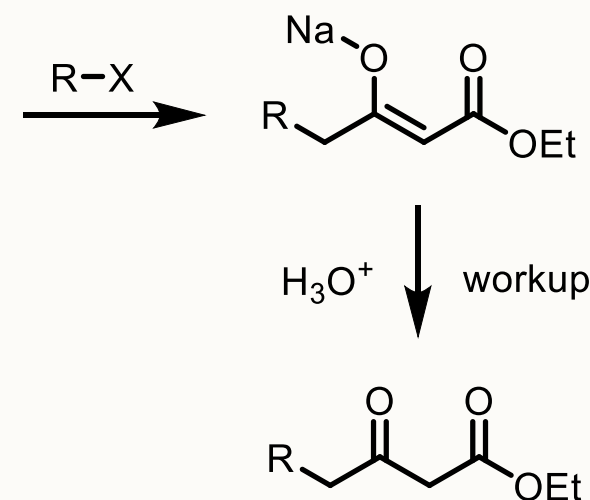
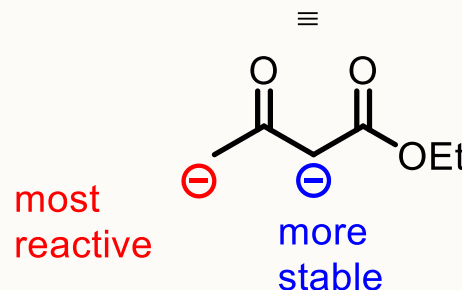


1st deprotonation occurs at the most acidic proton

A stronger base is required to deprotonate the less reactive/acidic proton.



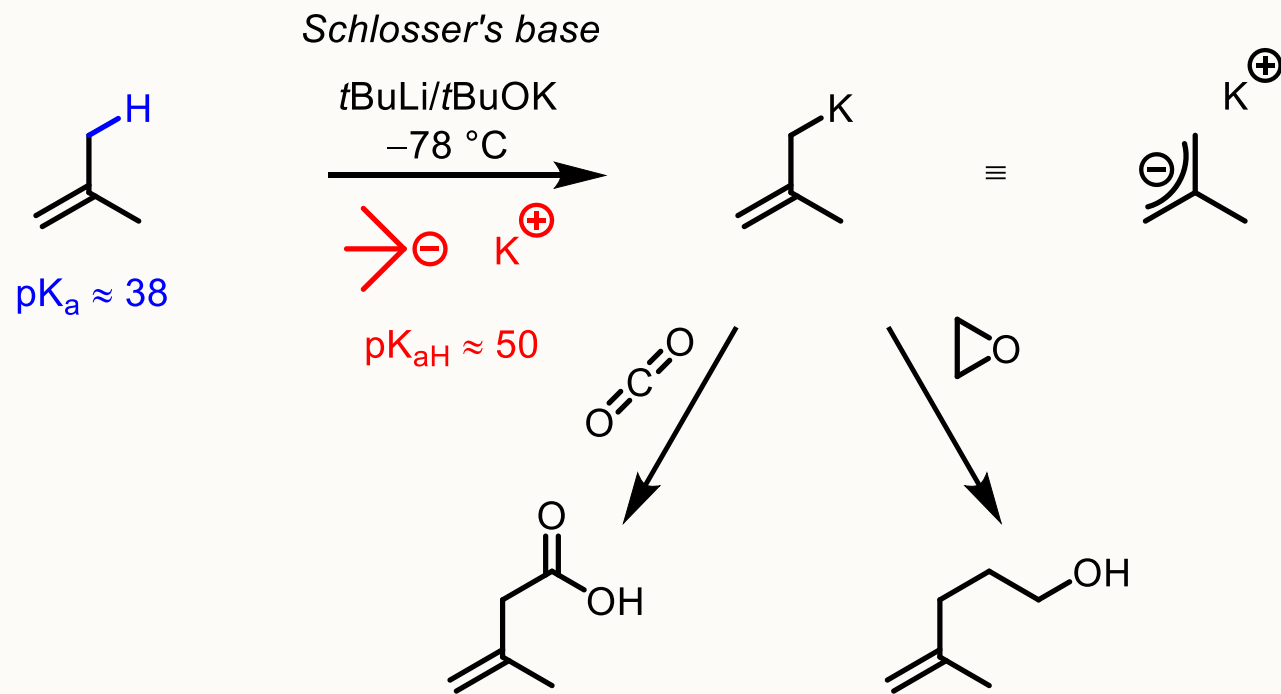
reaction with electrophiles occurs at the most reactive (least stabilised) position





Schlosser's base: "Superbase"

- The combination of two bases (an alkyllithium base and a group I metal alkoxide) gives rise to very powerful "superbases" that enable deprotonation at very weakly acidic positions.
- E.g.* Schlosser's base, one of the most powerful bases known, will abstract protons from allylic or benzylic positions and will even deprotonate benzene:



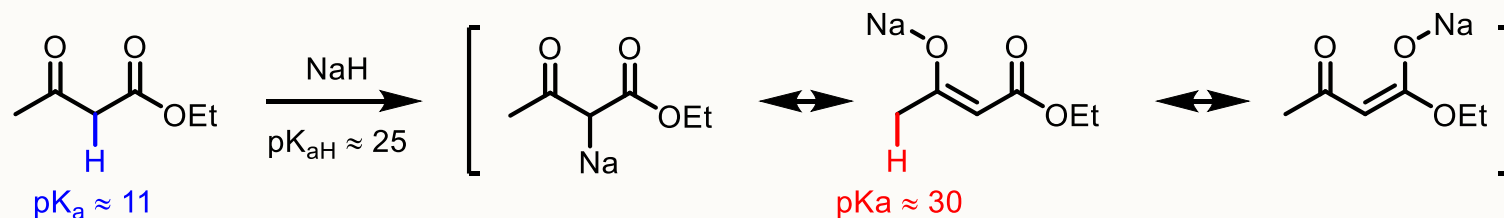


Summary

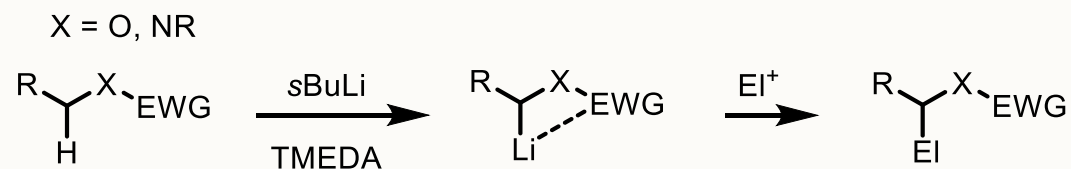
In this lecture, you learnt:

- how to make organolithiums by deprotonating acidic protons, e.g.

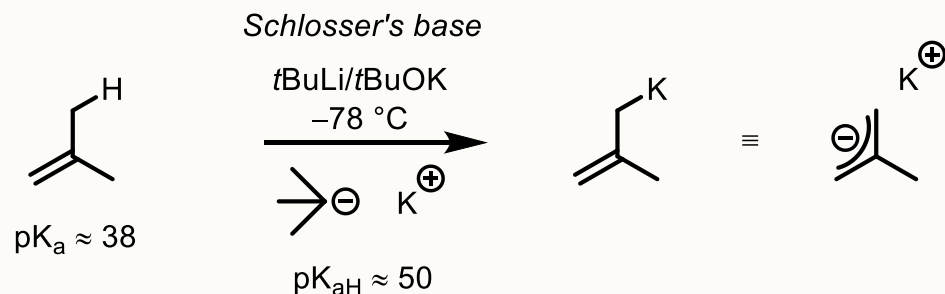
– enolates:



– *alpha* to heteroatoms:



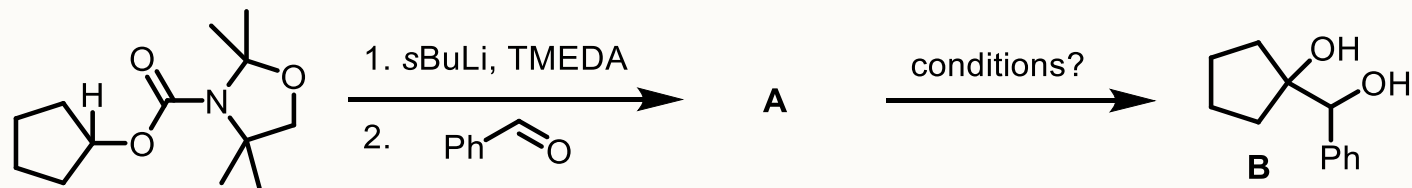
- how to combine an alkyllithium base and a group I metal alkoxide to generate “superbases” for the deprotonation of weakly acidic protons:





Practice questions

1. Provide curly arrow reactions mechanisms for the formation of product **A**, and suggest a structure for **A**.
2. Suggest reaction conditions and draw a curly arrow reaction mechanism for the formation of **B** from **A**.

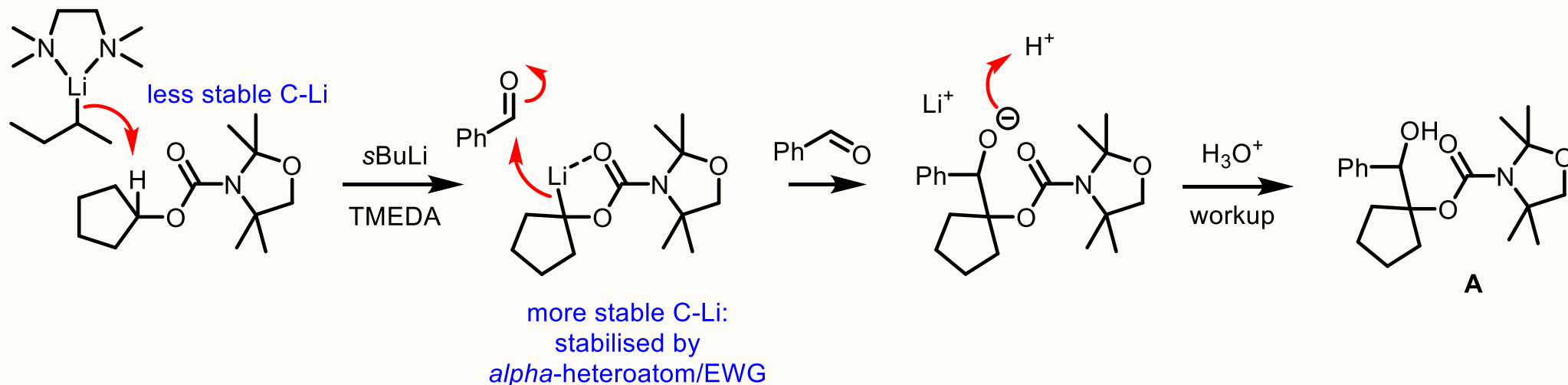




Lecture 3 practice questions – answers

1. Provide curly arrow reactions mechanisms for the formation of product **A**, and suggest a structure for **A**.

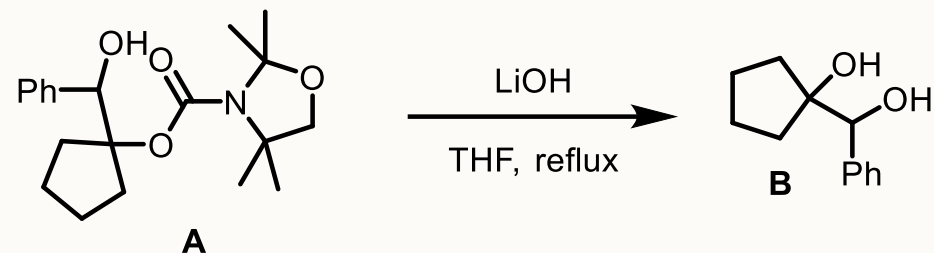
TMEDA makes sBuLi more reactive



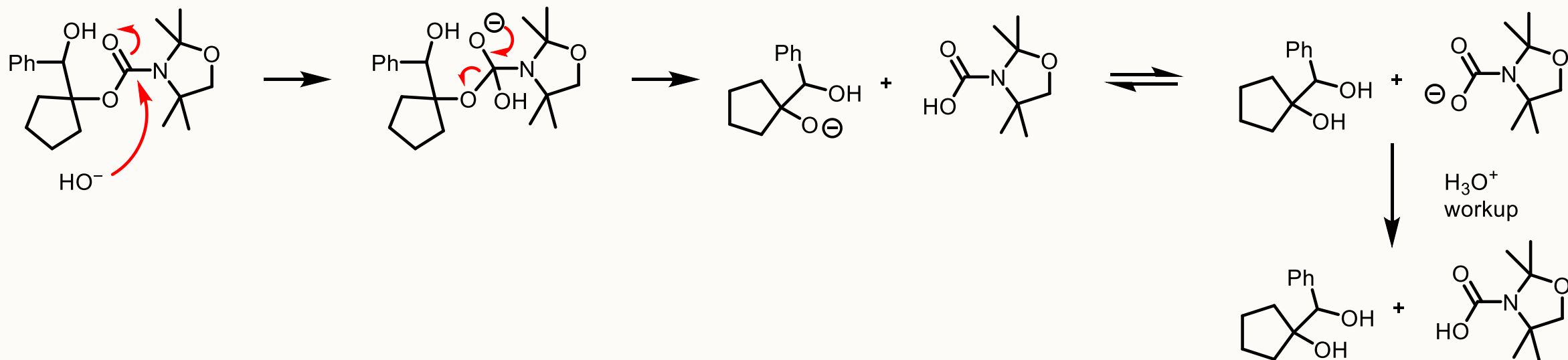


Lecture 3 practice questions – answers

2. Suggest reaction conditions and draw a curly arrow reaction mechanism for the formation of **B** from **A**.



The question does not ask for a reaction mechanisms, but you should be able to draw this:





University of
Nottingham

UK | CHINA | MALAYSIA

CHEM3065 Synthesis and Reactive Intermediates

O'Duill lecture 4

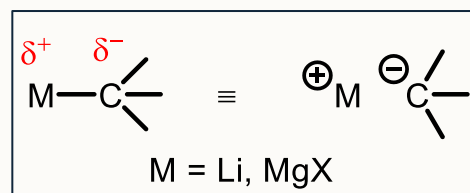
miriam.oduill@nottingham.ac.uk



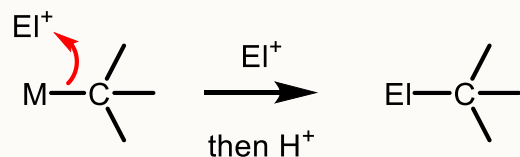
Recap: R–Li and R–MgBr

Previously, you learnt that:

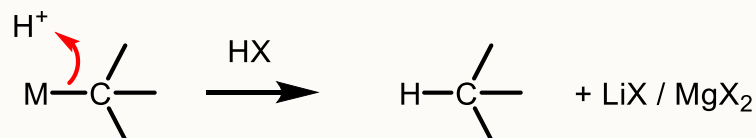
- organometallic reagents with electropositive metals have significant ionic character; they are highly reactive and unstable above cryogenic temperatures ($-78\text{ }^{\circ}\text{C}$).



- they are nucleophilic on carbon and react with electrophiles:

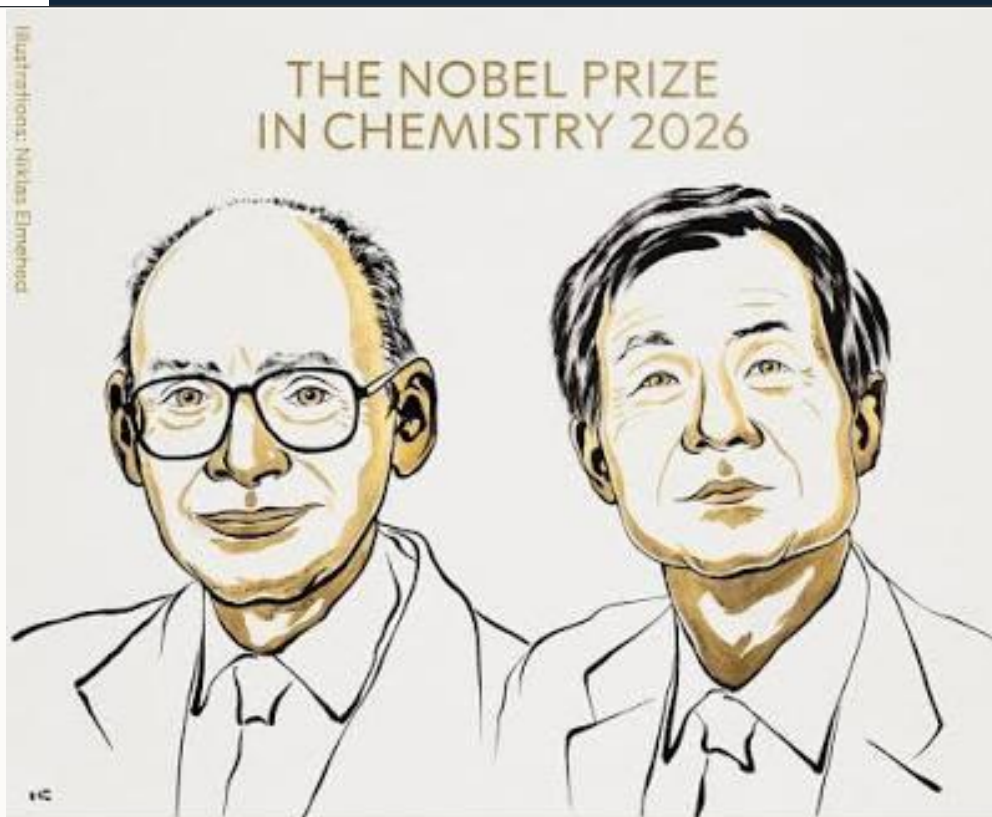


- they are strong bases and easily destroyed by weak acids, water and protic solvents:





Nobel Prize in Chemistry 2026

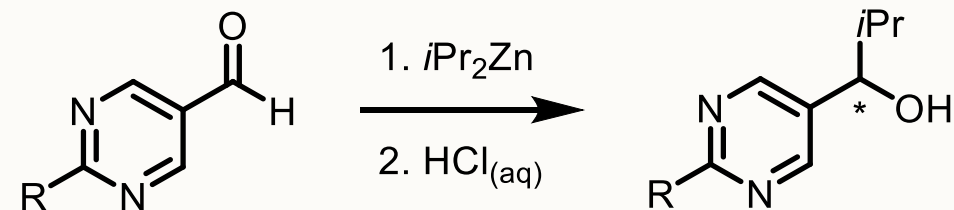


Henri B. Kagan

Kenso Soai

"for the discovery of non-linear effects and autocatalysis in asymmetric organic synthesis"

THE ROYAL SWEDISH ACADEMY OF SCIENCES



Draw a curly arrow reaction mechanism for the Soai reaction.



Lecture 4: Organocuprate Chemistry

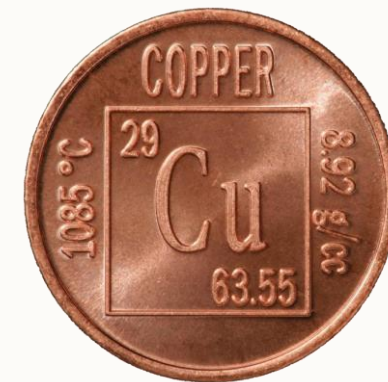
Organocuprate (copper) chemistry

Learning outcomes

In this lecture, you will learn:

- how to make organocuprate reagents;
- how the reactivity of organocuprate reagents differs from Grignard and organolithium reagents.

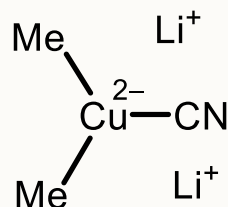
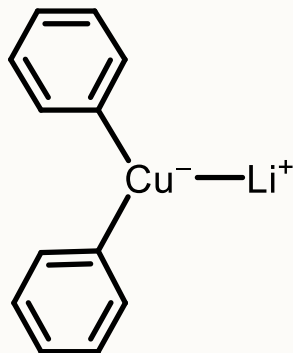
Recommended Reading: Clayden, Organic Chemistry, Chapter 22





Synthesis of Organocuprates

- Organocuprates (organocopper reagents) contain a carbon–copper bond.

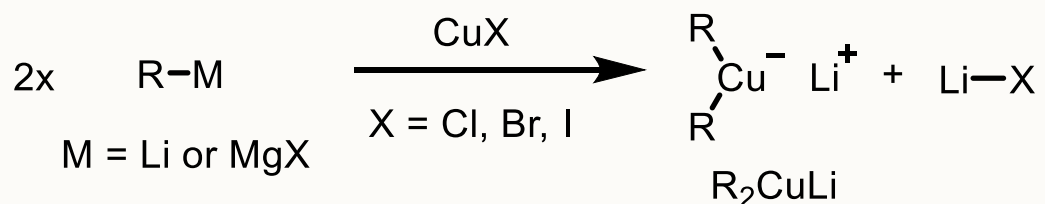


- When making organocuprates, similar factors need to be considered as when making Grignard reagents or organolithium reagents:
 - Need to use aprotic solvents (THF or Et_2O).
 - Unstable $> 0^\circ\text{C}$. (Note: This is more stable than organolithium reagents which usually require reaction temperatures of -78°C .)
 - Prepared and used “in situ”.

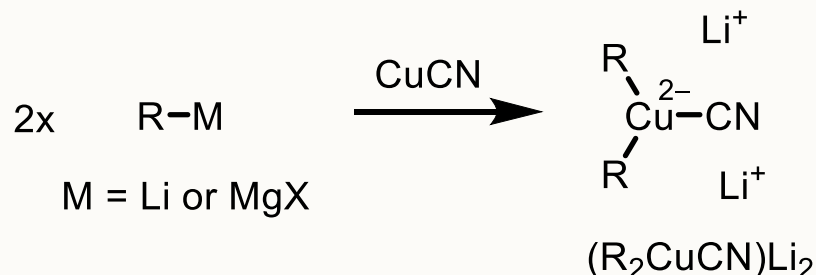


Synthesis of Organocuprates

- Organocuprates (organocopper reagents) can be made by transmetallation from an organolithium (or Grignard) and a copper salt.
- There are two types of organocuprates:
 - Lower-order cuprates (Gilman reagents): less reactive



- Higher-order cuprates (Lipshutz reagents): more reactive





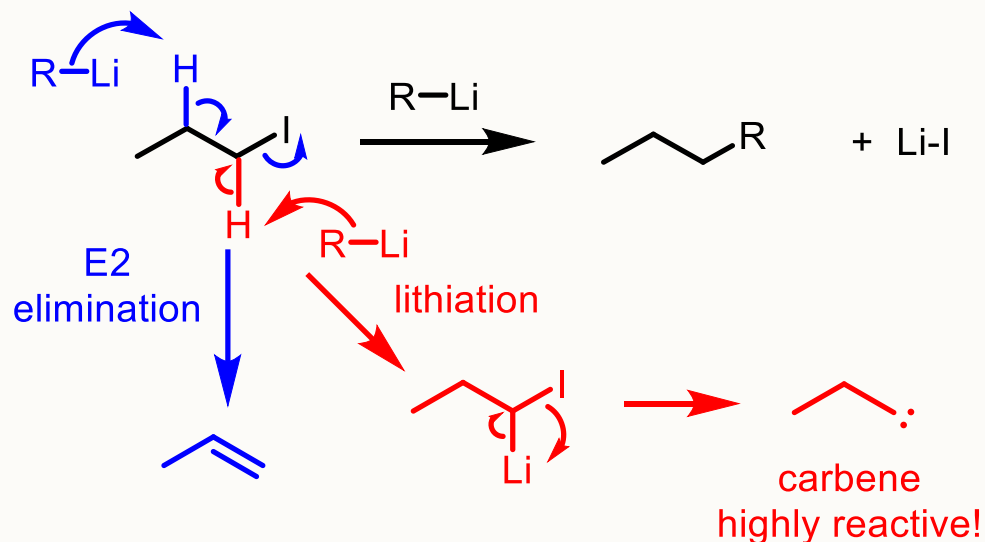
Reactivity of Organocuprates

- Organocuprates are nucleophilic and basic (like Grignard / organomagnesium and organolithium reagents), with two important differences:
 - Organocuprates are “**softer**” nucleophiles.
 - They are **less basic** than Grignard or organolithium reagents.
- This results in different reactivity.



Cuprate reactivity: Substitution reactions

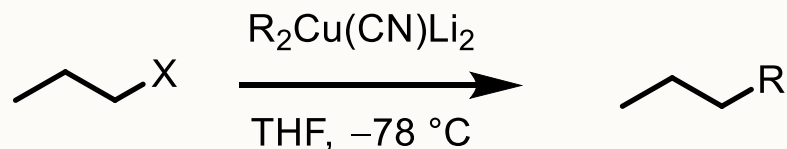
1. Cuprates are **less basic** than Grignard (R-MgBr) and organolithium (R-Li) reagents.
 - Problem: Because Grignard and organolithium reagents are strong bases, they do not cleanly undergo $\text{S}_{\text{N}}2$ reactions with alkyl halides because of competing elimination reactions:





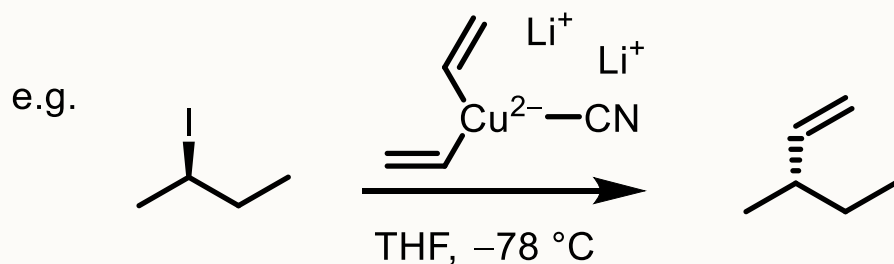
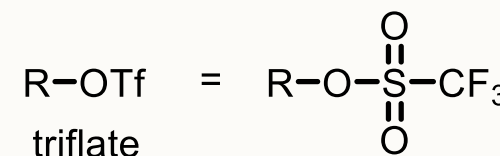
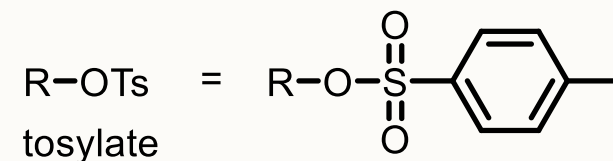
Cuprate reactivity: Substitution reactions

- Solution: Cuprates **are less basic** and undergo clean S_N2 reactions with alkyl halides or pseudohalides:



X = I, Cl, Br, OTs, OTf

pseudohalides:

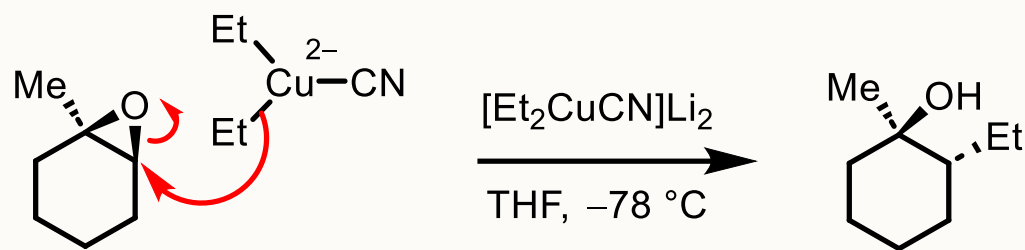


- Only one R-group is transferred. CN group always stays on Cu.
- S_N2 : inversion of stereochemistry.

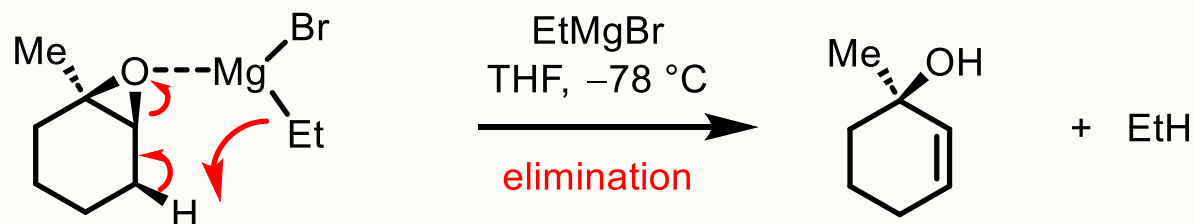


Cuprate reactivity: Ring-opening of epoxides

- Similarly, epoxides are cleanly ring-opened with cuprates, while Grignards or organolithiums are too basic and lead to elimination reactions:



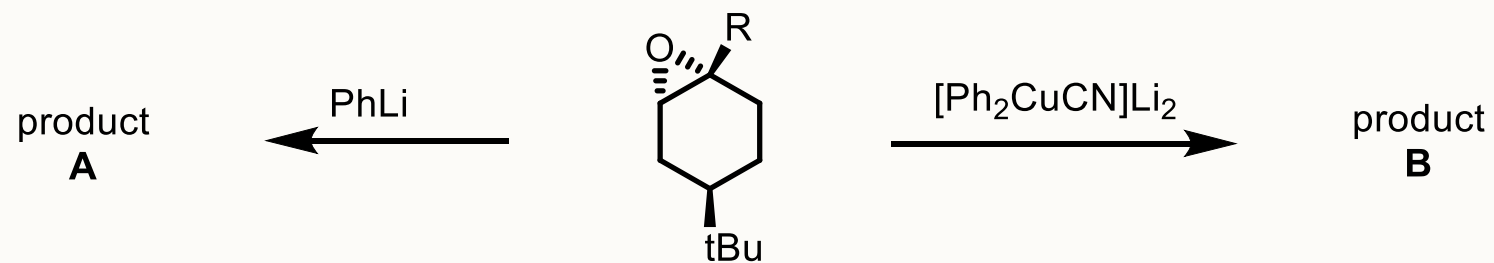
Epoxide opening is selective for the less hindered position (sterics).





Question

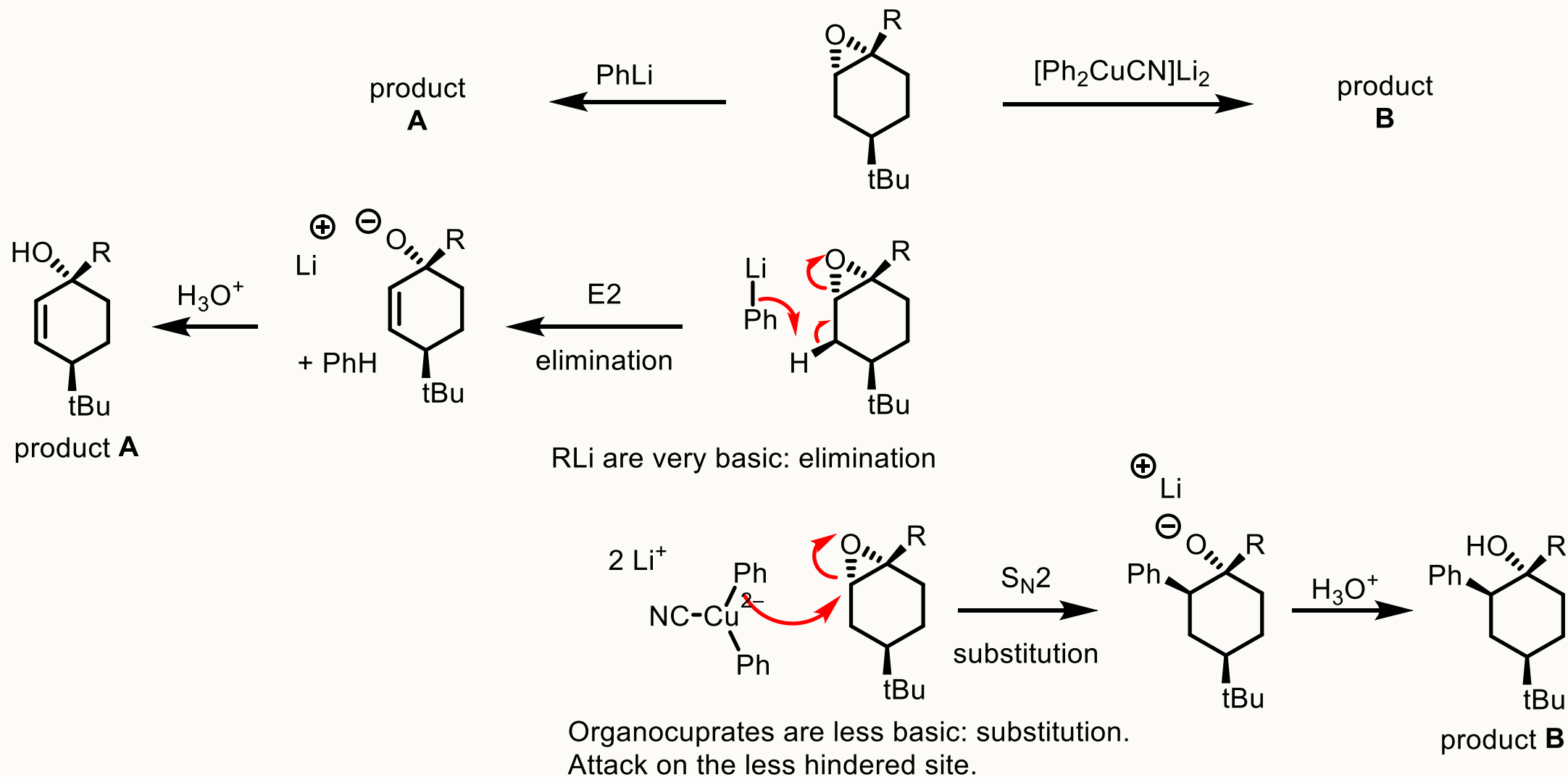
Predict the products (**A** and **B**) of the following two reactions:





Question

Predict the products (**A** and **B**) of the following two reactions:



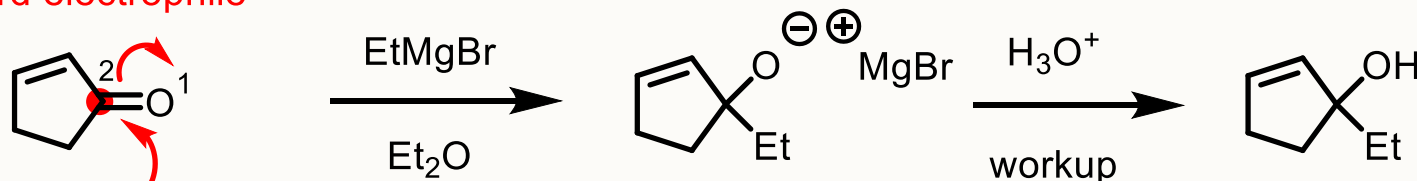


Cuprate reactivity: Conjugate addition

2. Cuprates are “**softer**” nucleophiles than Grignards and organolithium reagents.

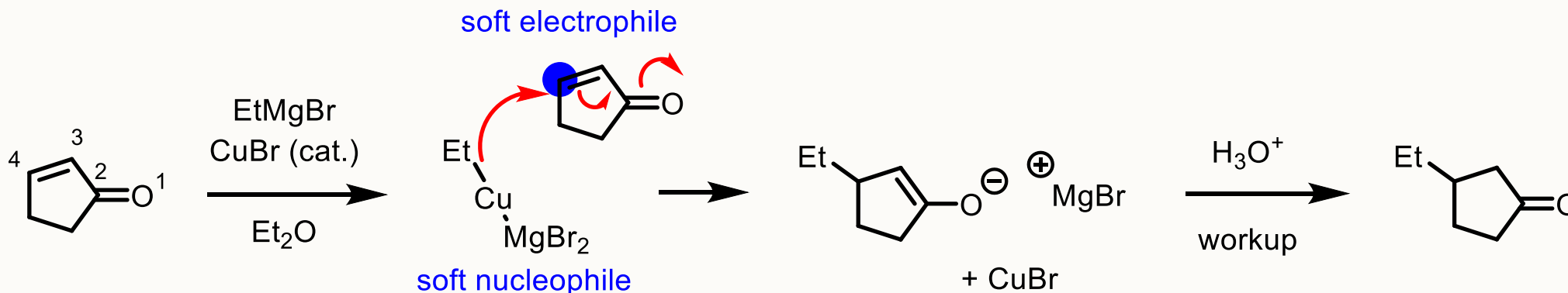
- Grignard reagents are hard nucleophiles: direct 1,2-addition to α,β -unsaturated ketones:

hard electrophile



hard nucleophile

- Organocuprates are **soft nucleophiles**: conjugate 1,4-addition:



Hard reacts with hard, soft reacts with soft



Hard and soft nucleophiles

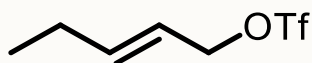
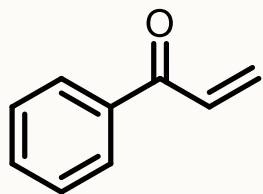
Hard reacts with hard, soft reacts with soft

- Hard nucleophiles/electrophiles: small, high charge density
e.g. RO^- , H_2N^- , $\text{R}_2\text{C}=\text{O}$, MeLi , MeMgBr
→ reactivity dominated by electrostatic interactions
- Soft nucleophiles / electrophiles: delocalised charge in large, 'diffuse' orbitals
e.g. RS^- , I^- , R_3P , α,β -unsaturated ketones and other conjugated alkenes, Me_2CuLi
→ reactivity dominated by HOMO–LUMO interactions

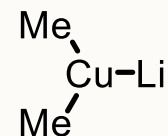
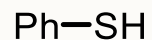


Question

1. Each of the molecules below has a hard and a soft electrophilic centre. Identify them.



2. Are the following nucleophiles hard or soft? Where will they react with the two molecules in question 1?

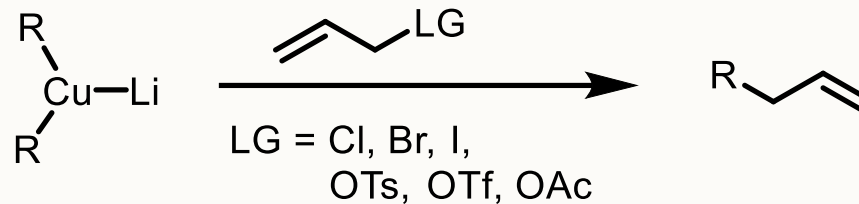




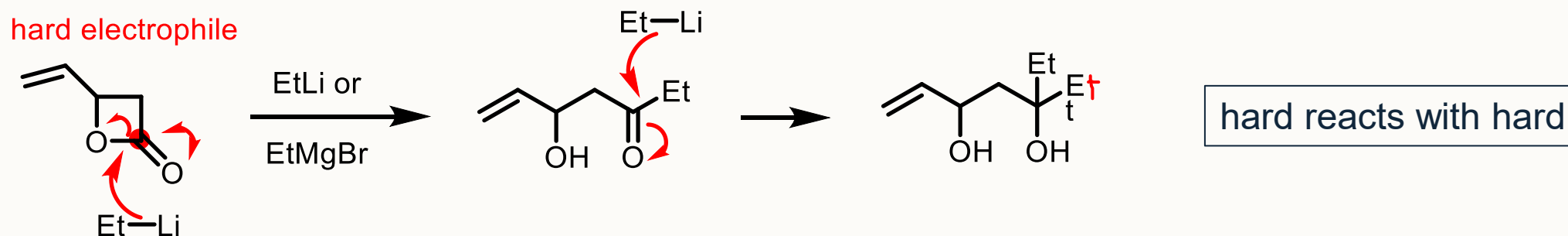
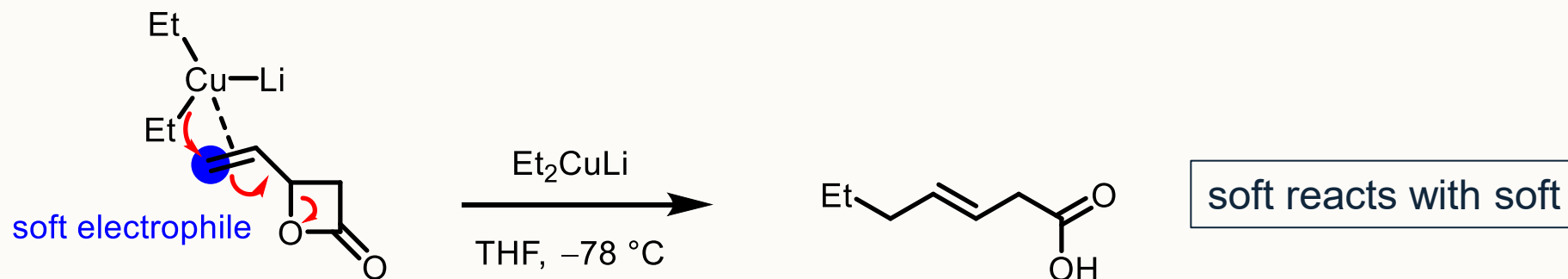
Cuprate reactivity: Conjugate addition

- Cuprates will cleanly displace a wide range of allyl substituted leaving groups.

- Soft nucleophiles: S_N2' reactions

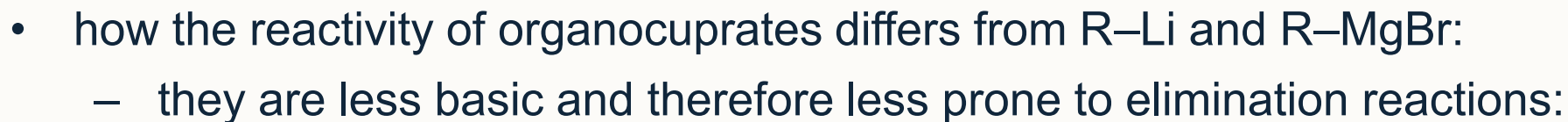


e.g.





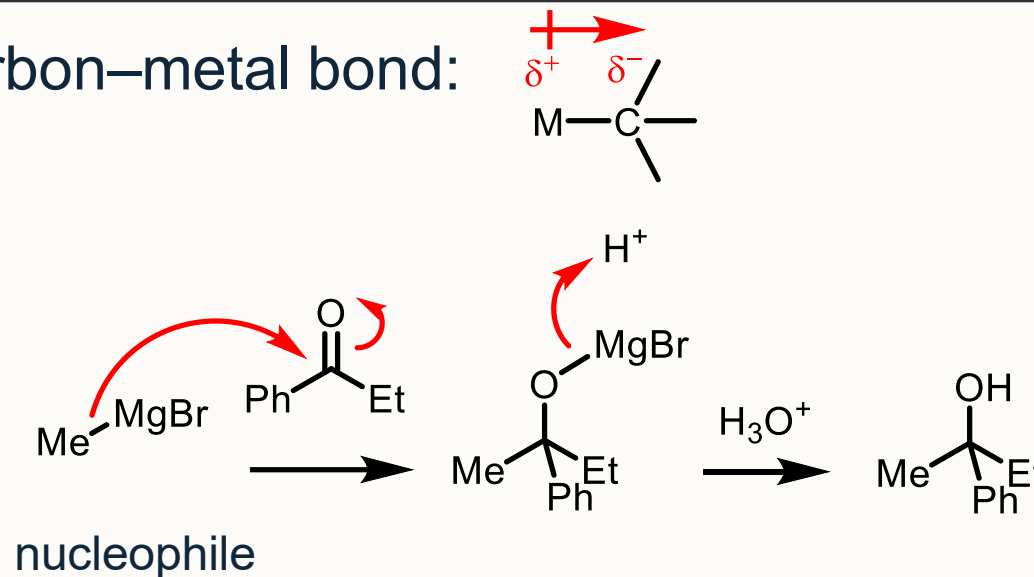
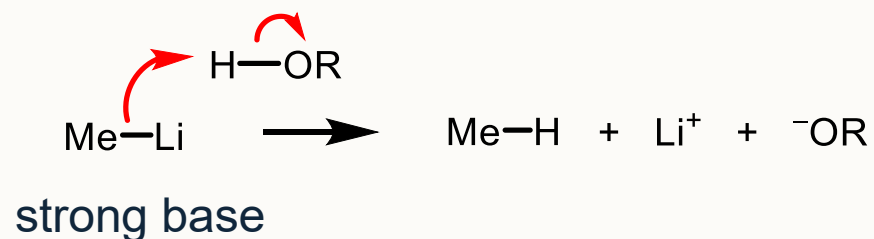
- how to make organocuprates by transmetallation from R-Li or R-MgBr





Summary: Organometallic chemistry

- Organometallic compounds contain a carbon–metal bond:
- They are highly reactive:

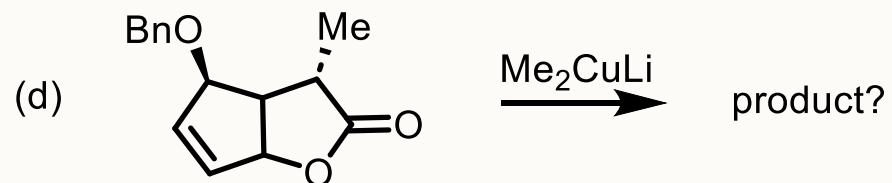
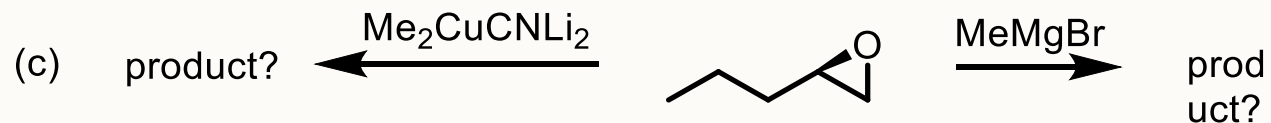
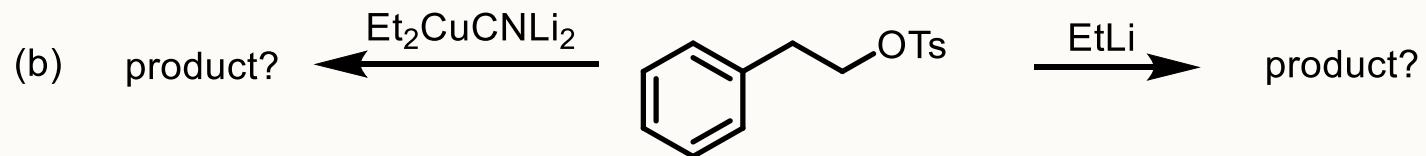
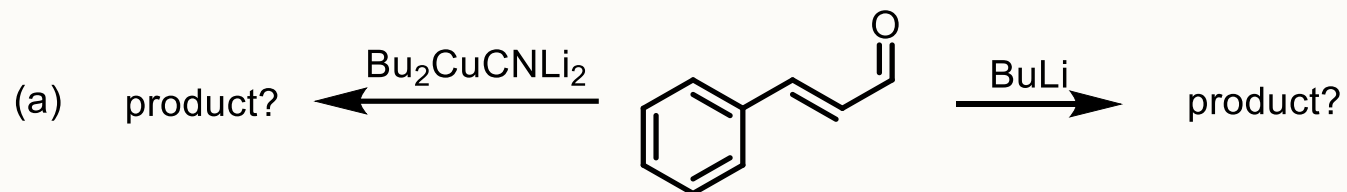


- They can be made by Li–Hal exchange, transmetallation, and deprotonation of acidic C–H bonds.
- The driving force in organometallic synthesis is the formation of a more stable C–M compound (i.e. better stabilisation of the negative charge on carbon) from a less stable C–M compound.
- In the next lecture block, we will learn about **transition metal chemistry** (e.g. Pd).



Lecture 4 - Practice questions

1. Predict the outcome of the following reactions:

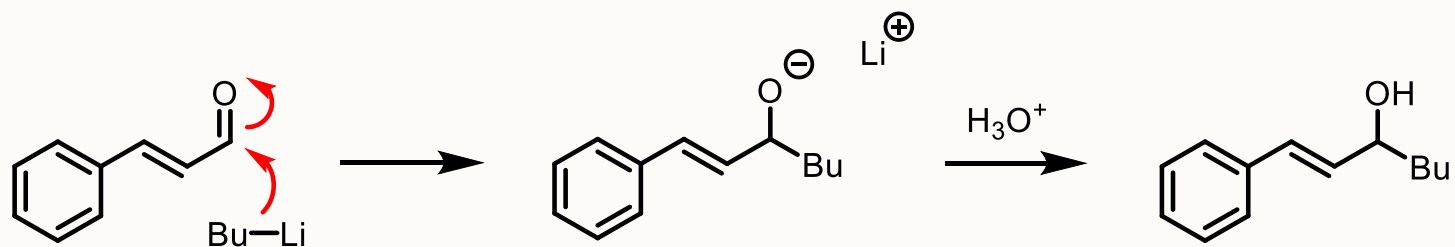




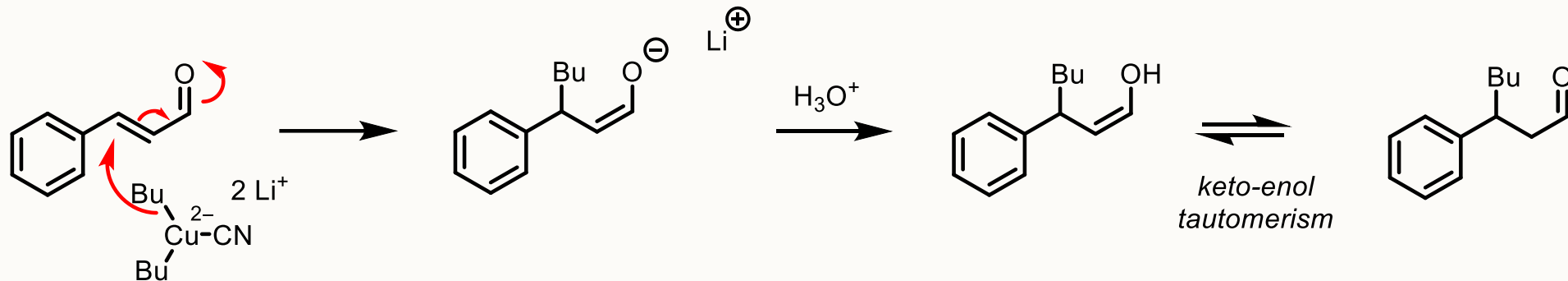
Lecture 4 practice questions – answers

1. Predict the outcome of the following reactions:

a)



hard nucleophile / electrophile



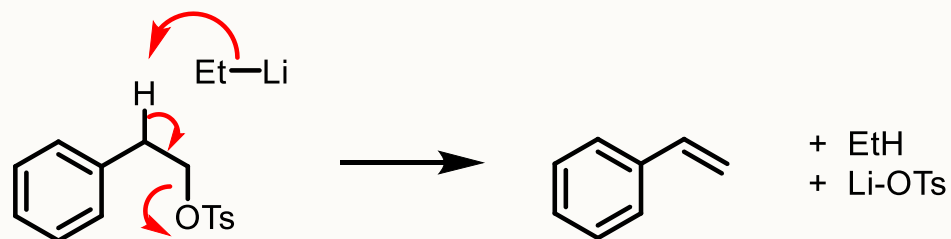
soft nucleophile / electrophile



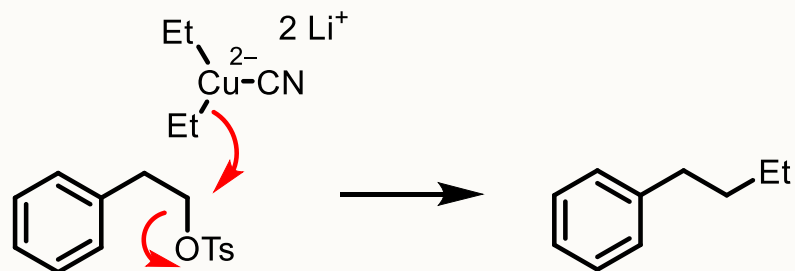
Lecture 4 practice questions – answers

1. Predict the outcome of the following reactions:

b)



organolithium reagents are very basic: E2 elimination



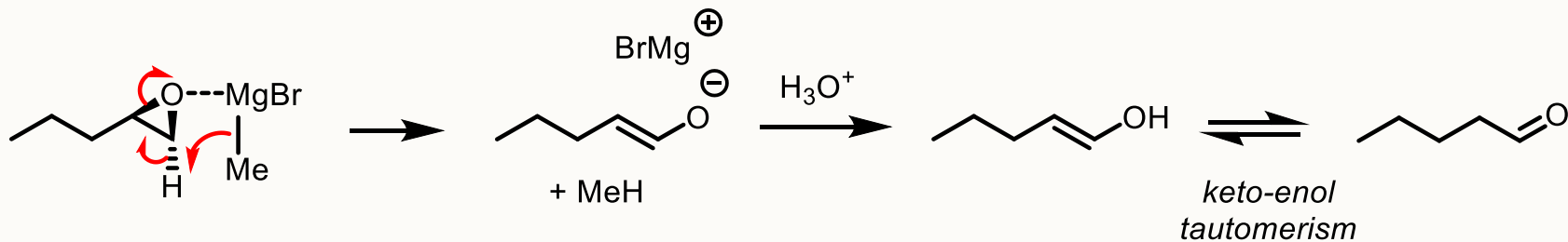
organocuprates are less basic: substitution (S_N2) reaction



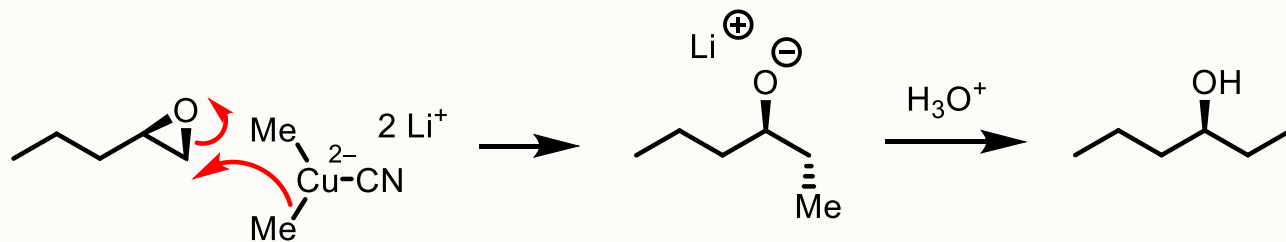
Lecture 4 practice questions – answers

1. Predict the outcome of the following reactions:

c)



Grignard reagents are very basic: E2 elimination



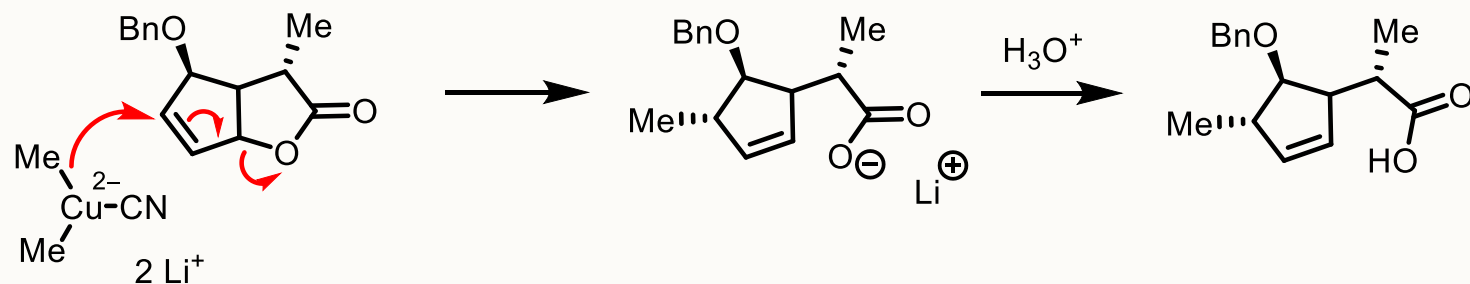
Organocuprates are less basic: substitution



Lecture 4 practice questions – answers

1. Predict the outcome of the following reactions:

d)



Soft nucleophiles attack at the soft electrophilic centre: $\text{S}_{\text{N}}2'$ reaction



University of
Nottingham

UK | CHINA | MALAYSIA

CHEM3065 Synthesis and Reactive Intermediates

O'Duill lectures 5+6

miriam.oduill@nottingham.ac.uk

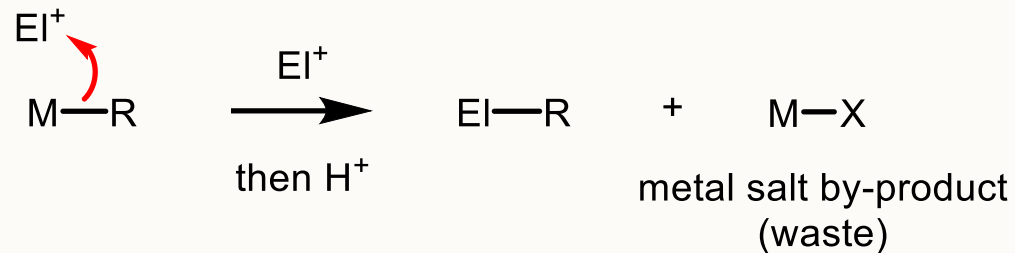


Course Overview

Part 1: Stoichiometric Organometallic Chemistry

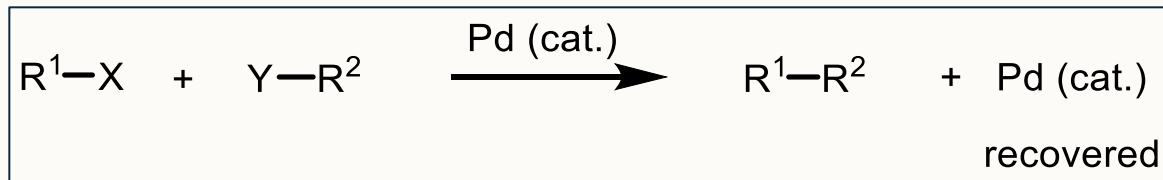
(Clayden, Chapter 9)

So far, we have covered stoichiometric reactions
(≥ 1 equivalent of metal required):



Part 2: Transition Metal Catalysis (Clayden, Chapter 40)

In the next section, we will learn about catalytic reactions
with palladium:





Lecture 5 + 6: Introduction to Palladium Catalysis

Introduction to Palladium Catalysis

Learning outcomes

In the next two lectures, you will learn:

- The effect of ligands on stability and reactivity of palladium catalysts;
- The effect of oxidation state and valence electron count on the reactivity of palladium catalysts;
- The three fundamental reactions that make up the catalytic cycle of the Suzuki cross-coupling reaction: oxidative addition, transmetallation and reductive elimination.
- How the coupling partner can be changed to give other cross-coupling reactions using the same fundamental steps.

Recommended Reading: Clayden, Organic Chemistry, Chapter 40



Transition metal catalysis

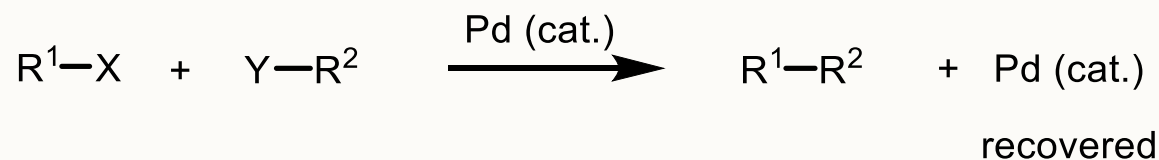


- Some of the most commonly used reactions in research and industry make use of transition metals.

- Four Nobel prizes have been awarded for work in this area:

2001 Asymmetric synthesis (Rh, Ru, Ti)
2005 Metathesis (Mo, Ru) [Stockman lectures]
2010 Cross-coupling (Pd) **[these lectures]**
2022 Click chemistry (Cu)

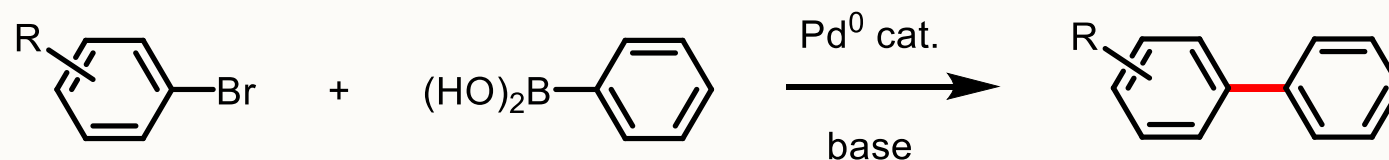
- This course will focus on palladium-catalysed cross-coupling reactions. These reactions are powerful transformations for C–C bond formation:



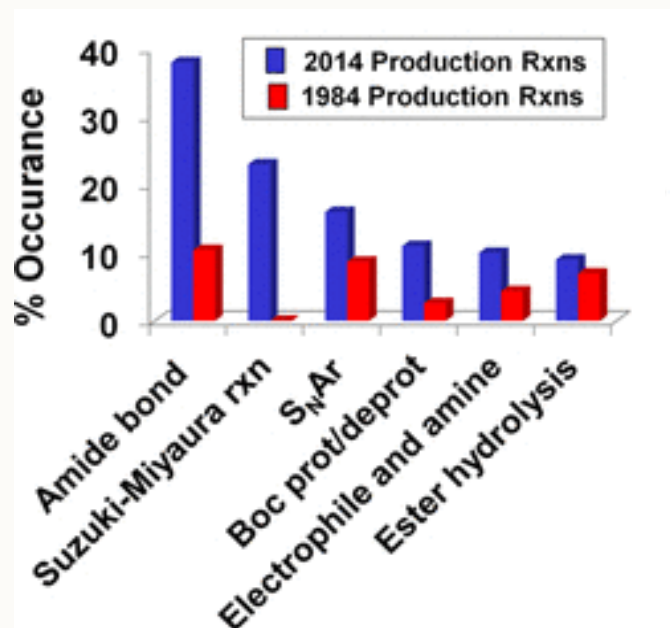


Introduction to Pd cross-coupling chemistry: The Suzuki reaction

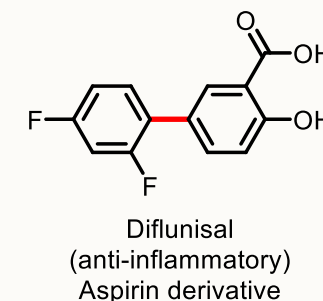
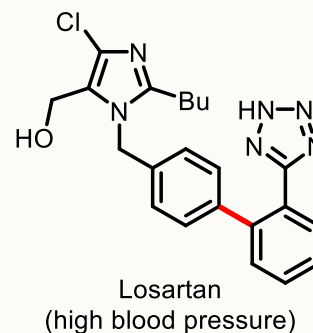
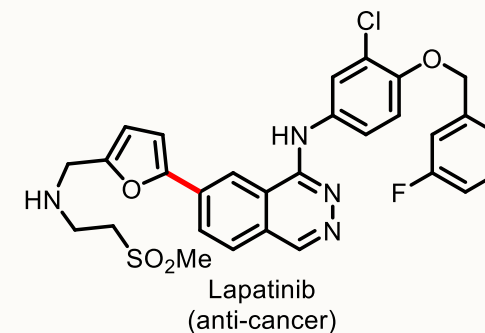
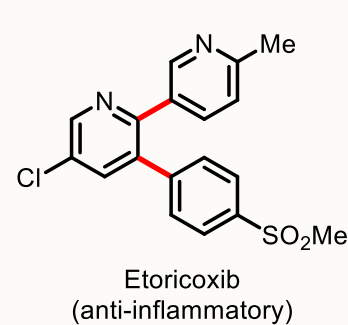
The Suzuki reaction is the second most common reaction in medicinal chemistry.



Examples of pharmaceuticals made via Suzuki reactions:

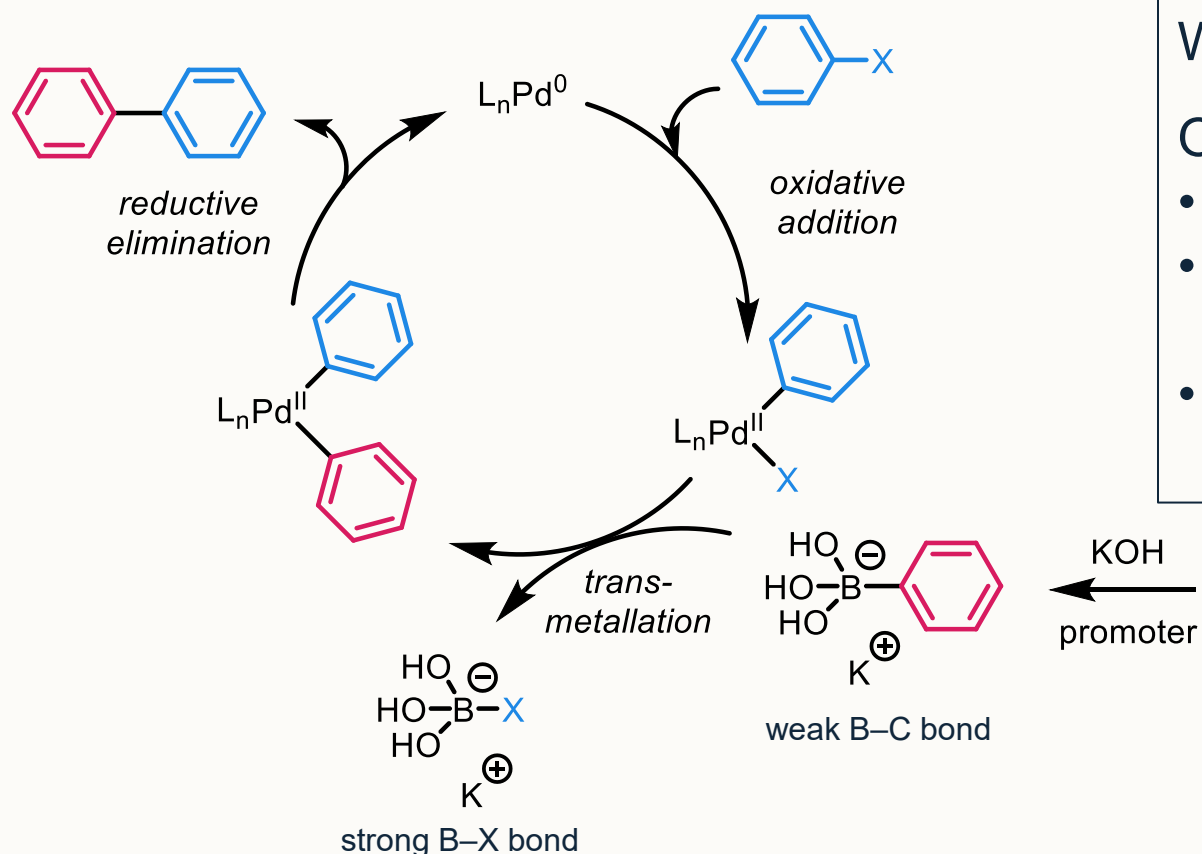
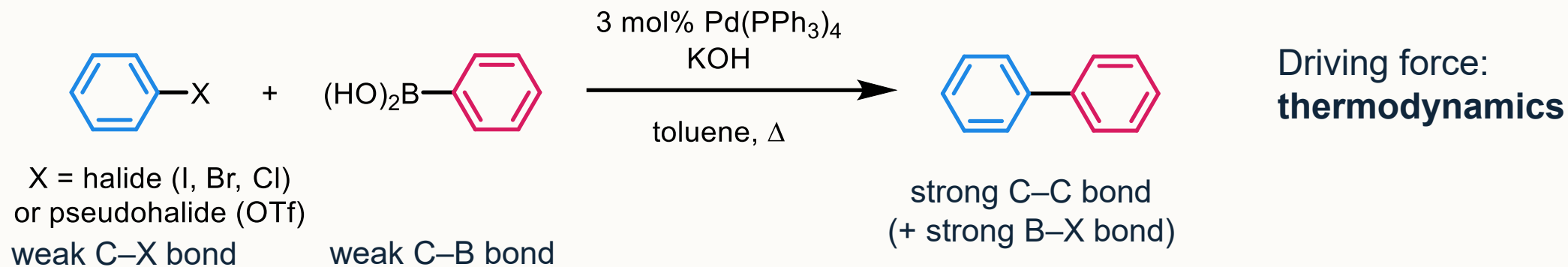


Source: *J. Med. Chem.* **2016**, 59, 4443





Pd cross-coupling reactions: Mechanism of the Suzuki reaction



What is going on here?

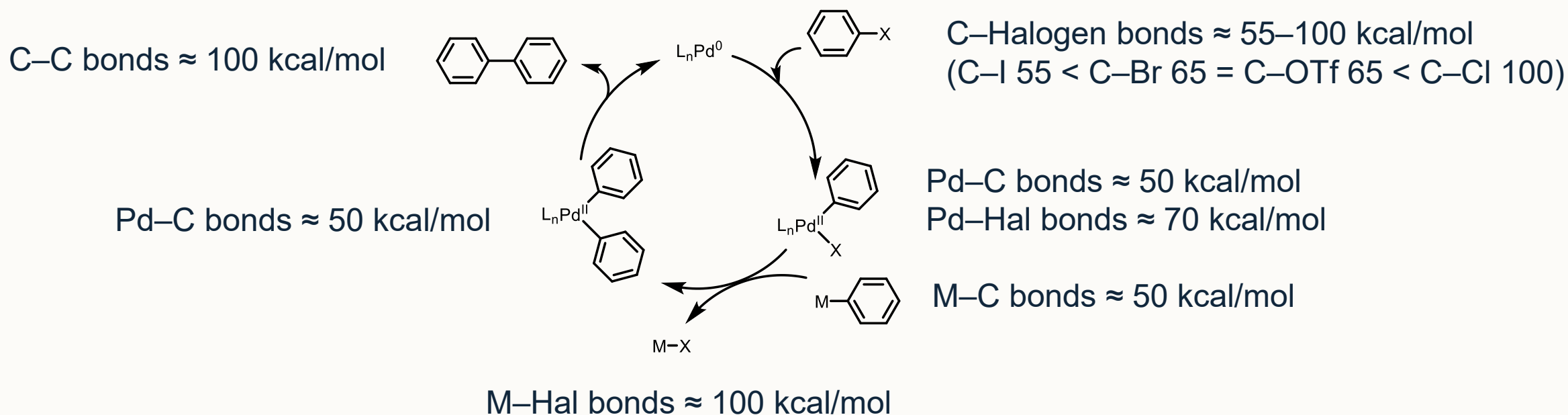
Over the next 4 lectures, we will discuss:

- the properties of the Pd catalyst,
- the fundamental steps that make up the catalytic cycle,
- how the catalytic cycle can be changed to give different cross-coupling reactions.



Pd cross-coupling reactions: Mechanism of the Suzuki reaction

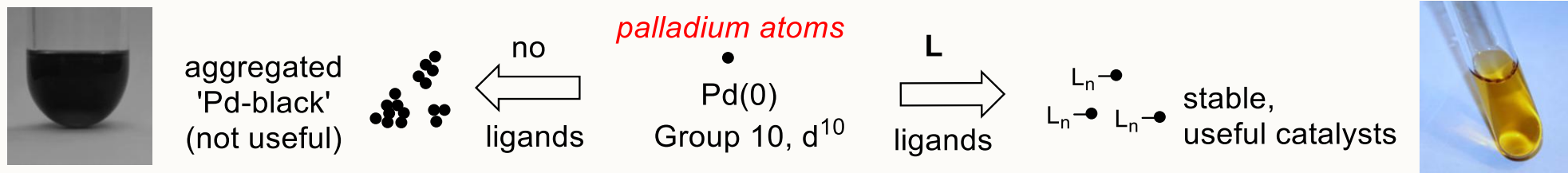
- The driving force for most Pd catalysed cross-coupling reactions is **thermodynamics**: the formation of stronger bonds from weaker bonds.
- A rough guide to bond strengths:
 - C–C and C–H bonds are strong
 - C–X / C–M bonds are weak
 - M–X bonds are strong





The metal catalyst

- Ligands are required to stabilise the metal catalyst:



- The nature of the ligands affects the oxidation state and number of electrons of a metal complex and therefore its reactivity.

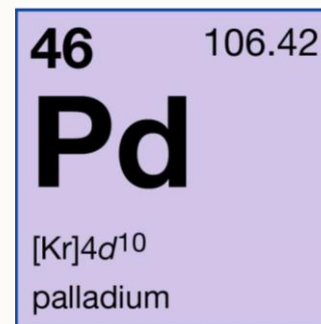


The metal catalyst

- The oxidation state and number of electrons of a metal complex determine its reactivity.

oxidation state = 0 – (formal charge of ligands)

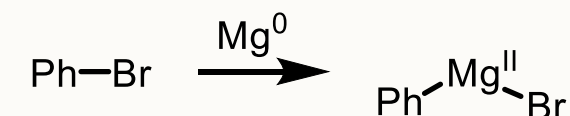
electron count = (Pd valence electrons) + (electrons donated by ligands)
= (group number – oxidation state) + (electrons donated by ligands)



4	5	6	7	8	9	10	11	12
22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn
40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd
72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg
104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn

Ligand	Formal charge	Electrons donated
Anionic ligands (Cl ⁻ , -CN, -OR)	-1	2
Neutral σ -donor ligands (:PR ₃ , :NR ₃ , :OR ₂ , :SR ₂ , :CO, :NCR)	0	2
alkyl, aryl (η^1)	-1	2
alkene (η^2)	0	2

Note: We've (briefly) seen oxidation states before:



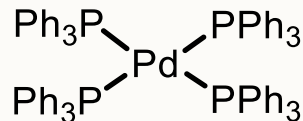


The metal catalyst

- Consider some common palladium pre-catalysts:

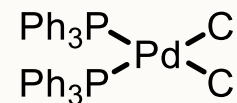
$$\begin{aligned}\text{OS} &= 0 - (\text{ligand charge}) \\ e^- &= (10 - \text{OS}) + (\text{ligand } e^-)\end{aligned}$$

formal charge: 0 electrons: 2



oxidation state = $0 - 0 = 0$ Pd(0)
electrons: $10 + (4 \times 2) = 18 e^-$
coordinationally saturated

formal charge: 0 formal charge: -1
electrons: 2 electrons: 2



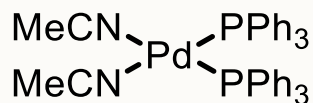
oxidation state = $0 - (2 \times -1) = 2$ Pd(II)
electrons: $(10 - 2) + (4 \times 2) = 16 e^-$
coordinationally saturated

- 18- and 16-electron complexes are coordinationally saturated and unreactive. Reactive, unsaturated ($14 e^-$) complexes are formed by ligand dissociation in solution.



Question

Determine the Pd oxidation state and electron count in the following complex:



MeCN: and Ph_3P :
neutral σ -donor ligands
formal charge: 0
electrons donated: 2

Oxidation state ?

Electrons ?

Coordinatively saturated or unsaturated?

Reactivity?

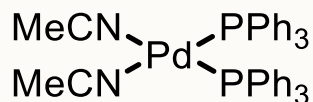
$$\begin{aligned} \text{OS} &= 0 - (\text{ligand charge}) \\ e^- &= (10 - \text{OS}) + (\text{ligand } e^-) \end{aligned}$$

Ligand	Formal charge	Electrons donated
Anionic ligands (Cl^- , $-\text{CN}$, $-\text{OR}$)	-1	2
Neutral σ -donor ligands ($:\text{PR}_3$, $:\text{NR}_3$, $:\text{OR}_2$, $:\text{SR}_2$, $:\text{CO}$, $:\text{NCR}$)	0	2
alkyl, aryl	-1	2



Question

Determine the Pd oxidation state and electron count in the following complex:



MeCN: and Ph_3P :
neutral σ -donor ligands
formal charge: 0
electrons donated: 2

oxidation state: Pd(0)
electrons: $10 + (4 \times 2) = 18 \text{ e}^-$
coordinationally saturated: unreactive

$$\begin{aligned} \text{OS} &= 0 - (\text{ligand charge}) \\ \text{e}^- &= (10 - \text{OS}) + (\text{ligand e}^-) \end{aligned}$$

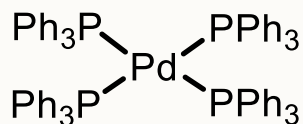
Ligand	Formal charge	Electrons donated
Anionic ligands (Cl^- , $-\text{CN}$, $-\text{OR}$)	-1	2
Neutral σ -donor ligands ($:\text{PR}_3$, $:\text{NR}_3$, $:\text{OR}_2$, $:\text{SR}_2$, $:\text{CO}$, $:\text{NCR}$)	0	2
alkyl, aryl	-1	2



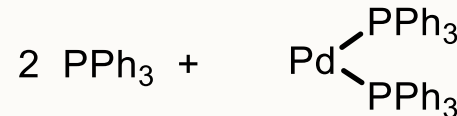
The metal catalyst

- 18- and 16-electron complexes are coordinatively saturated and unreactive. Reactive, unsaturated (14 e⁻) complexes are formed by ligand dissociation in solution:

formal charge: 0 electrons: 2



ligand dissociation



oxidation state = 0 – 0 = 0 Pd(0)
electrons: 10 + (4 x 2) = 18 e⁻
coordinatively saturated: unreactive

oxidation state: Pd(0)
electrons: 10 + (2 x 2) = 14 e⁻
coordinatively unsaturated: reactive

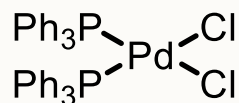
- Pd(0) complexes (d¹⁰) are electron-rich and highly **nucleophilic**.



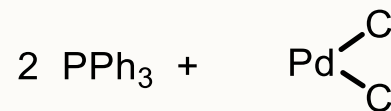
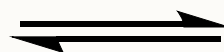
The metal catalyst

- 18- and 16-electron complexes are coordinatively saturated and unreactive. Reactive, unsaturated (14 e⁻) complexes are formed by ligand dissociation in solution:

formal charge: 0 formal charge: -1
electrons: 2 electrons: 2



ligand dissociation



oxidation state = 0 - (2x -1) = 2 Pd(II)
electrons: (10 - 2) + (4 x 2) = 16 e⁻
coordinatively saturated: unreactive

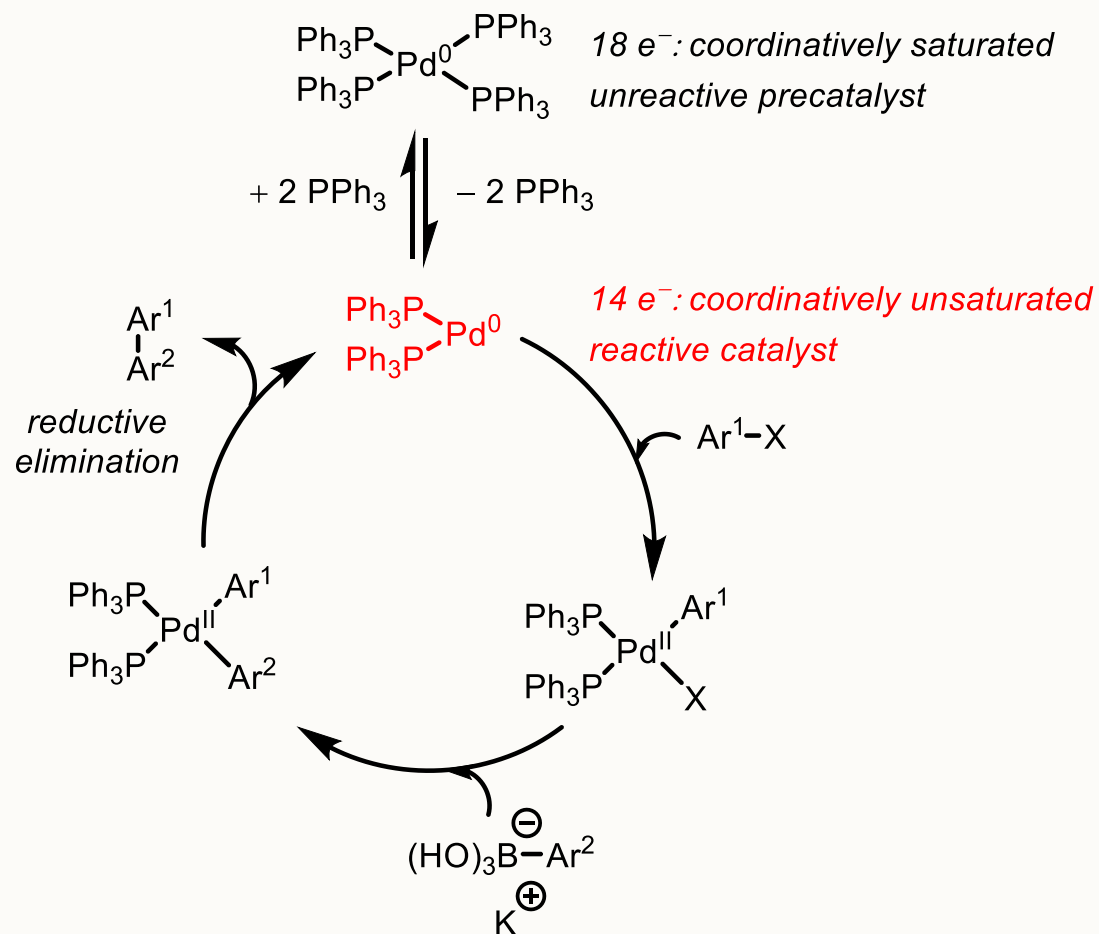
oxidation state: Pd(II)
electrons: (10 - 2) + (2 x 2) = 14 e⁻
coordinatively unsaturated: reactive

- Pd(II) complexes (d⁸) are electron-poor and highly **electrophilic**.



The metal catalyst

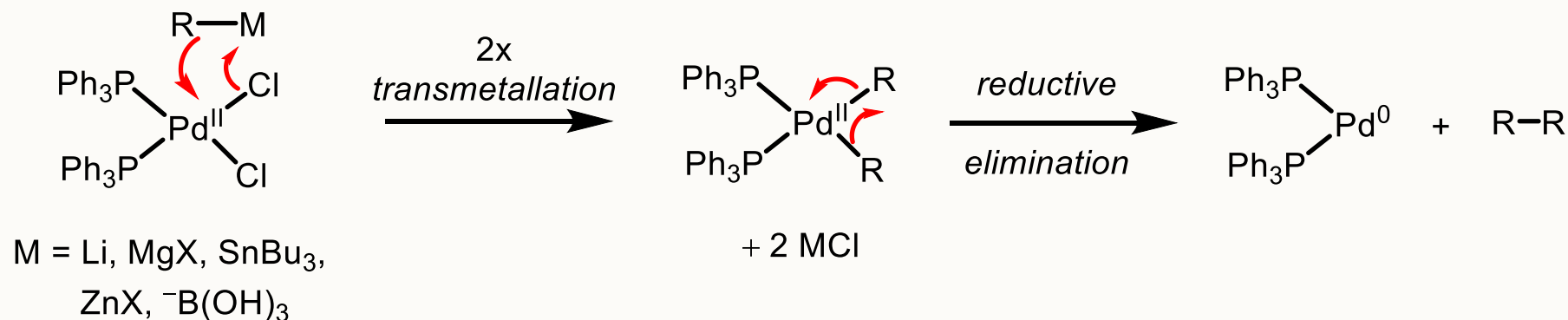
- The first step in a catalytic cycle is usually formation of the reactive catalyst from an unreactive pre-catalyst:



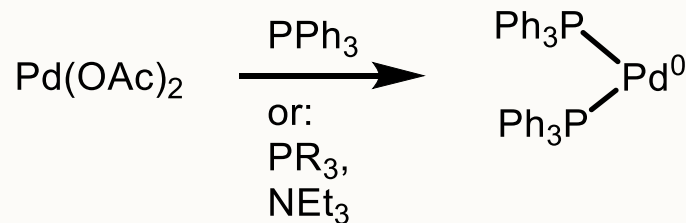


Other ways of generating active Pd(0) catalysts

- A reactive Pd(0) catalyst can also be generated from Pd(II) pre-catalysts:
- Option 1: Reduction of $L_n\text{PdX}_2$ (X = halide or pseudohalide) with an organometallic (M–R is often the coupling partner in cross-coupling reactions, present in excess):



- Option 2: Reduction of Pd(OAc)₂ with phosphines:

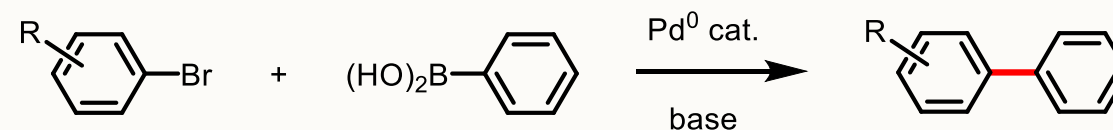
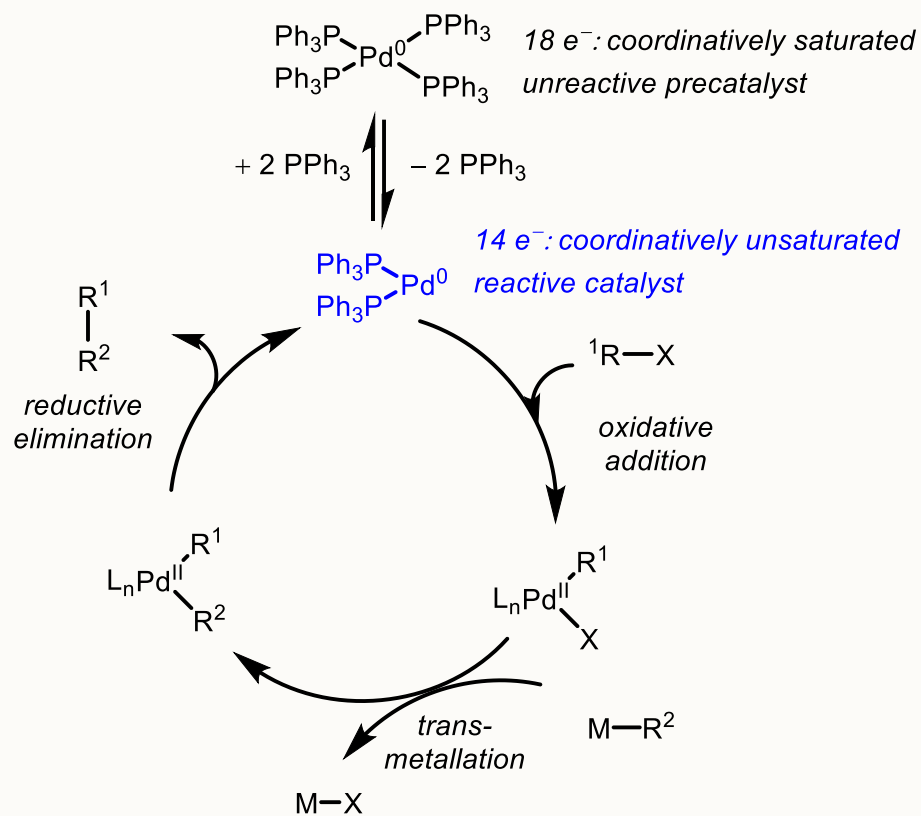




Summary

In the last lecture, you learnt:

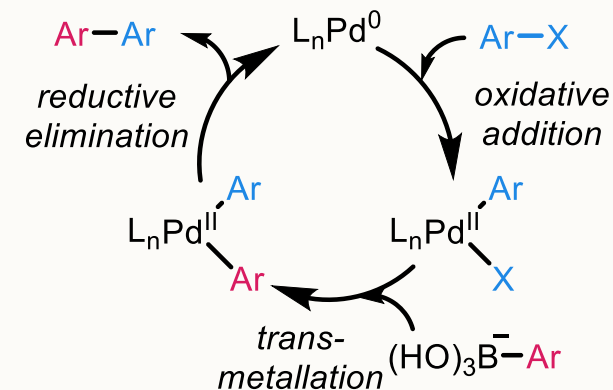
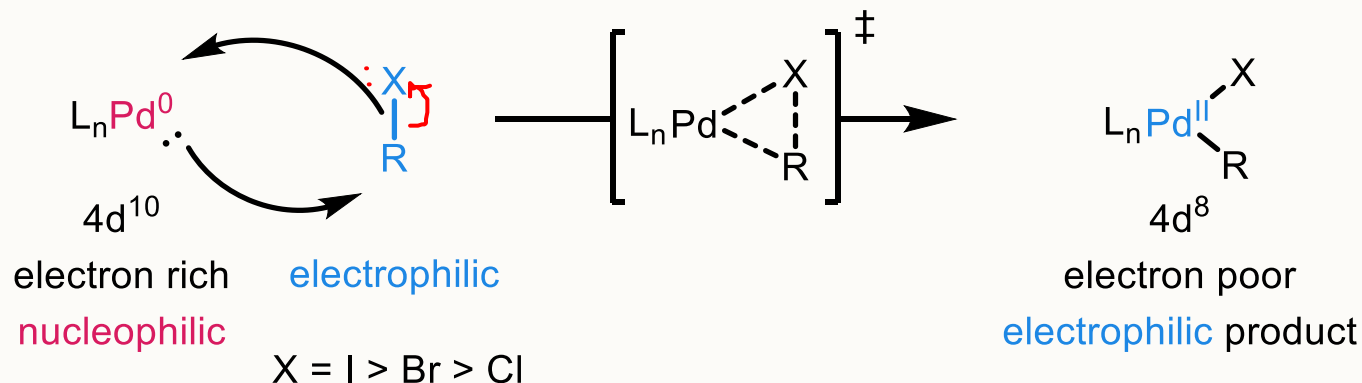
- How to determine oxidation state and electron count of Pd complexes
- How this determines their reactivity:
 - Pd(II) complexes (d^8) are electron-poor and **electrophilic**.
 - Pd(0) complexes (d^{10}) are electron-rich and **nucleophilic**.



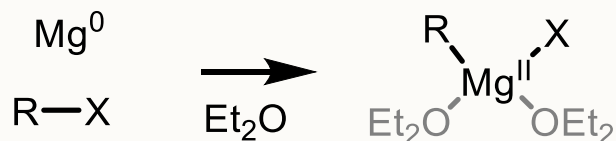


Fundamental reactions: Oxidative addition

- Pd(0) is nucleophilic and undergoes oxidative addition reactions:



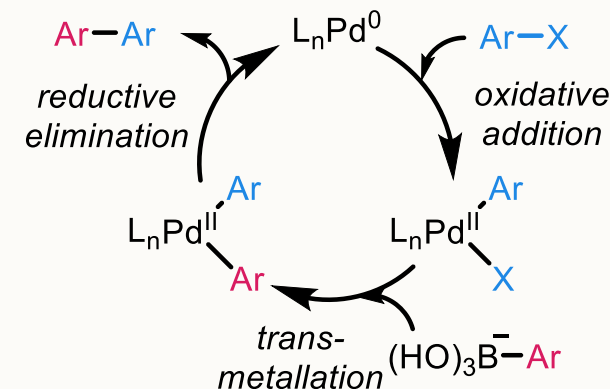
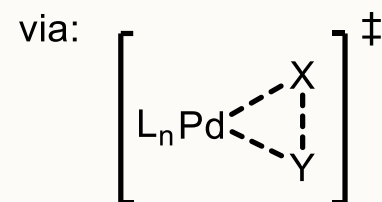
- The reaction requires two free coordination sites on Pd.
 - Selective *cis*-addition of X and R to the metal centre (concerted reaction).
 - The metal is oxidised from Pd(0) to Pd(II), hence the name *oxidative* addition.
 - It is difficult to show transition metal reactivity with curly arrows. For a 3D animation of the process, see: <https://www.chemtube3d.com/suzuki/>
- We have seen oxidative addition before: Grignard reagents (lecture 1).



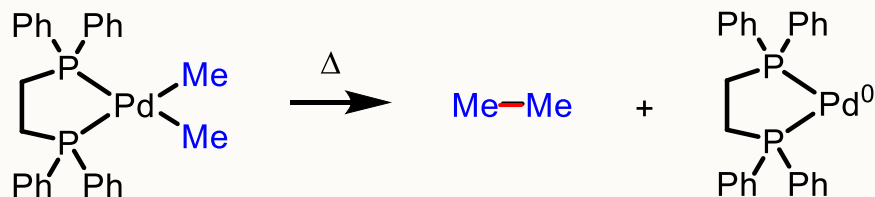


Fundamental reactions: Reductive elimination

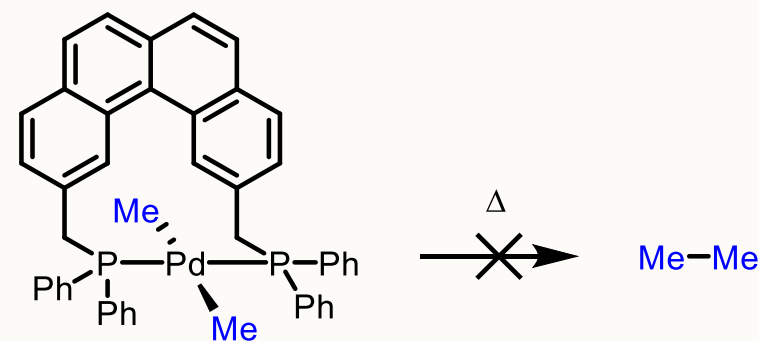
- Oxidative addition is reversible. The reverse process is called reductive elimination:



- Reductive elimination removes (eliminates) metal atoms and forms new single bonds (X-Y). The metal is reduced from Pd(II) to Pd(0) in the process.
- The substituents undergoing reductive elimination (X and Y) need to be *cis* to each other:



ligands *cis*:
reductive elimination occurs.

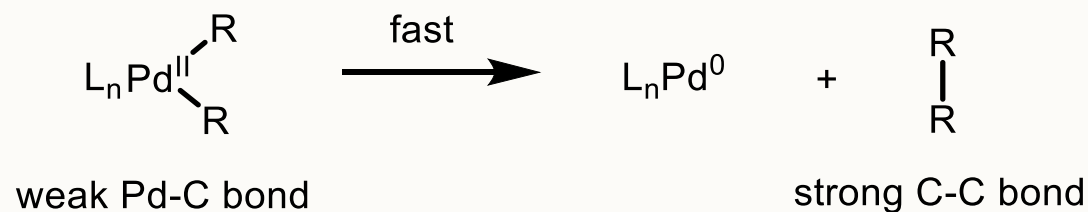


ligands *trans*:
reductive elimination does not occur.

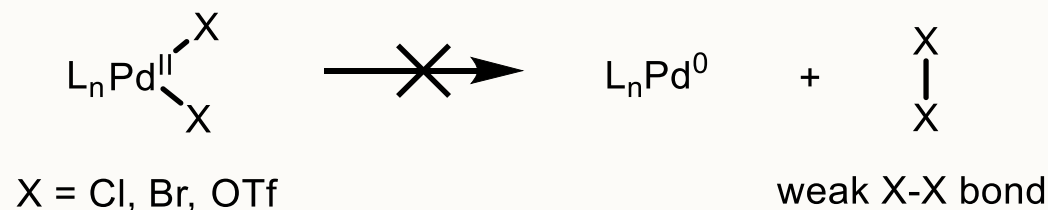


Fundamental reactions: Reductive elimination

- Driving force: thermodynamics (formation of stronger bonds).
 - Reductive elimination is easy and fast when strong bonds are formed:



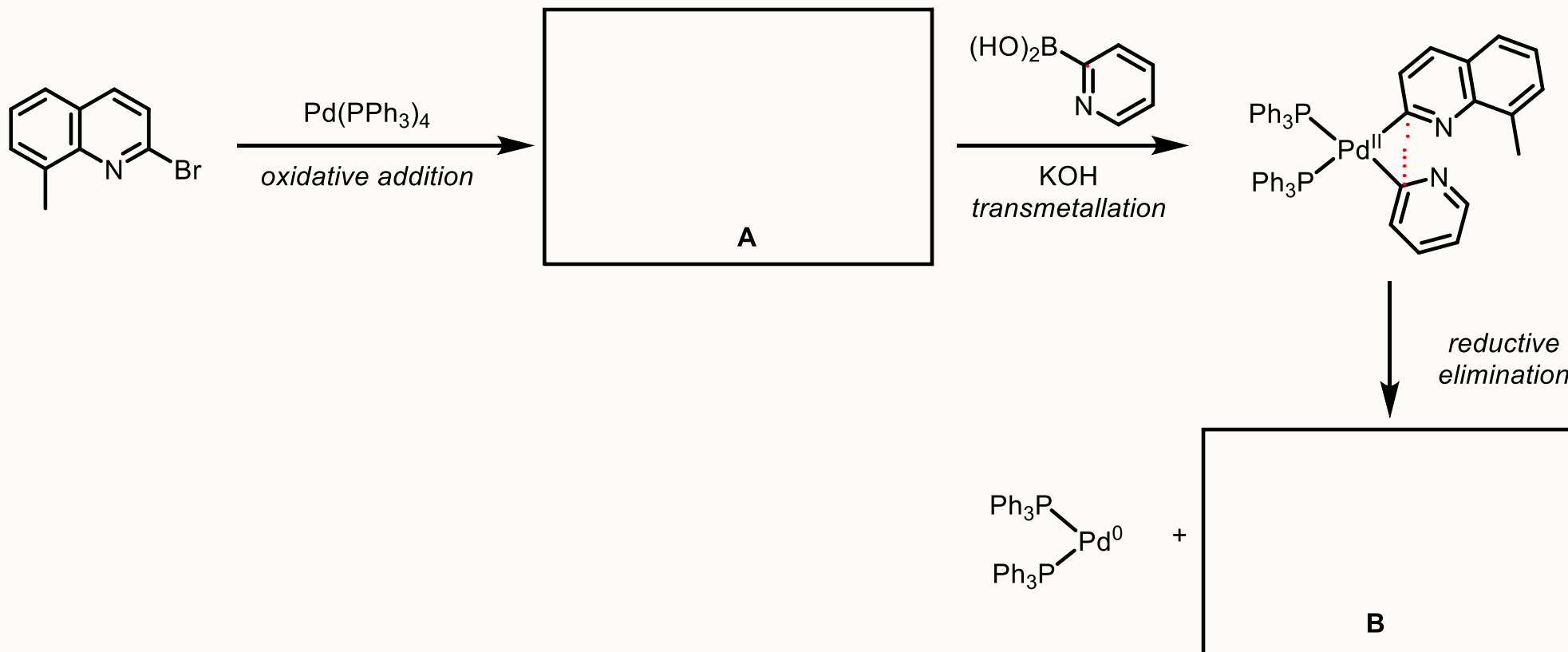
- It does not occur if the new bond would be weak:





Question

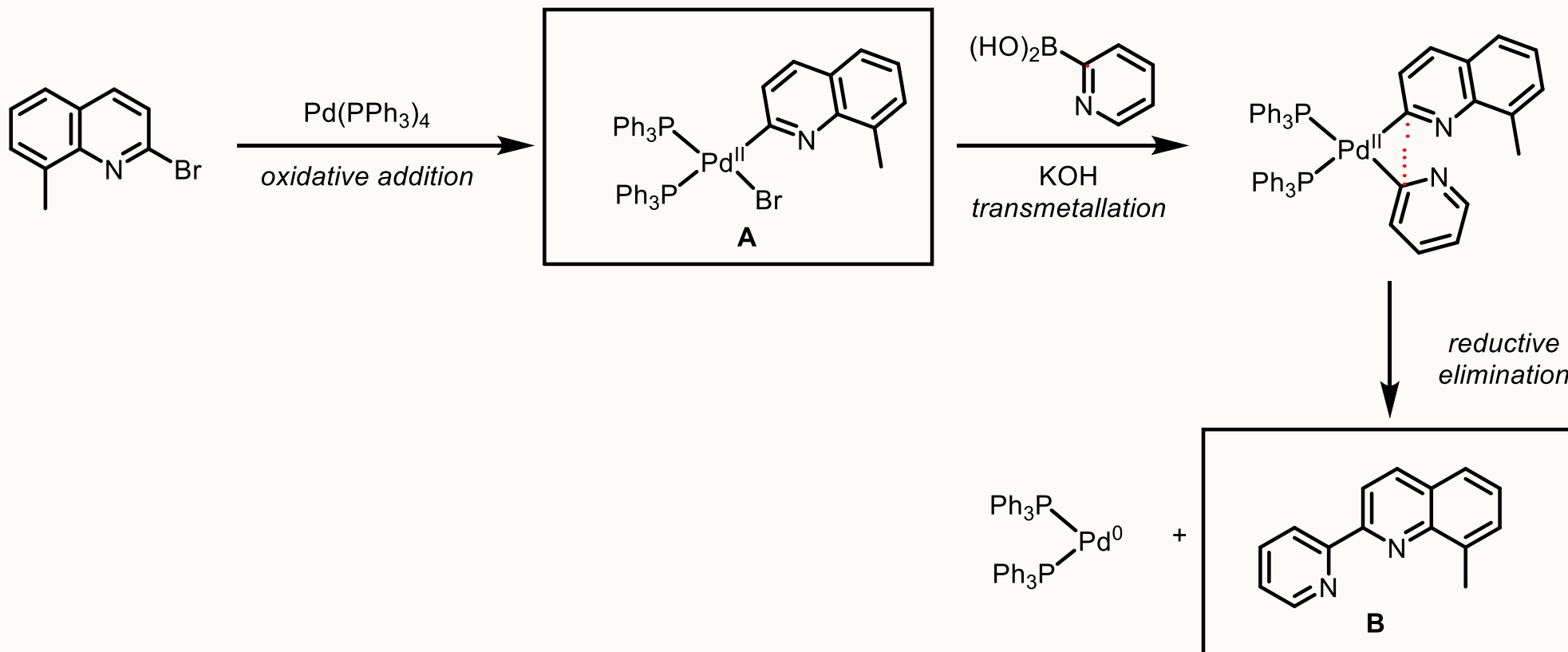
Draw the missing intermediates / products **A** and **B**:





Question

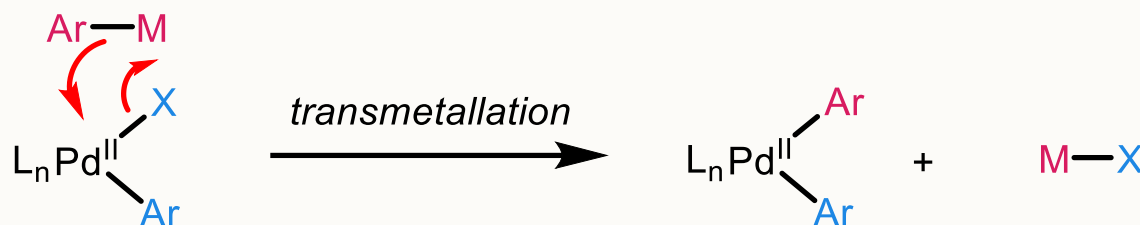
Draw the missing intermediates / products **A** and **B**:





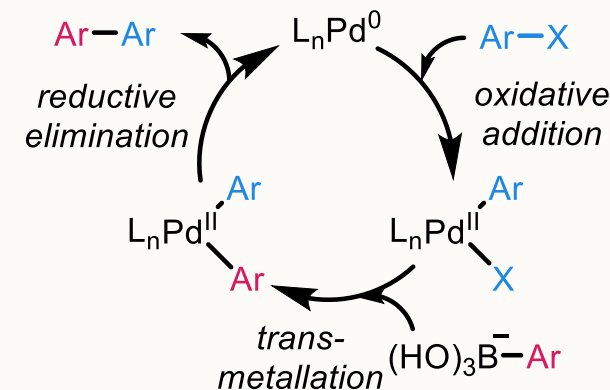
Fundamental reactions: Transmetallation

- Transmetallation transfers a carbon ligand from one metal (e.g. Li, Mg, Cu, Zn, B, Si, Sn) to another metal (e.g. Pd).

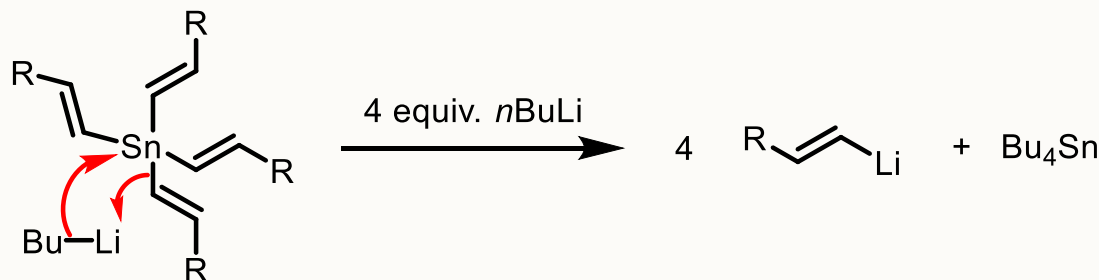


$M = \text{ZnX}, \text{SnBu}_3, ^-\text{B}(\text{OH})_3$, etc.

driving force:
strong M-X bond



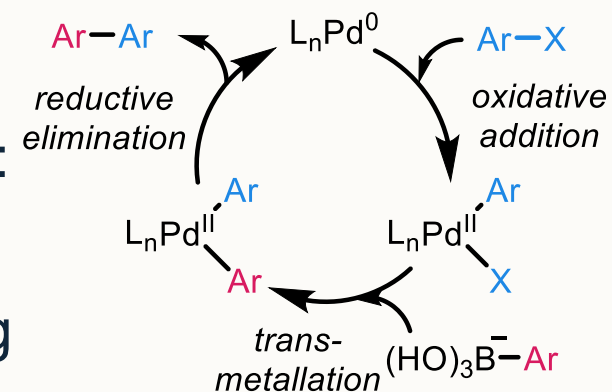
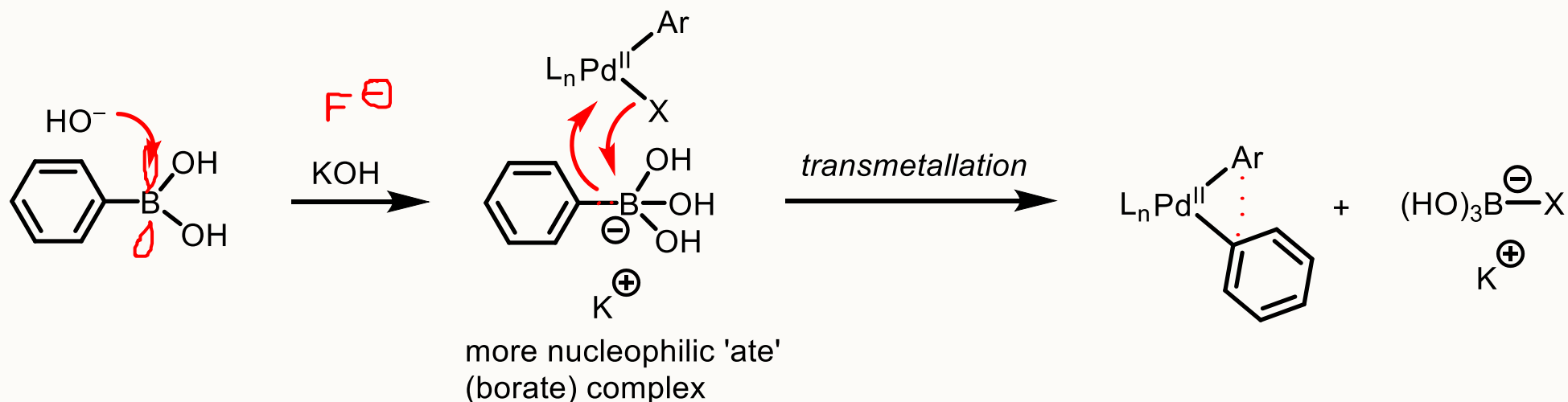
- This step is important, because it allows the transfer of different groups onto palladium which can then be coupled together in the reductive elimination step.
- We have seen transmetallation before: tin-lithium exchange (lecture 2).





Fundamental reactions: Transmetallation

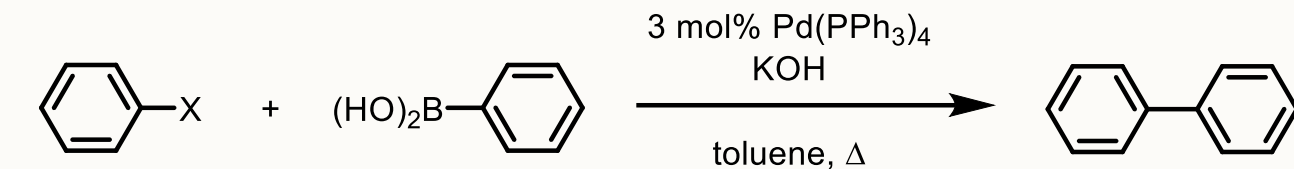
- What is the role of the base in the Suzuki reaction?
- Boronic acids are not very nucleophilic (C–B bond not very polarised): transmetallation is slow.
- The base acts as an activator, increasing nucleophilicity by generating a negatively charged 'ate' complex, and speeds up transmetallation:



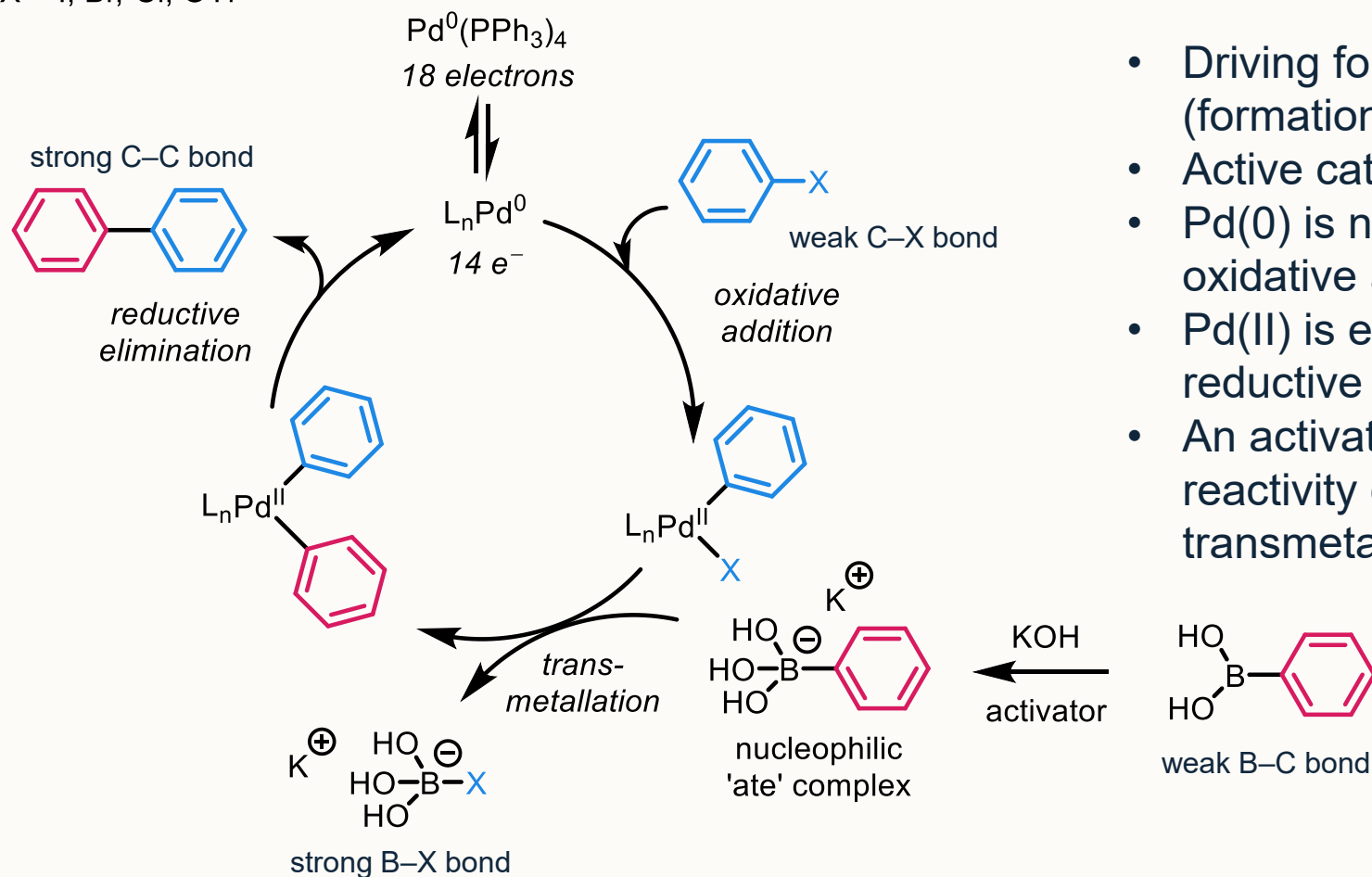
- Other activators can be used, e.g. CsF (F^- has a very high affinity for B) .



Summary: The Suzuki reaction



X = I, Br, Cl, OTf

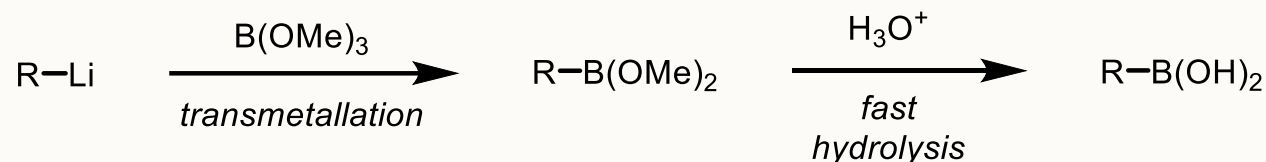


- Driving force: thermodynamics (formation of strong C–C and B–X bonds).
- Active catalyst is coordinatively unsaturated.
- Pd(0) is nucleophilic (electron-rich) and undergoes oxidative addition.
- Pd(II) is electrophilic (electron-poor) and undergoes reductive elimination.
- An activator (HO^- or F^-) is required to increase the reactivity of the boronic acid coupling partner for transmetallation.

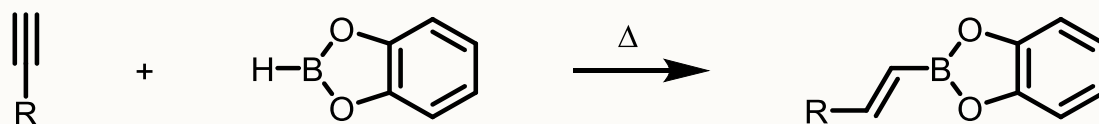


Boronic acids: the coupling partners in Suzuki reactions

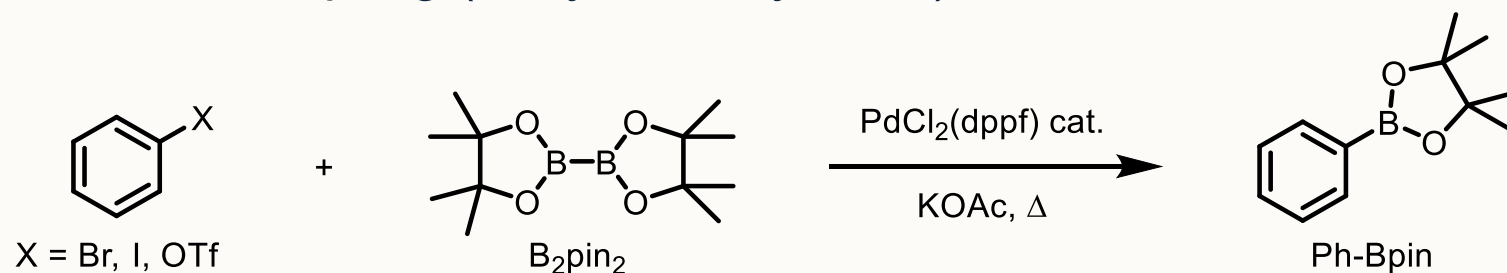
- Boronic acids and esters are readily available reagents that can be made in different ways.
 - Transmetallation from organolithium reagents:



- Hydroboration of alkynes and alkenes:



- Pd cross-coupling (Miyaura borylation):

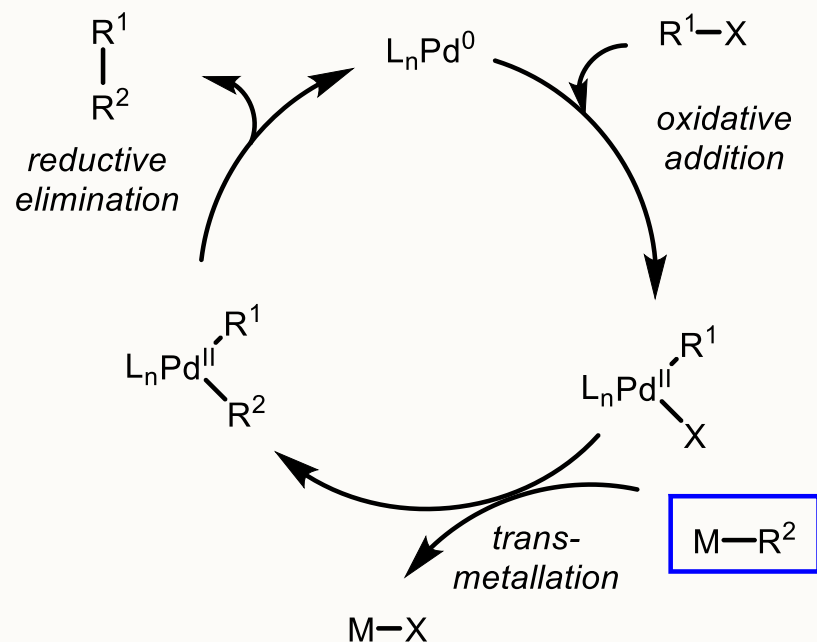


- But if the required boronic acid is not available, we can do a different cross-coupling reaction.



Alternative coupling partners

- If the boronic acid / ester coupling partner for a Suzuki reaction is not available, a different transmetallating reagent can be used:



$M = SnBu_3$	Stille reaction
$M = ZnX$	Negishi reaction
$M = Li$	Murahashi reaction
$M = SiMe_3$	Hiyama reaction

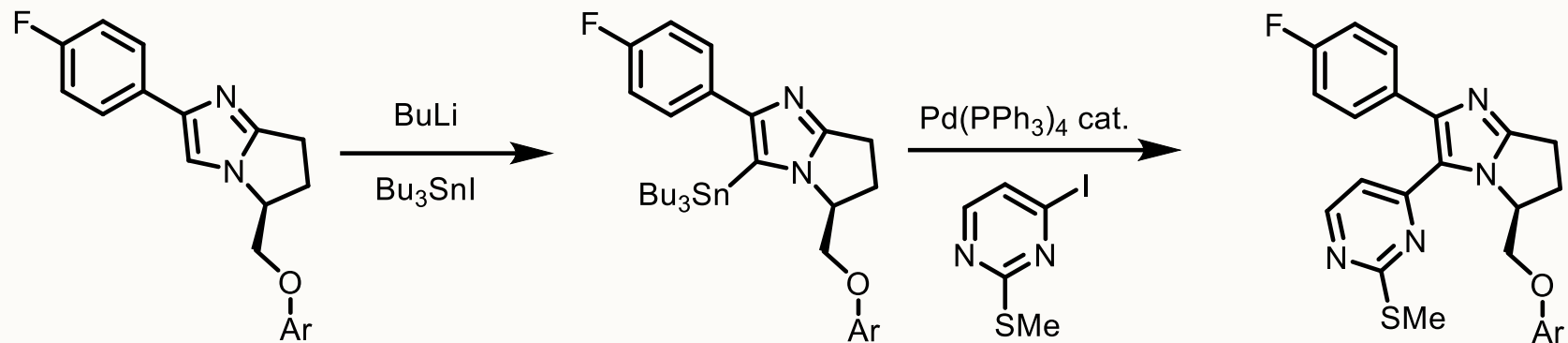


Alternative coupling partners

	Advantages	Disadvantages
Suzuki ($M = B(OH)_2$)	Very reliable, good substrate scope. Boronic acids readily available.	Activation necessary.
Hiyama ($M = SiMe_3$)		Similar reactivity to $R-B(OH)_2$: activation necessary.
Stille ($M = SnBu_3$)	Good functional group compatibility. More reactive than $R-B(OH)_2$: no activator necessary.	Very toxic!
Negishi ($M = ZnX$)	Good functional group compatibility. More reactive than $R-B(OH)_2$: no activator necessary.	Organozinc species are very air and moisture sensitive.
Murahashi ($M = Li$)	More reactive than $R-B(OH)_2$: no activator necessary.	Organolithium species are incompatible with many functional groups.



Example in medicinal chemistry



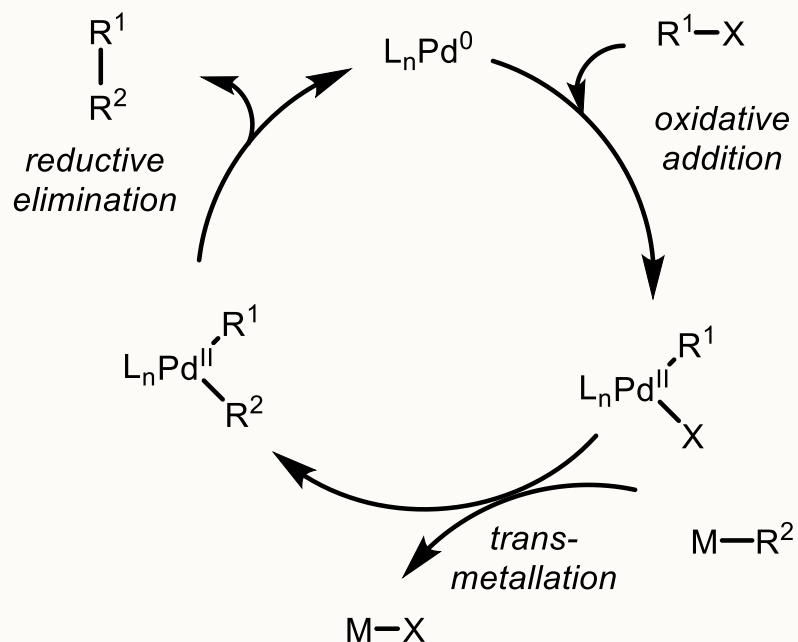
JNK3 inhibitor
drug target for
neurodegenerative disorders



Summary

In the last two lectures, you learnt about:

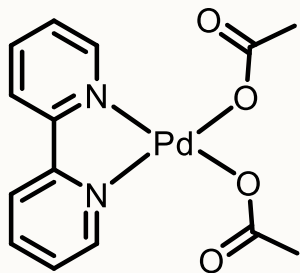
- The stability and reactivity of palladium catalysts: Palladium catalysts are more stable than organometallic reagents (R-MgBr and R-Li).
- The three fundamental reactions that make up the catalytic cycle of the Suzuki cross-coupling reaction (a powerful transformation for C–C bond formation): oxidative addition, transmetalation and reductive elimination.



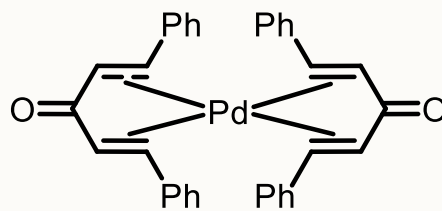


Practice questions

1. Determine the Pd oxidation state and electron count of the following complexes:

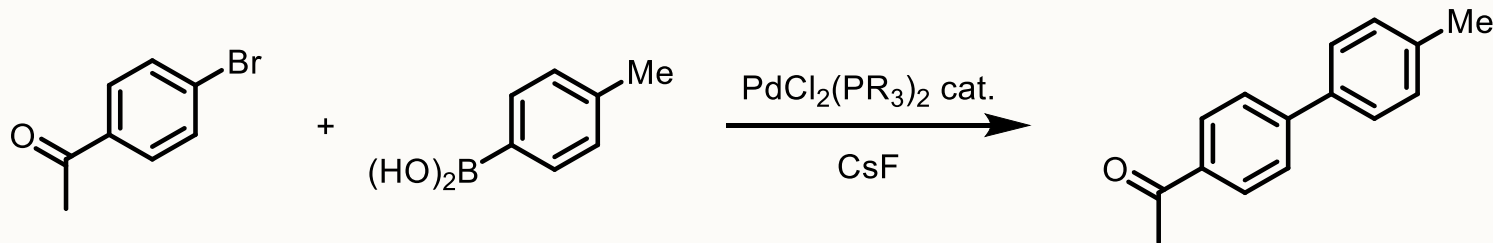


(bipy)Pd(OAc)₂



Pd(dba)₂

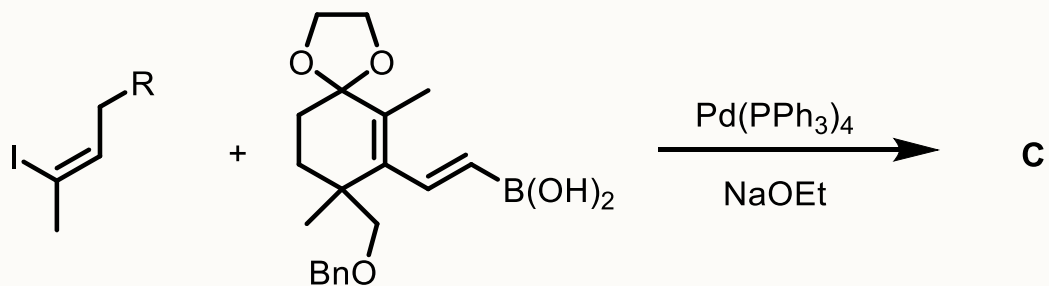
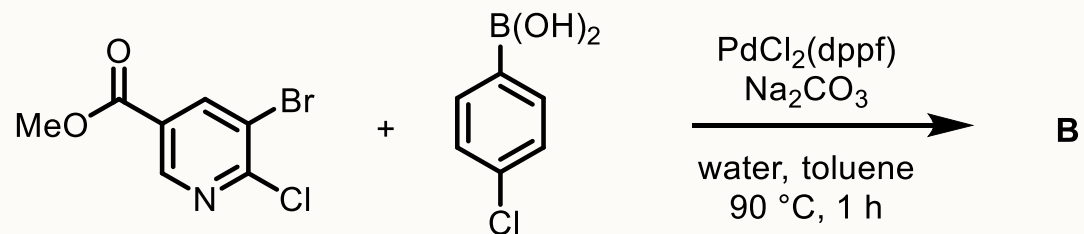
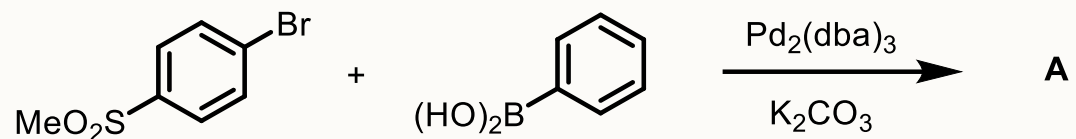
2. Draw a catalytic cycle for the following Suzuki reaction:





Practice questions

3. Draw the product of the following Suzuki reactions:

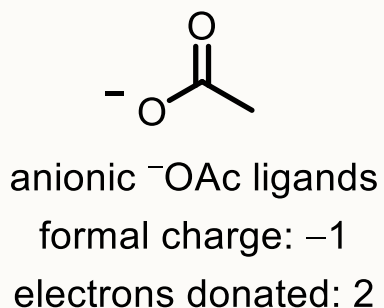
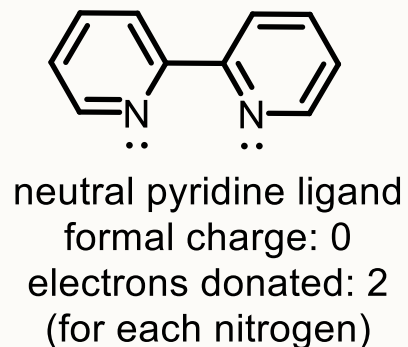
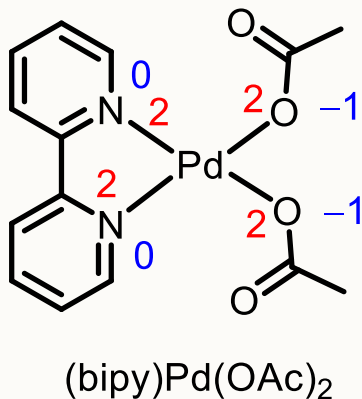




Lecture 5+6 practice questions – answers

1. Determine the Pd oxidation state and electron count in the following complexes:

formal charge: electrons:



$$\text{oxidation state} = 0 - [2 \times (-1)] = 2: \text{Pd}^{\text{II}}$$

$$\text{electrons: } (10 - 2) + (4 \times 2) = 16 e^-$$

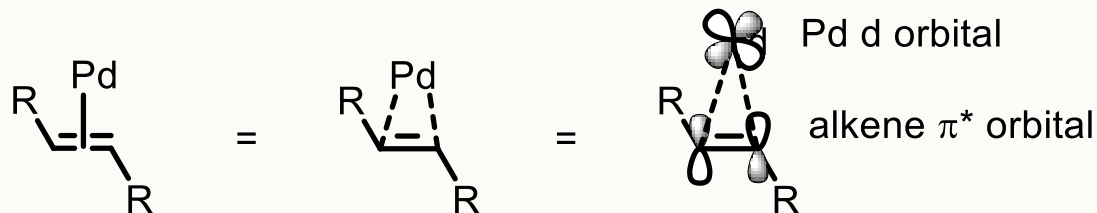
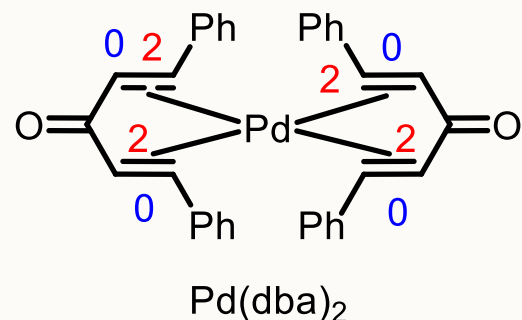
$$\begin{aligned} \text{oxidation state} &= 0 - (\text{ligand charge}) \\ e^- &= (10 - \text{OS}) + (\text{ligand } e^-) \end{aligned}$$



Lecture 5+6 practice questions – answers

1. Determine the Pd oxidation state and electron count in the following complexes:

formal charge: electrons:



alkene ligand (η^2 bonding: the metal interacts with π^* orbitals on both alkene carbons)

formal charge: 0

electrons donated: 2

(for each alkene)

oxidation state = $0 - [4 \times 0] = 0$: Pd⁰

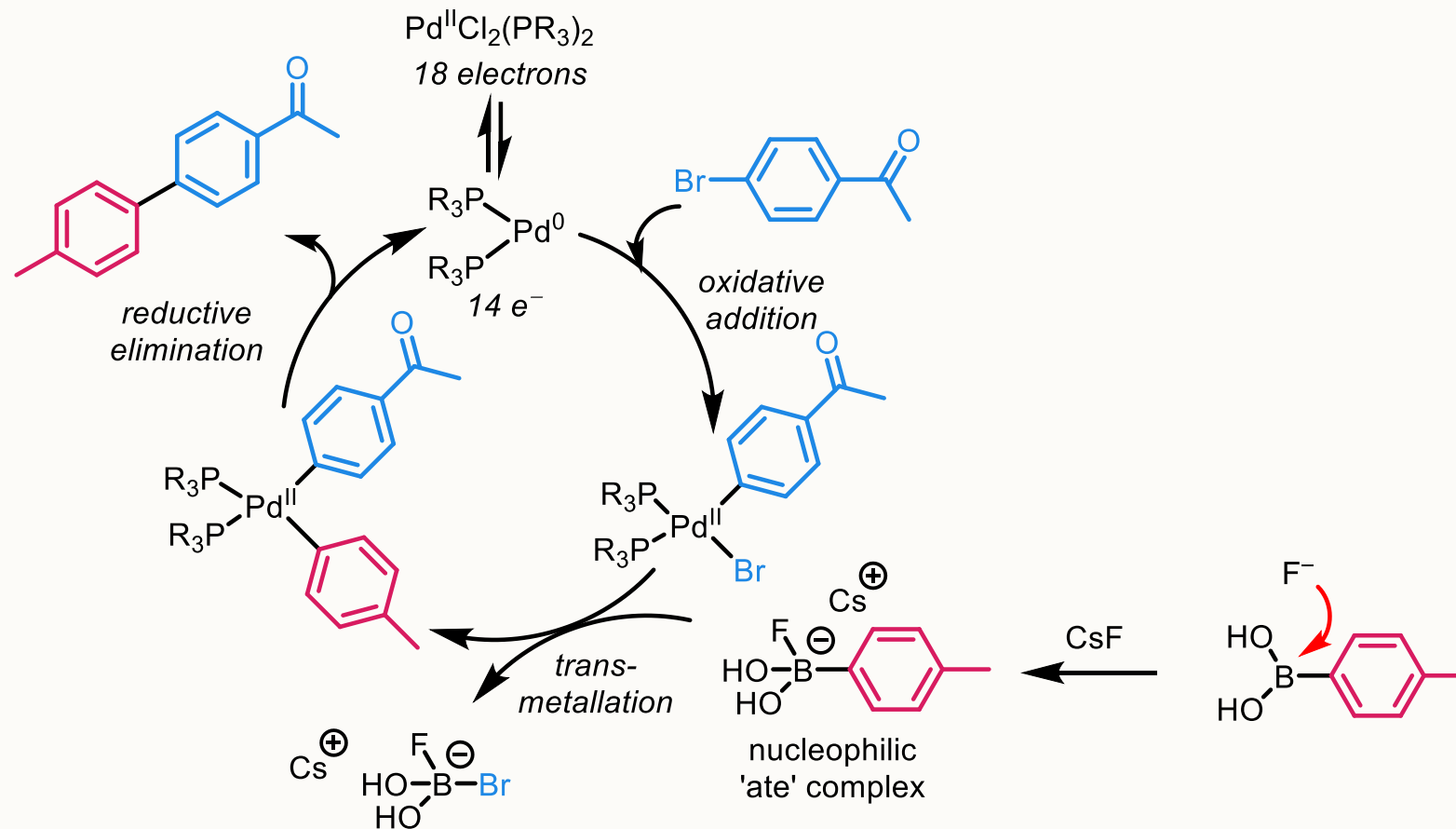
electrons: $10 + (4 \times 2) = 16 \text{ e}^-$

oxidation state = $0 - (\text{ligand charge})$
 $\text{e}^- = (10 - \text{OS}) + (\text{ligand e}^-)$



Lecture 5+6 practice questions – answers

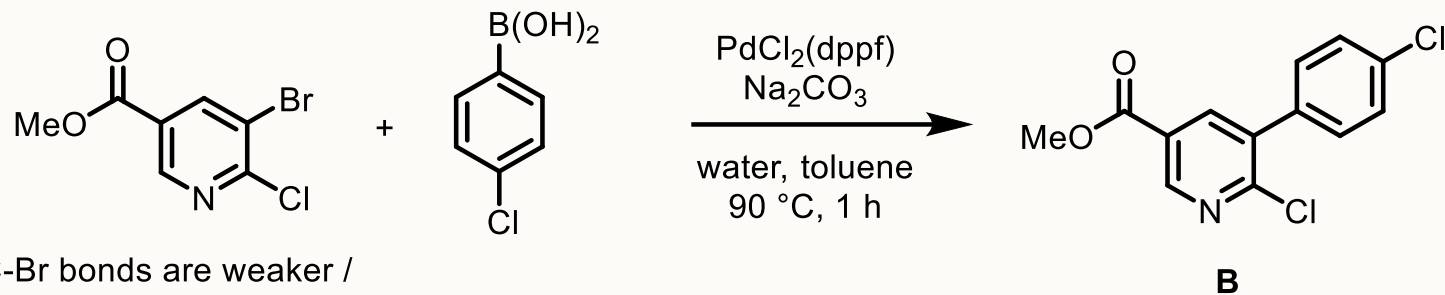
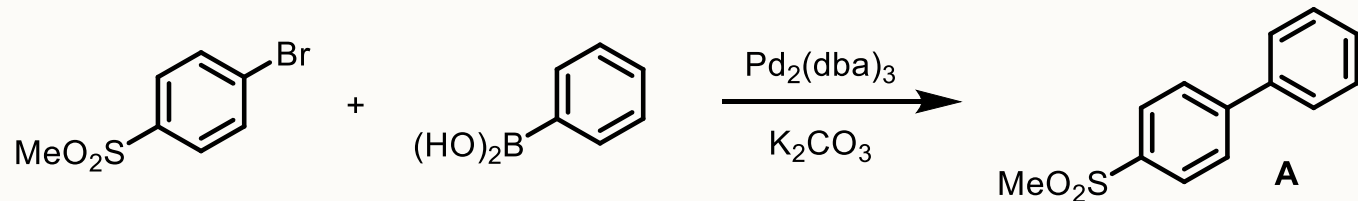
2. Draw a catalytic cycle for the following Suzuki reaction:



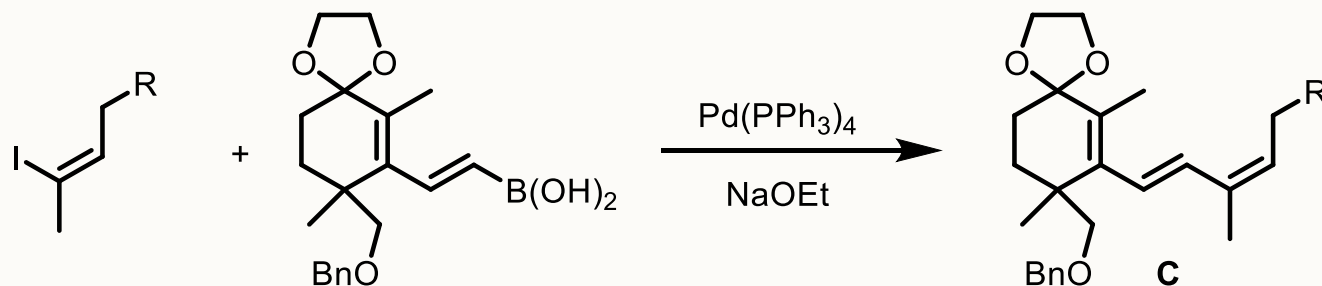


Lecture 5+6 practice questions – answers

3. Draw the product of the following Suzuki reactions:



C-Br bonds are weaker /
more reactive than C-Cl bonds



Alkenes can also be coupled in Suzuki reactions.



University of
Nottingham

UK | CHINA | MALAYSIA

CHEM3065 Synthesis and Reactive Intermediates

O'Duill lecture 7

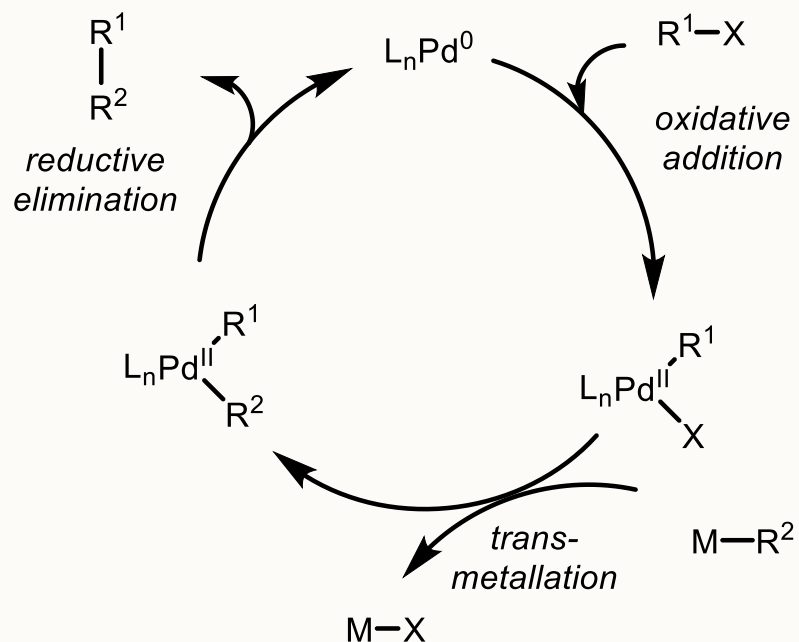
miriam.oduill@nottingham.ac.uk



Recap lectures 5+6

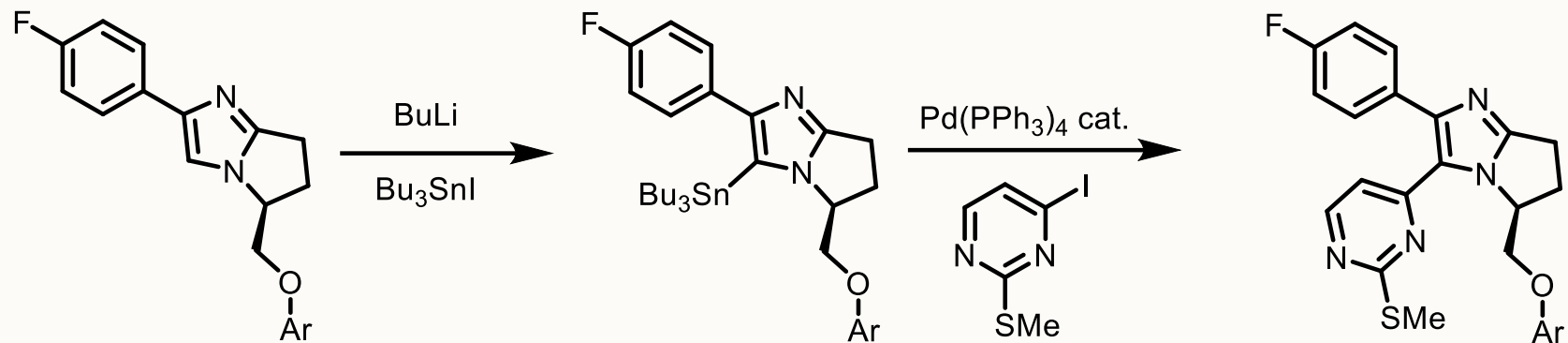
In the last two lectures, you learnt about:

- The stability and reactivity of palladium catalysts;
- the three fundamental reactions that make up the catalytic cycle of the Suzuki cross-coupling reaction: oxidative addition, transmetalation and reductive elimination.





Example in medicinal chemistry



JNK3 inhibitor
drug target for
neurodegenerative disorders



Topic 7: The Heck reaction

The Heck reaction

Learning outcomes

In this lecture, you will learn about:

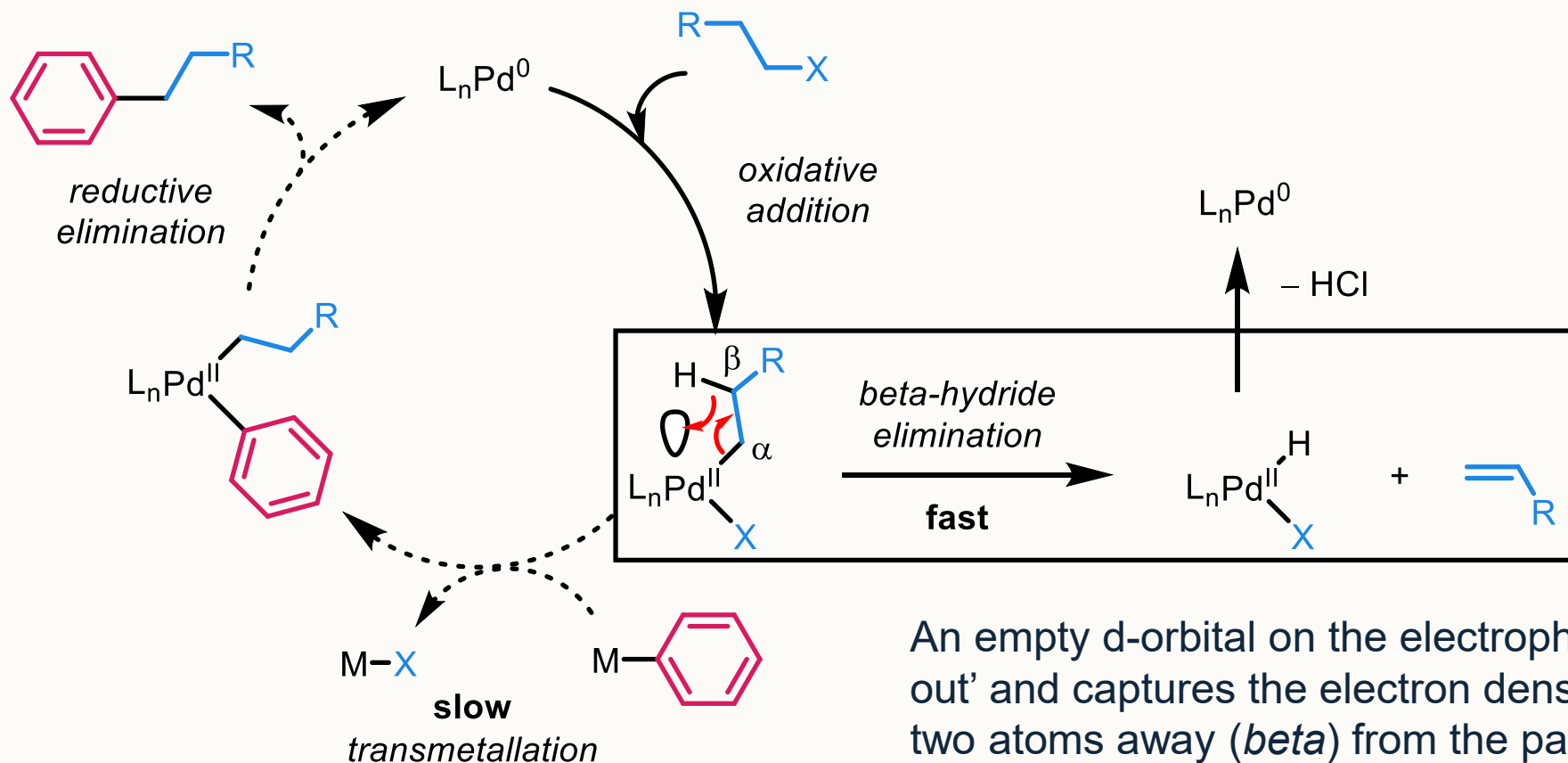
- two more fundamental reactions in palladium catalysis: *beta*-hydride elimination and ligand migration / carbometallation;
- their role in the Heck reaction.
- How allylic electrophiles react with soft nucleophiles under Pd catalysis.

Recommended Reading: Clayden, Organic Chemistry, Chapter 40



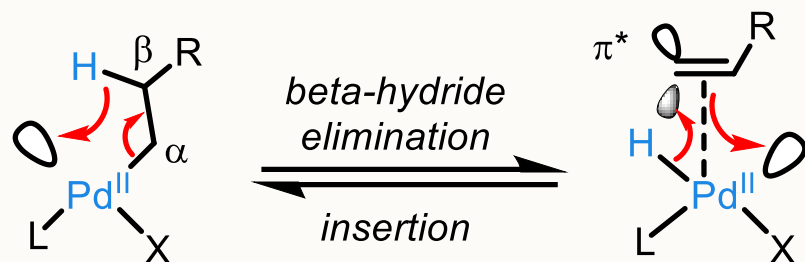
Fundamental reactions: β -Hydride elimination

- Alkyl halides ($R(sp^3)-X$) are rarely used in Pd cross-coupling reactions because the Pd(II) σ -alkyl complex rapidly decomposes by *beta*-hydride elimination:



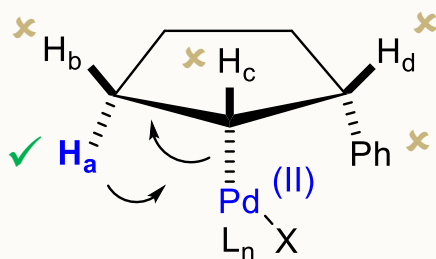


Fundamental reactions: β -Hydride elimination



For a 3D animation of this process, see:
<https://www.chemtube3d.com/pdheck/>

- A *cis* free coordination site on palladium is required.
- Palladium is not oxidised or reduced in this process.
- β -Hydride elimination is **syn** specific, *i.e.* only H_a is eliminated in this complex:

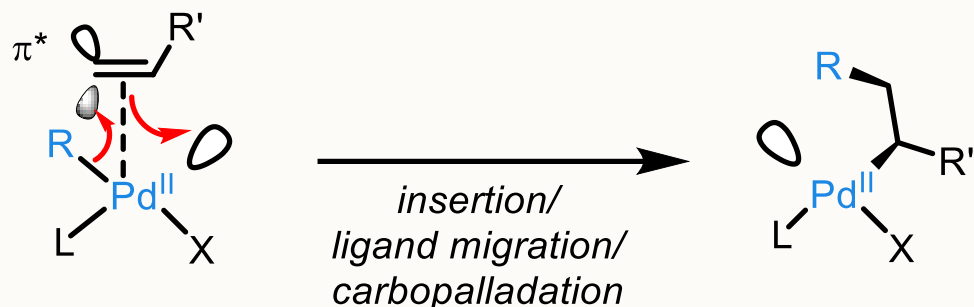


- β -Hydride elimination is reversible. The reverse process is called insertion.



Fundamental reactions: Insertion, Carbometallation / Ligand migration

- Carbons (R groups) can undergo insertion reactions as well. In this case, we call the process ligand migration or carbometallation.

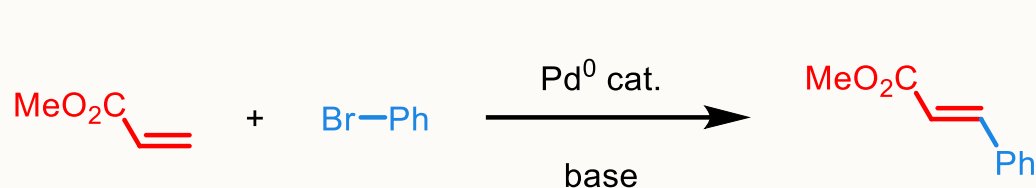


- Pd is not oxidised or reduced.
- The reaction is **syn**-specific (R and Pd add to the same face of the alkene).
- Regioselectivity: R attaches to the less substituted end of the double bond (to avoid steric clash with the substituents on the alkene).
- The reverse process does not occur readily.



The Heck Reaction

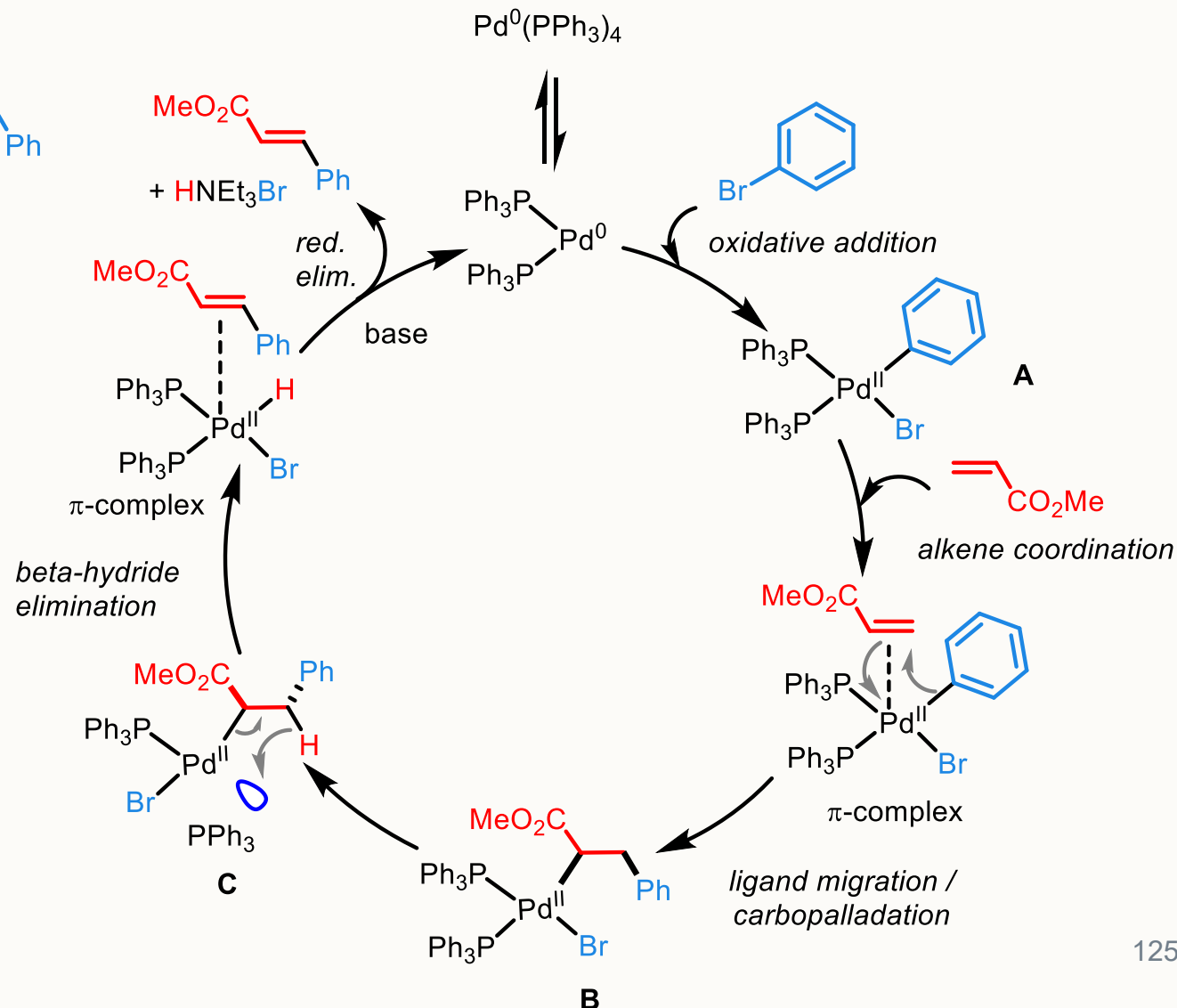
- β-Hydride elimination and carbopalladation are important steps in the Heck reaction:



A: Pd^{II} is electrophilic: coordinates to electron-rich alkene.

B: Carbopalladation: Pd-C and C-Ph bonds form at the same time, so these groups are *cis* to each other, but Pd and H must be *cis* for β-H elimination to occur: rotate this C-C bond.

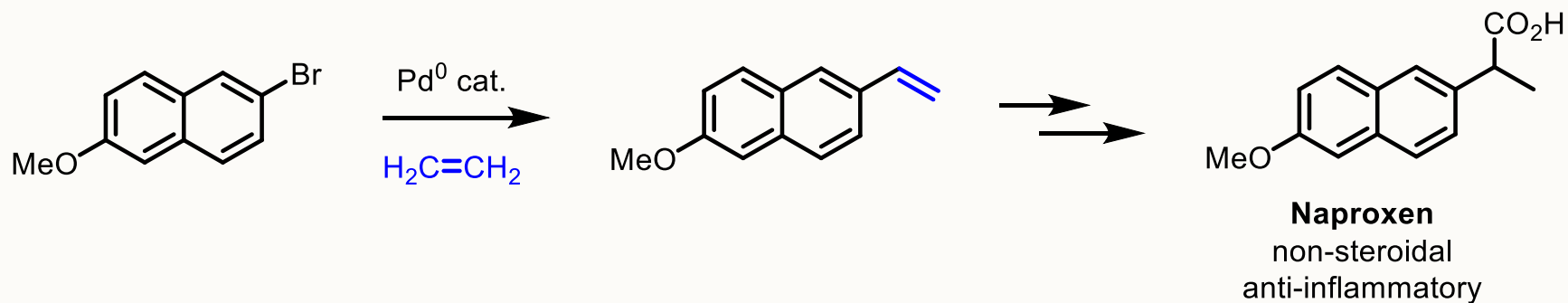
C: Dissociation of PPh₃ gives a free coordination site (empty d orbital) on Pd required for β-H elimination.





The Heck reaction: An example from medicinal chemistry

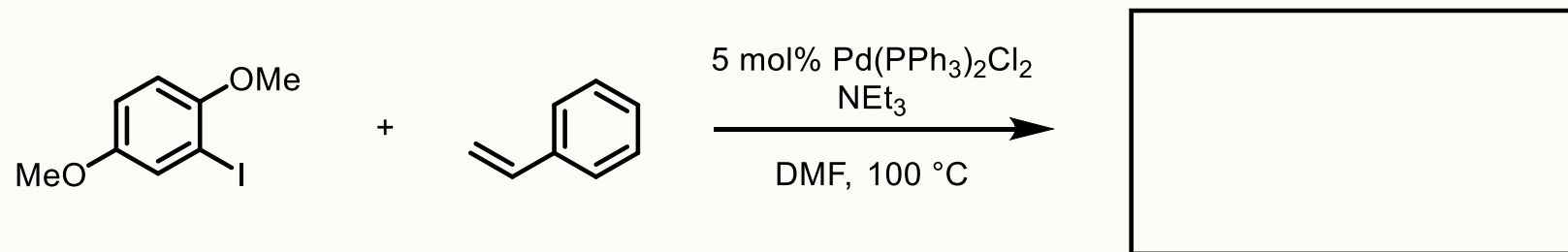
- Heck reaction in the synthesis of Naproxen:



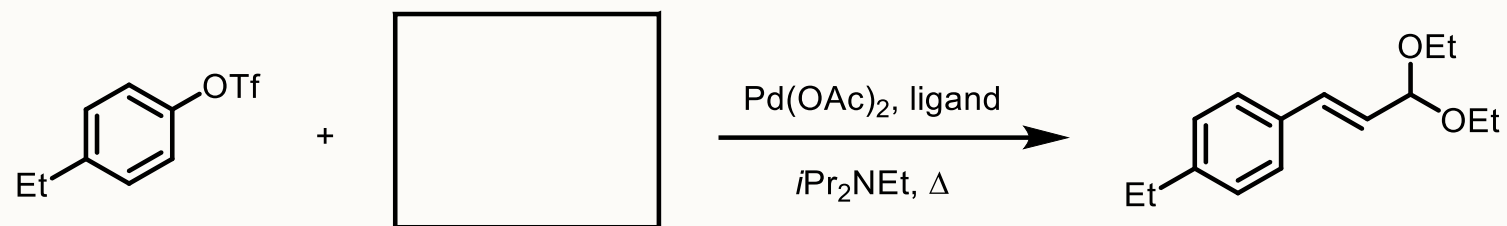


Questions

1. What is the product of the following Heck reaction:



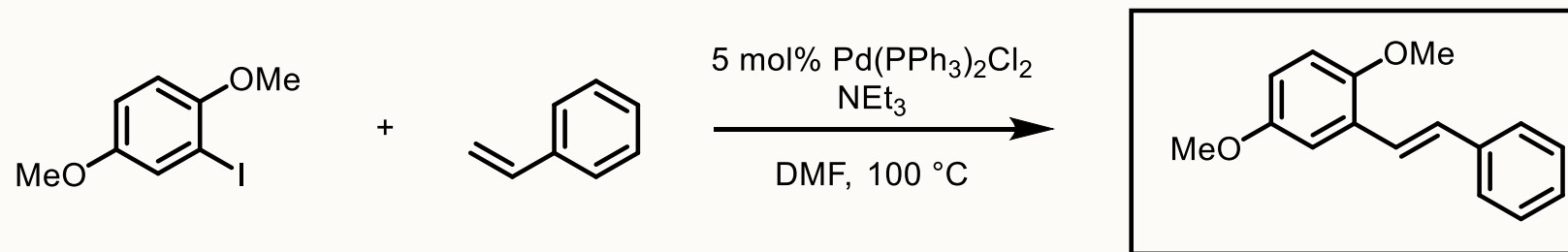
2. Propose a reagent for the following Heck reaction:



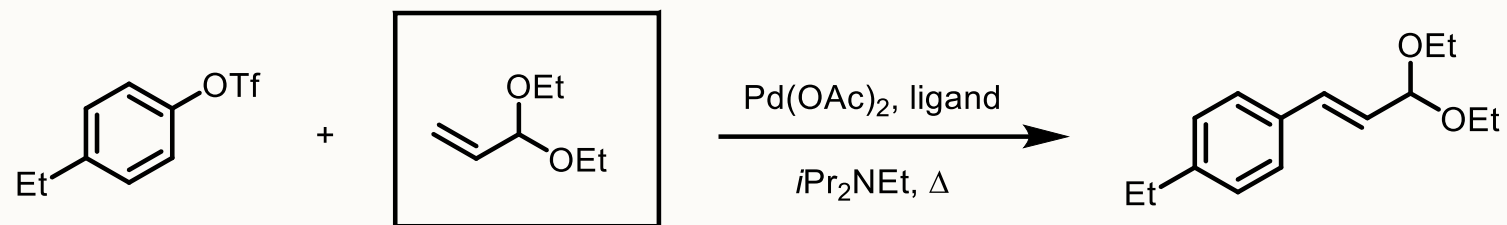


Questions

1. What is the product of the following Heck reaction:



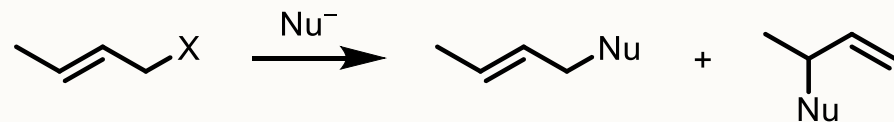
2. Propose a reagent for the following Heck reaction:



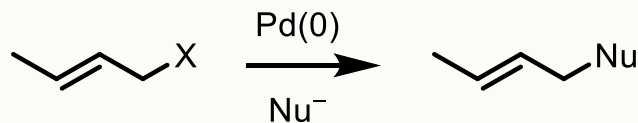


Pd catalysed allylation: The Tsuji-Trost reaction

- We saw previously that allyl electrophiles can undergo S_N2 and S_N2' reactions. This often gives a mixture of products:

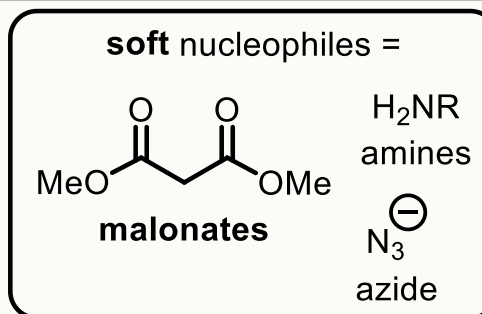
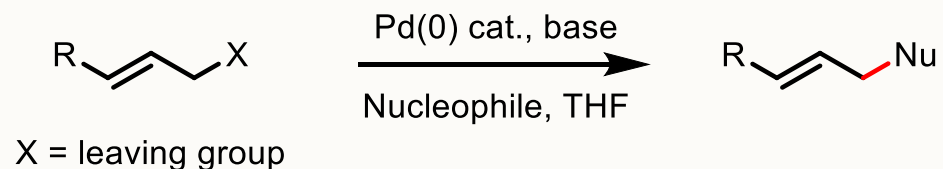


- Palladium catalysis allows for highly stereo- and regioselective allylation:

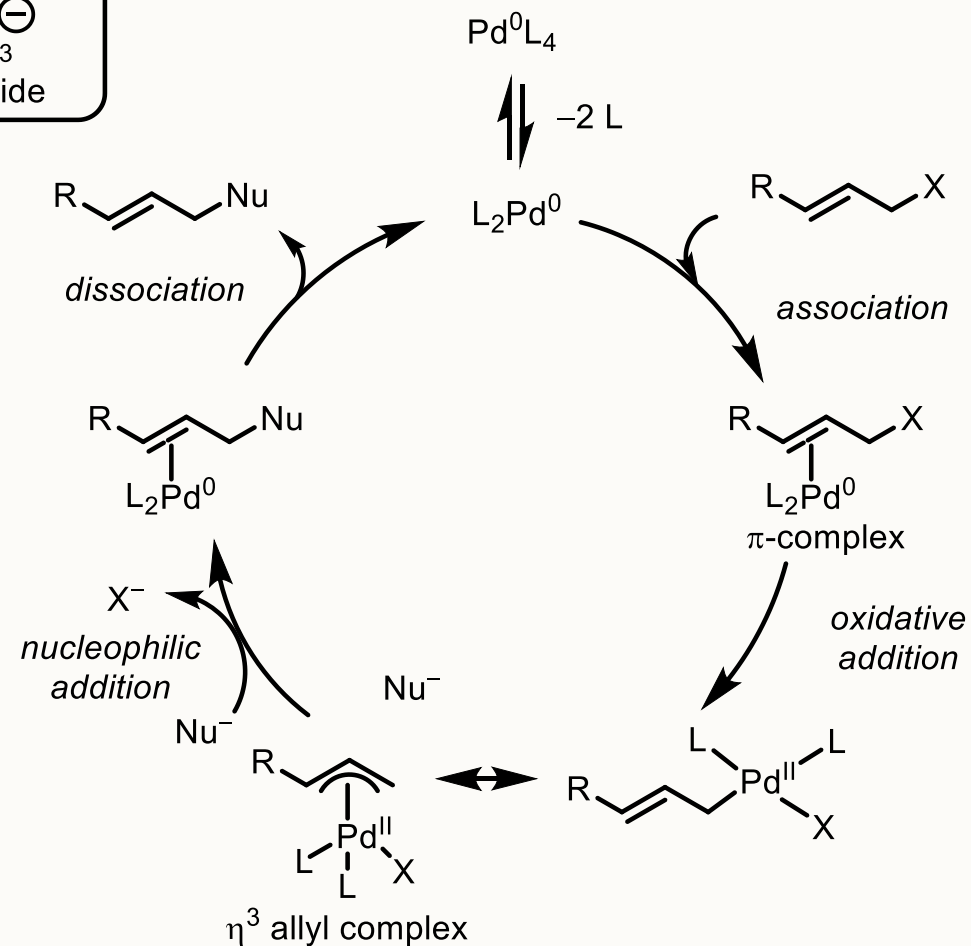
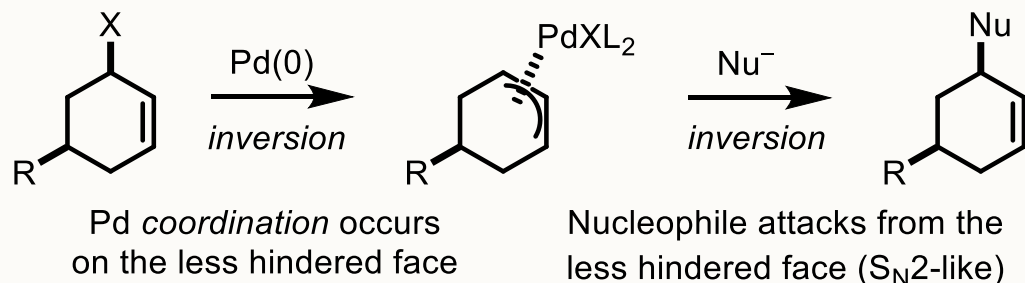




The Tsuji-Trost reaction



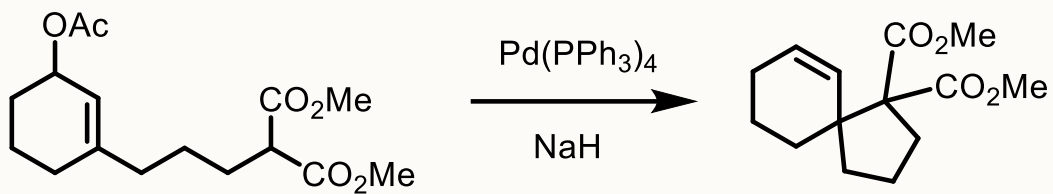
- Pd(0) coordinates to the alkene before undergoing oxidative addition to form a Pd-allyl complex stabilised by conjugation.
- The nucleophile attacks the sterically **less hindered** allylic position.
- The reaction occurs with retention of stereochemistry:



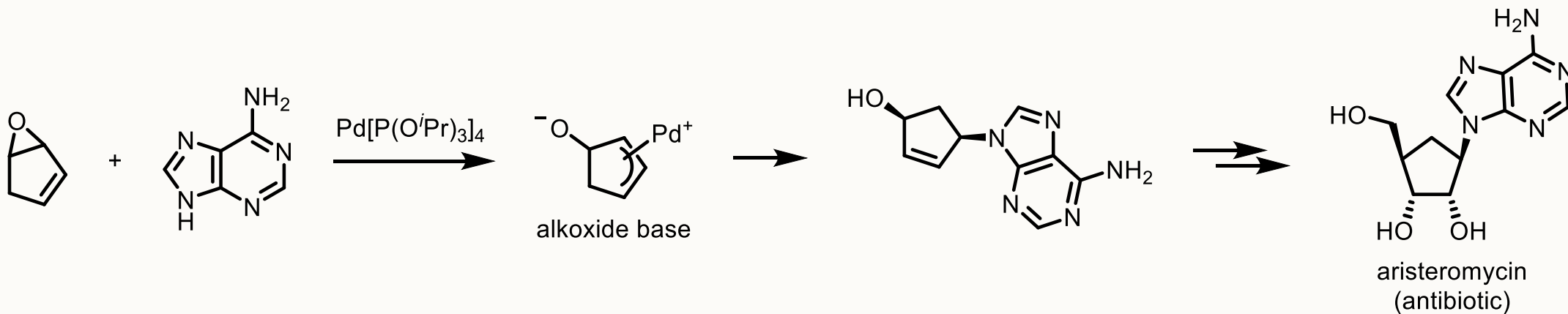


The Tsuji-Trost reaction: examples

- Intramolecular reactions give rings:



- Vinyl epoxides provide their own base:

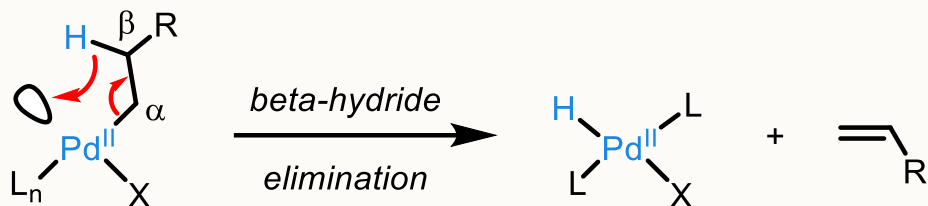




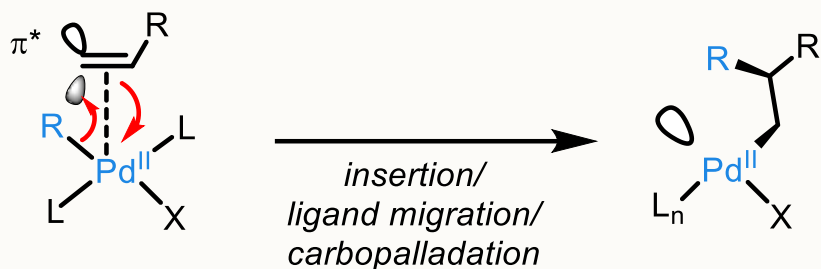
Summary Topic 7

In this part of the lecture, you learnt:

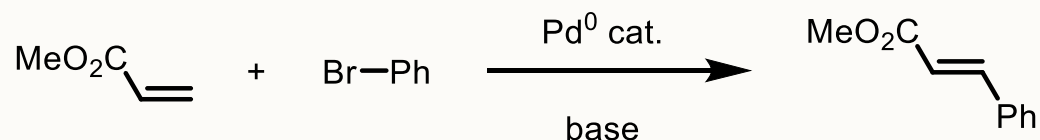
- that Pd(II) σ -alkyl complexes undergo rapid *beta*-hydride elimination:



- that electrophilic Pd(II) complexes can react with alkenes:



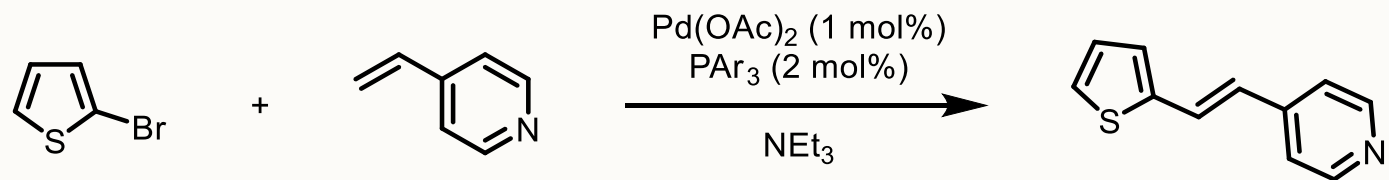
- how these two processes play a key role in the Heck cross-coupling reaction:



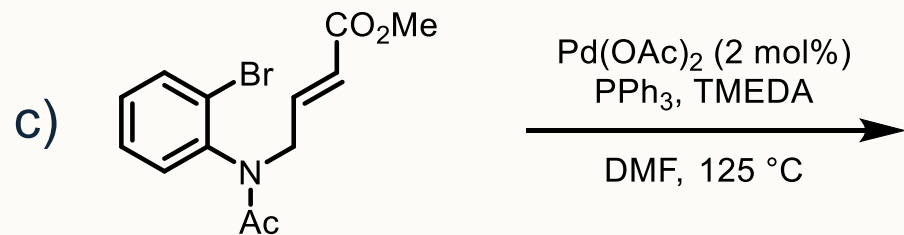
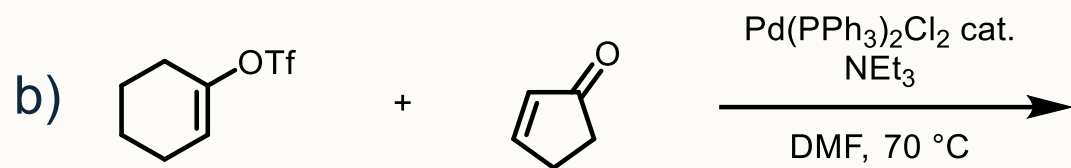
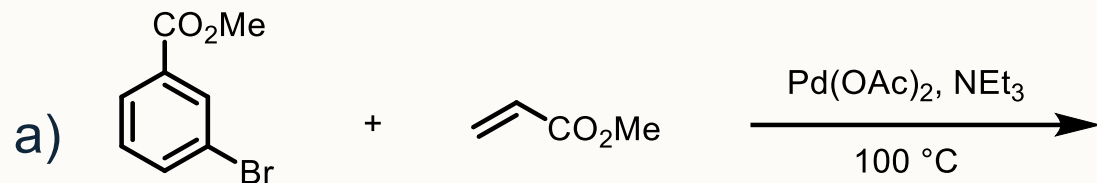


Practice questions

1. Draw the catalytic cycle for the following Heck reaction:



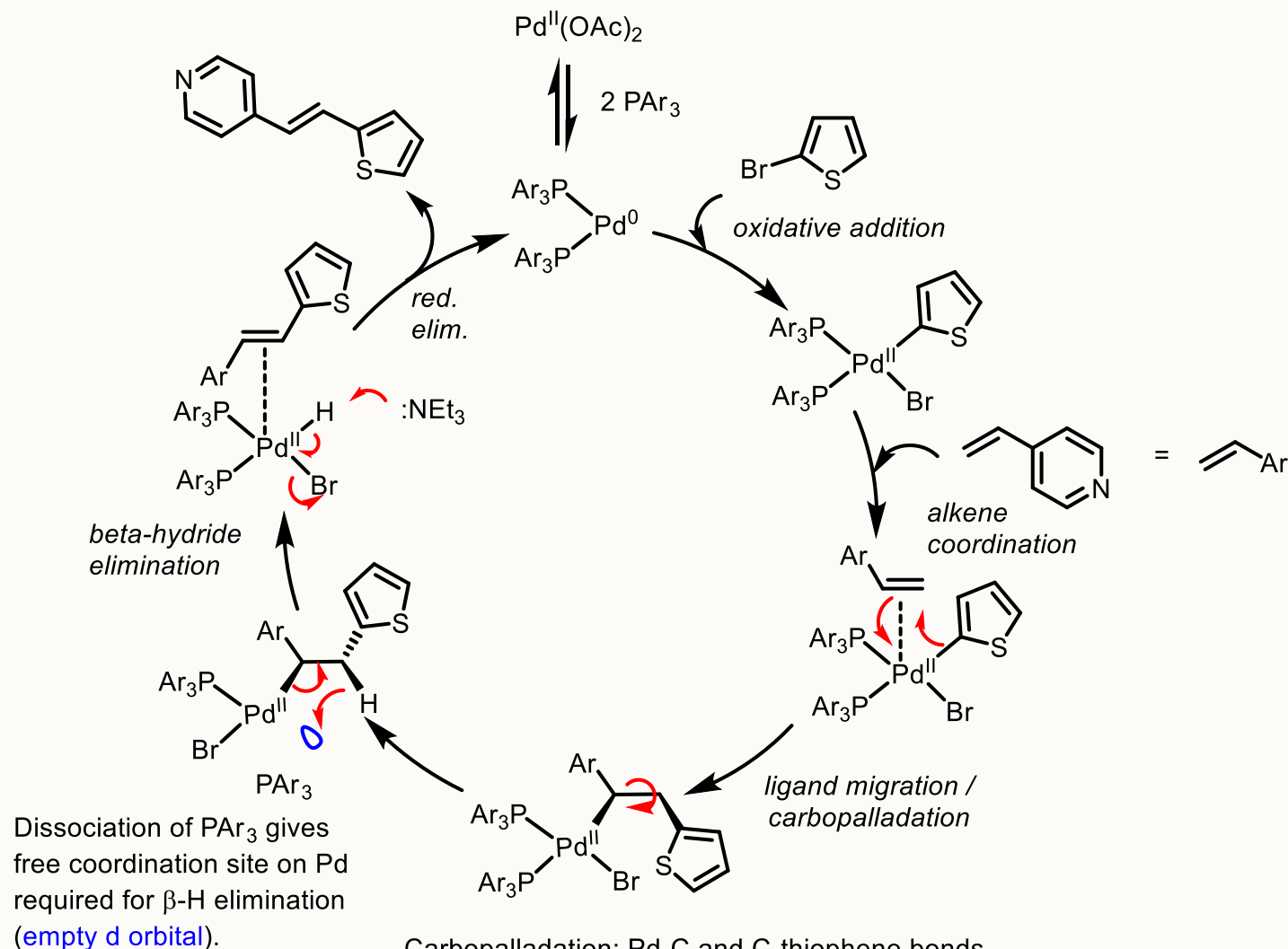
2. Identify the products of the following Heck reactions:





Lecture 7 practice questions – answers

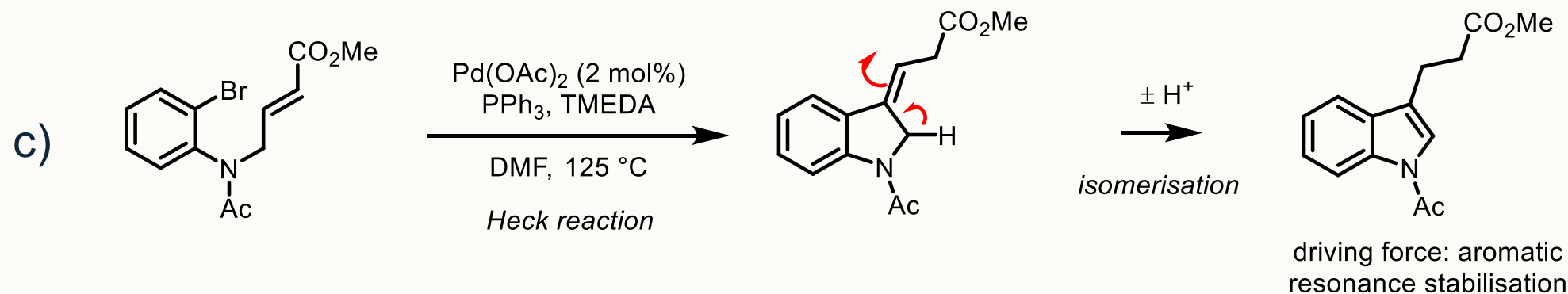
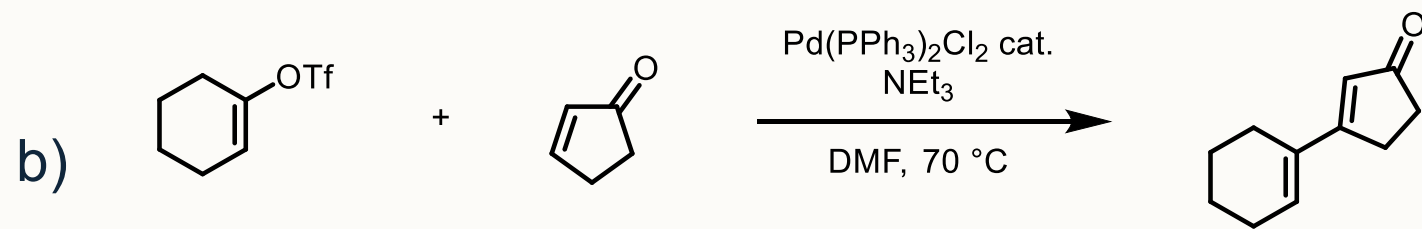
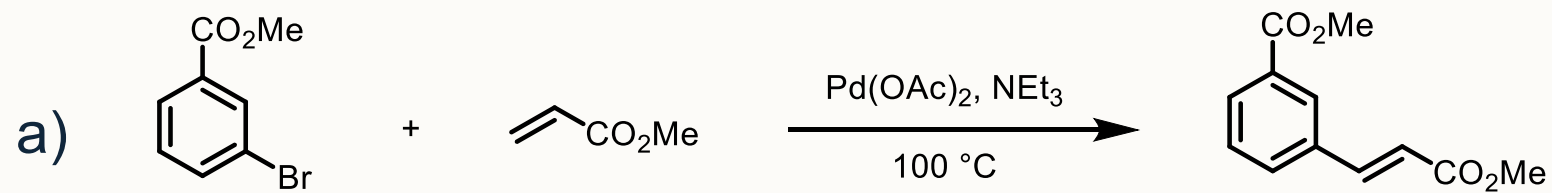
1. Heck catalytic cycle:





Lecture 7 practice questions – answers

2. Identify the products of the following Heck reactions:





University of
Nottingham

UK | CHINA | MALAYSIA

CHEM3065 Synthesis and Reactive Intermediates

O'Duill lecture 8

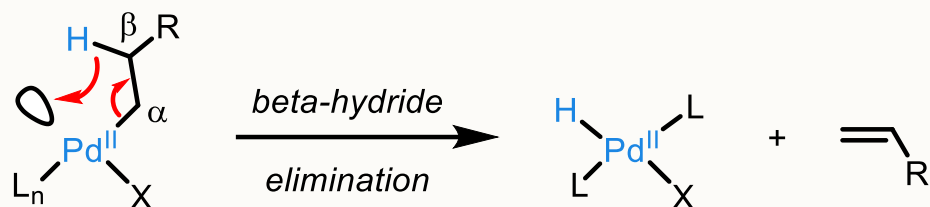
miriam.oduill@nottingham.ac.uk



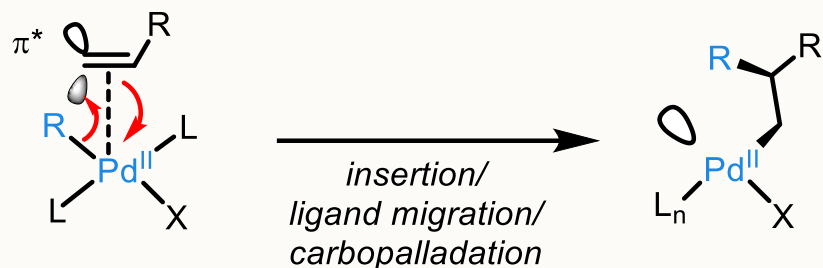
Recap lecture 7

In the last lecture, you learnt:

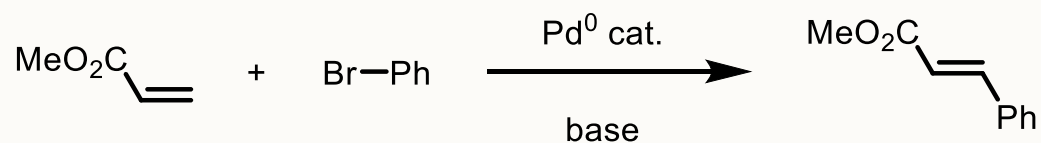
- that Pd(II) σ -alkyl complexes undergo rapid *beta*-hydride elimination:



- that electrophilic Pd(II) complexes can react with alkenes:



- how these two processes play a key role in the Heck cross-coupling reaction:





Lecture 8: The Buchwald-Hartwig reaction

The Buchwald-Hartwig reaction

Learning outcomes

In this lecture, you will learn:

- how to form C–N bonds using palladium catalysis,
- how this reaction compares to S_NAr chemistry.

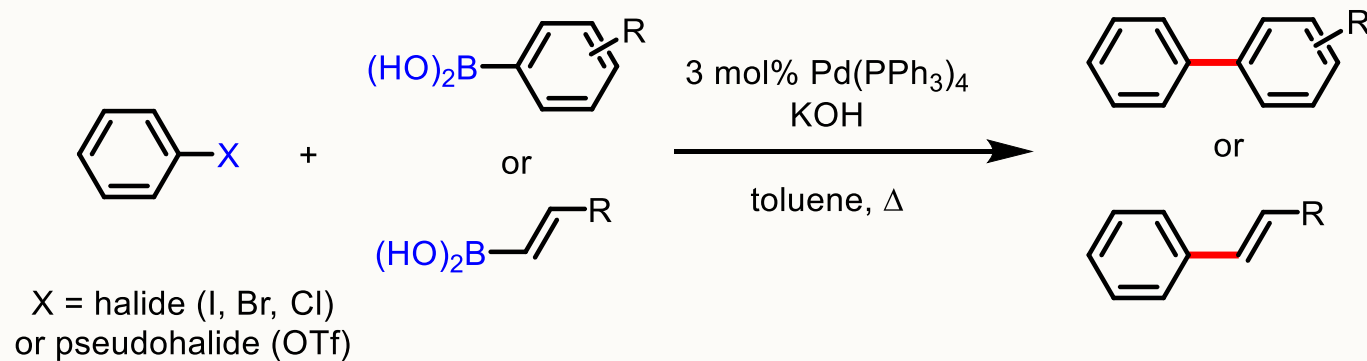
Recommended Reading: Clayden, Organic Chemistry, Chapter 40



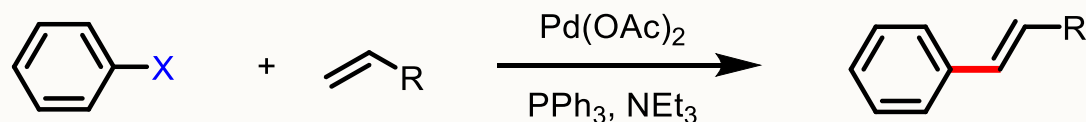
Recap: Pd catalysed cross-coupling reactions

- The reactions we have seen so far, have been C–C cross-coupling reactions:

- Suzuki reaction:



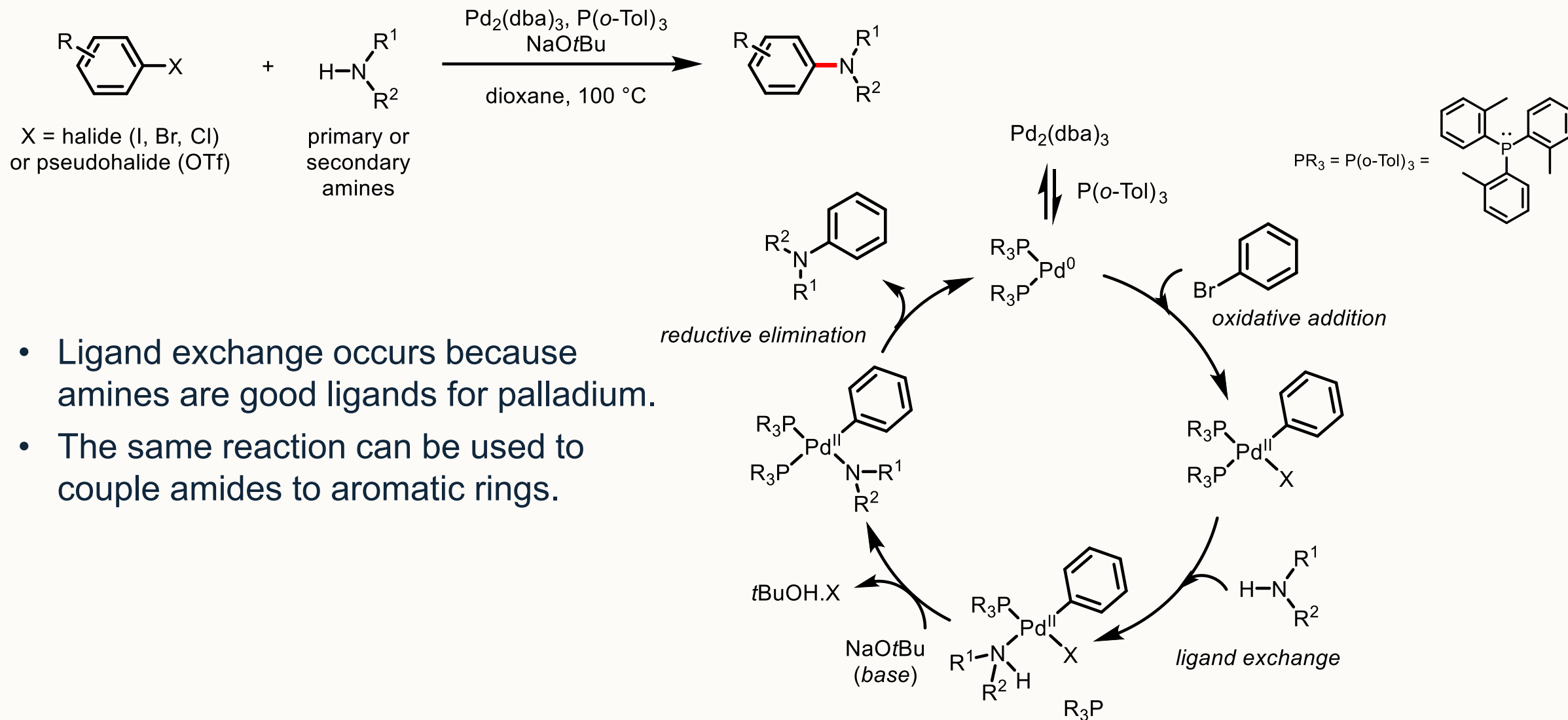
- Heck reaction:



- But it is also possible to form carbon–heteroatom bonds through Pd cross-coupling reactions.



The Buchwald-Hartwig reaction: C–N formation

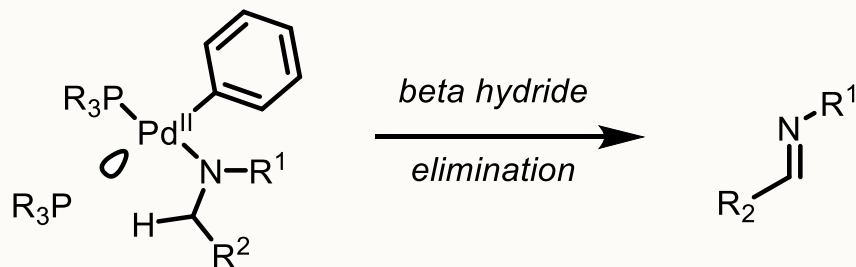


- Ligand exchange occurs because amines are good ligands for palladium.
- The same reaction can be used to couple amides to aromatic rings.

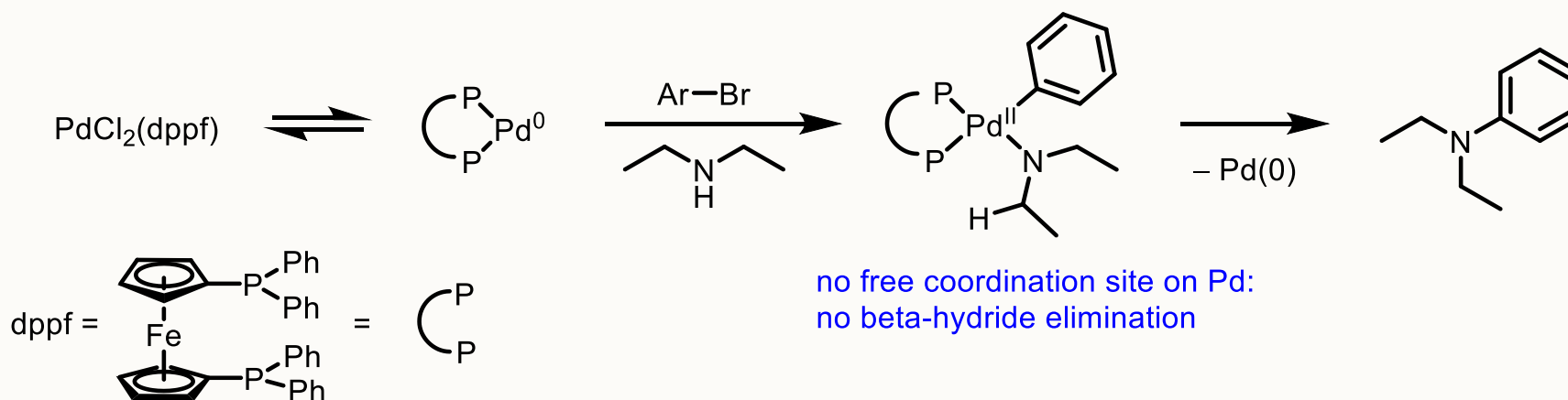


The Buchwald-Hartwig reaction: C–N formation

- When alkyl amines are used in this reaction, competing *beta*-hydride elimination can lead to unwanted by-products:



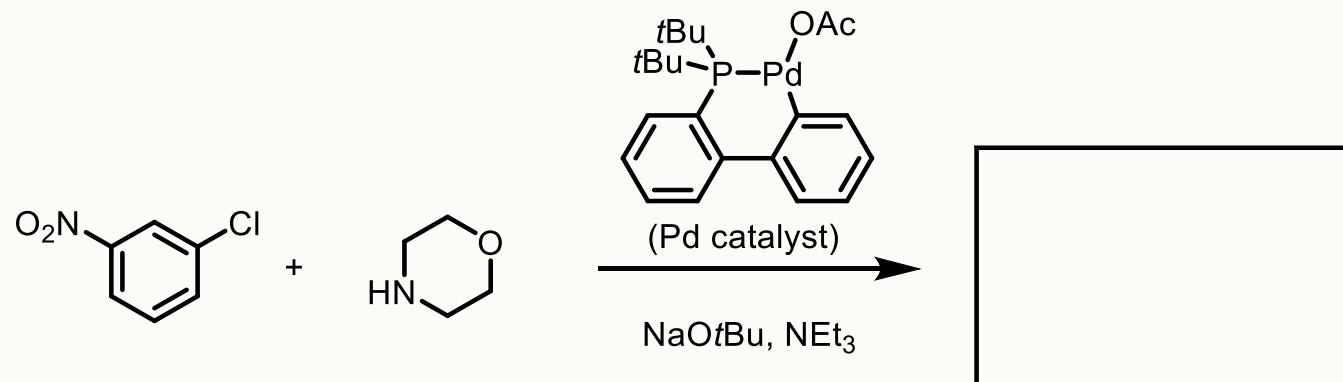
- Chelating phosphine ligands can suppress *beta*-hydride elimination by blocking the vacant coordination site required for this process, e.g. dppf:



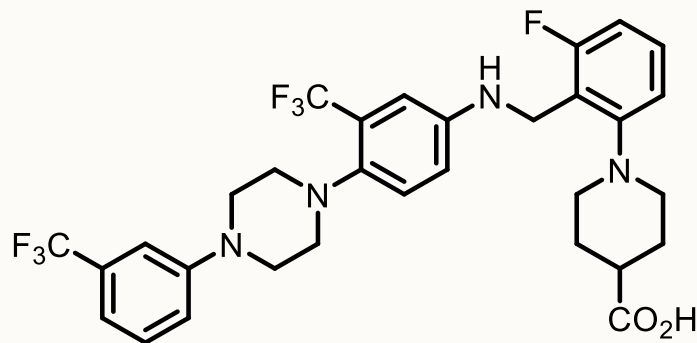


Question

Draw the product of the following Buchwald-Hartwig cross-coupling reaction:



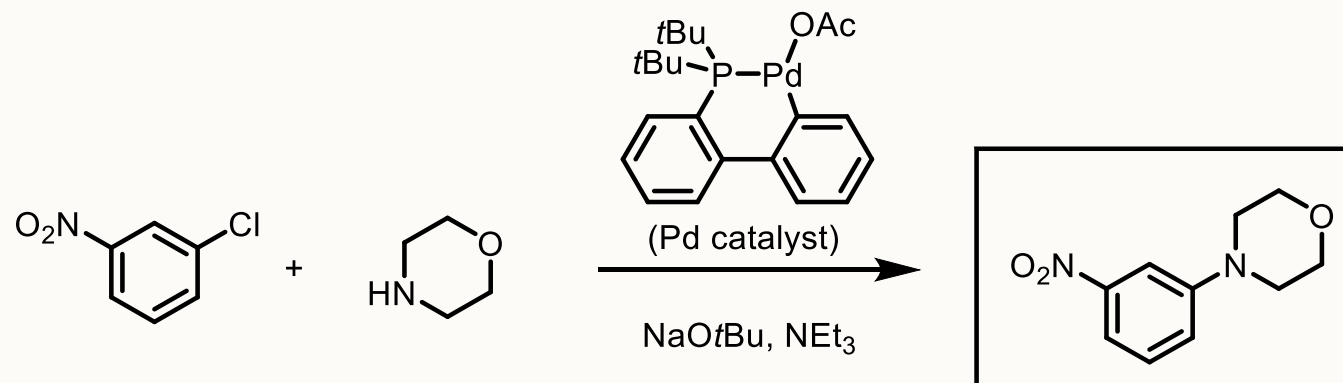
The molecule below is a drug to control blood clotting. Identify the bonds that could be made via Buchwald-Hartwig cross coupling.



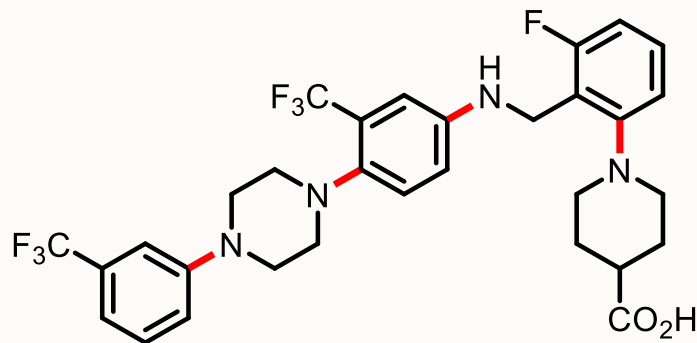


Question

Draw the product of the following Buchwald-Hartwig cross-coupling reaction:



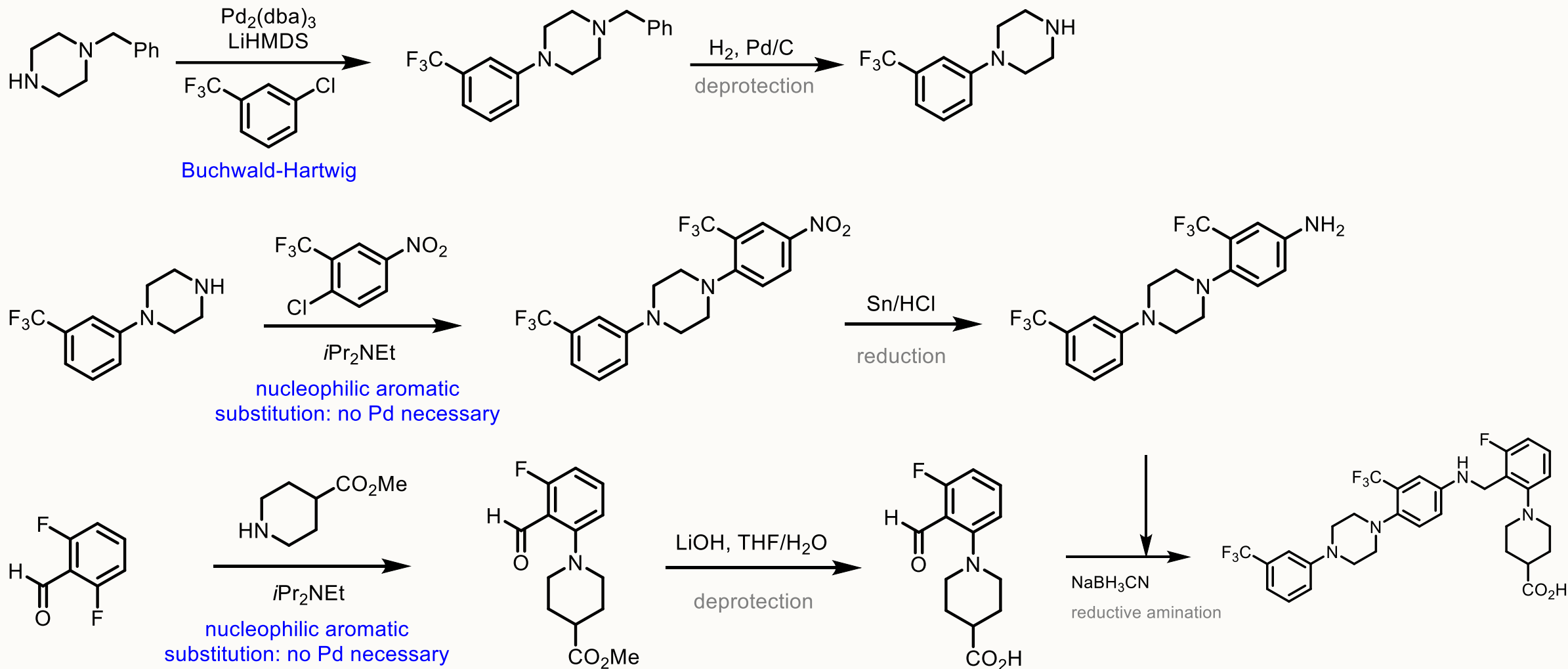
The molecule below is a drug to control blood clotting. Identify the bonds that could be made via Buchwald-Hartwig cross coupling.





Application in medicinal chemistry

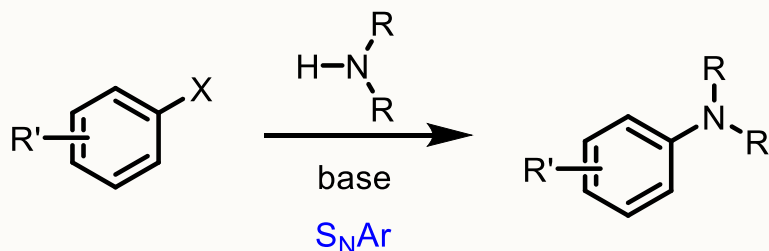
In the med chem synthesis of this drug, one Pd-catalysed step was used:





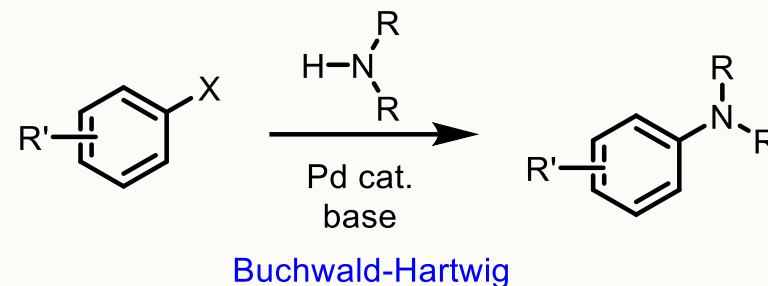
Pd catalysis vs. S_NAr

The previous slide showed that the Buchwald-Hartwig coupling achieves the same as nucleophilic aromatic substitution (S_NAr). So what are the differences?



Nucleophilic aromatic substitution:

- Leaving group: $F > Cl > Br > I$
- Regiochemistry: There must be an electron-withdrawing group ($R' = F, NO_2, CF_3$, etc.) *ortho* or *para* to the leaving group
- No expensive Pd catalyst required.



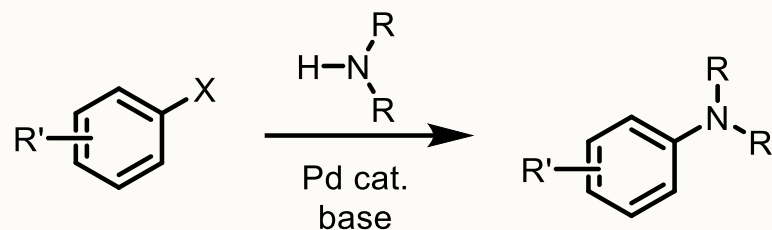
Buchwald-Hartwig reaction:

- Leaving group: $I > Br > Cl \gg F$
Iodide is the best at the oxidative addition step, but chloride works as well (aryl chlorides are cheaper).
- Regiochemistry: Any substitution pattern (R') works.



Summary

In this lecture, you learned how to form C–N bonds using palladium catalysis and when this is a powerful alternative to S_NAr chemistry.

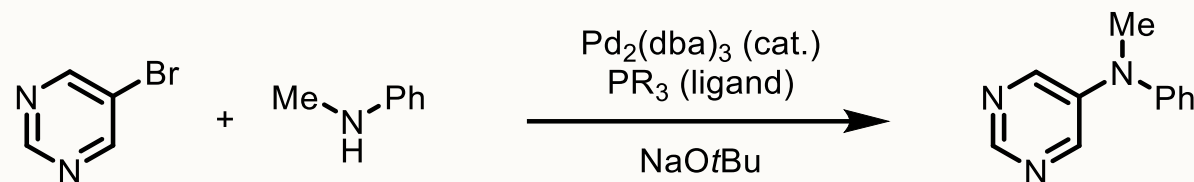


Buchwald-Hartwig

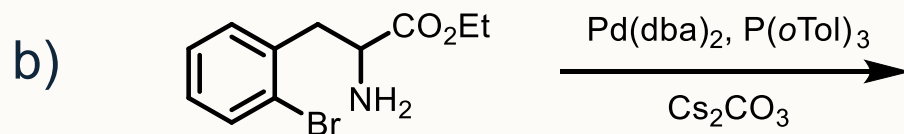
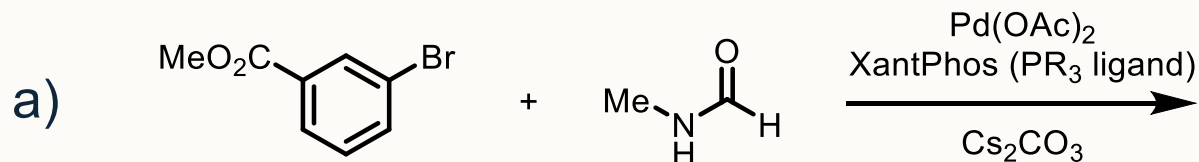


Practice questions

1. Draw the catalytic cycle for the following Buchwald-Hartwig reaction:



2. Identify the products of the following Heck reactions:

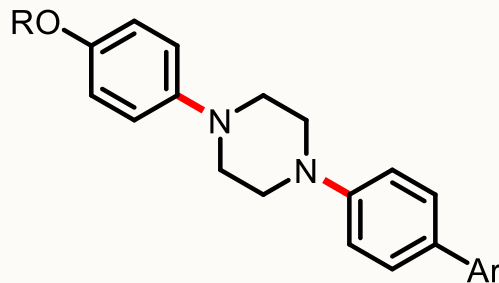




Practice questions

3. The two bonds highlighted in red in the anti-fungal drug (Sopranox) below can be made via Pd-catalysed Buchwald-Hartwig reactions.

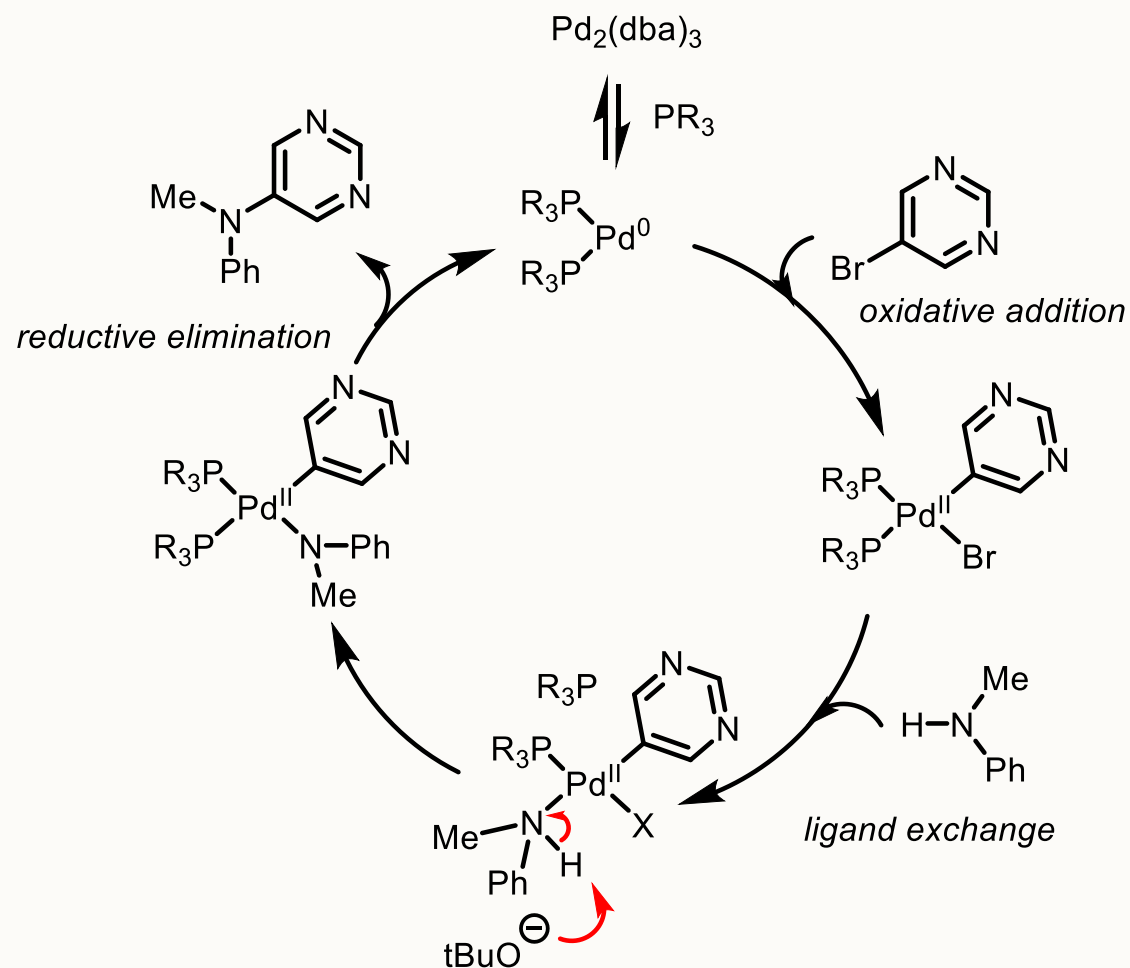
- Suggest a three-step synthesis for this molecule (reagents and conditions for each step).
- Why is it not possible to use an S_NAr strategy for the synthesis of this molecule?





Answers to practice questions 8

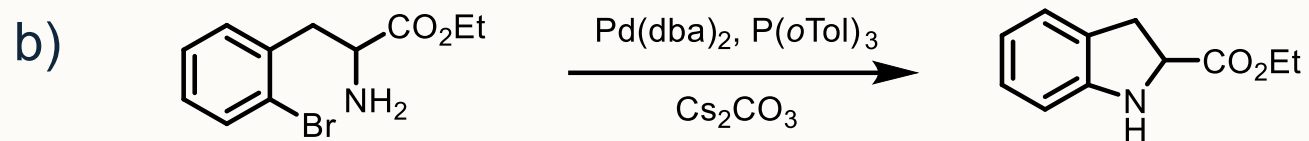
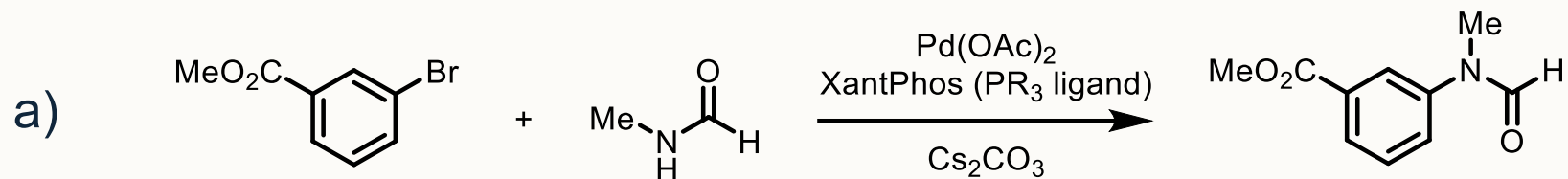
1. Draw the catalytic cycle for the following Buchwald-Hartwig reaction:





Answers to practice questions 8

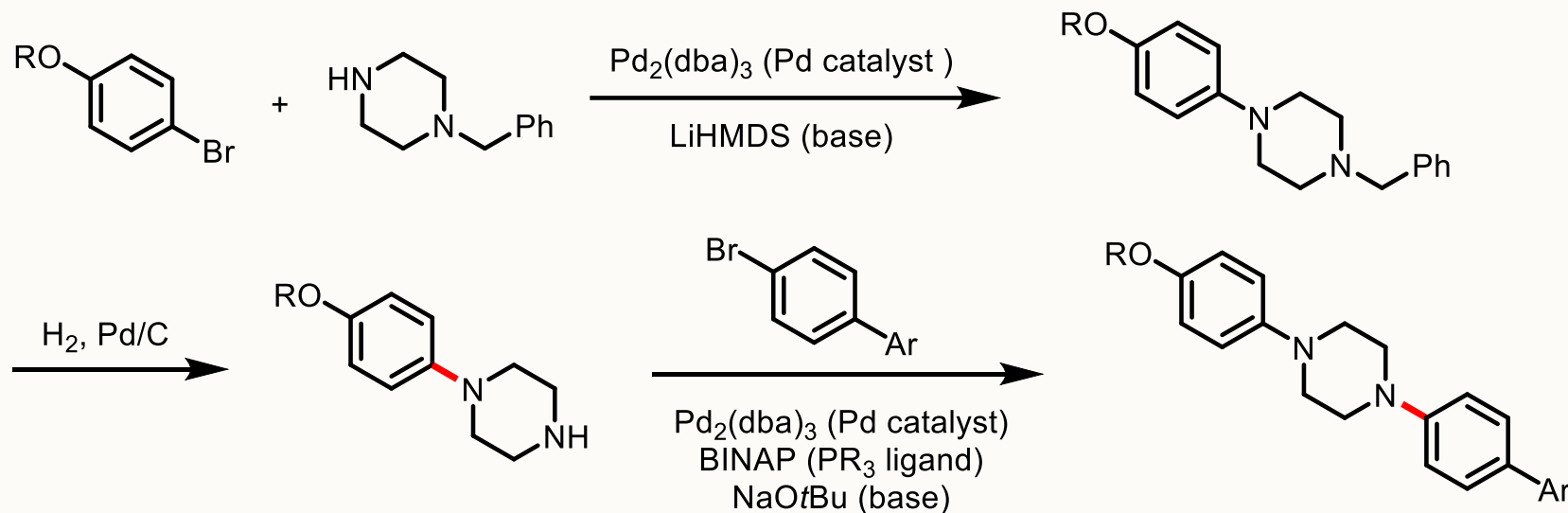
2. Identify the products of the following Heck reactions:





Answers to practice questions 8

3. a) Suggest a three-step synthesis for this molecule (reagents and conditions for each step).



b) Why is it not possible to use an $\text{S}_{\text{N}}\text{Ar}$ strategy for the synthesis of this molecule?

$\text{S}_{\text{N}}\text{Ar}$ reactions require electron-deficient aromatic substrates (electron-withdrawing groups in the *ortho*- and *para*-position relative to the leaving group). The aromatic substrates required for this synthesis are electron-rich and therefore will not undergo reaction with nucleophiles.