CHEM3065 Synthesis and Reactive Intermediates

O'Duill lecture 1

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How is the course structured?

Lectures

- Thu, 11 am: Miriam O’Duill – Organometallic chemistry
  Fri, 11 am: Rob Stockman
- Attendance recorded via QR code
- Lecture recordings and slides provided on Moodle
- Don’t fall behind!

Tutorials

- In person, tutorial question sheets on Moodle
- Check your timetables

Labs

- In person
- Check your timetables and groups

Expectations

What I expect of you

- Attendance of 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, 2nd edition (available as an e-book on the library website):
    https://ebookcentral.proquest.com/lib/nottingham/reader.action?docID=1591368

What you can expect of me

- Lecture material provided on Moodle in a timely fashion
- Short practice questions throughout to consolidate material and prepare you for exams
- Answers to questions in class or by email: university can be hard, so don't be afraid to ask for support!

Course Overview

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

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!

Lecture 1: Introduction to organometallic reagents

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

Learning outcomes

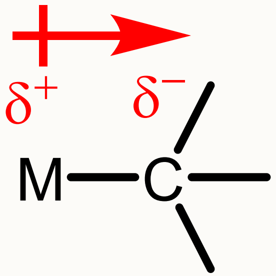
In this lecture, you will learn to:

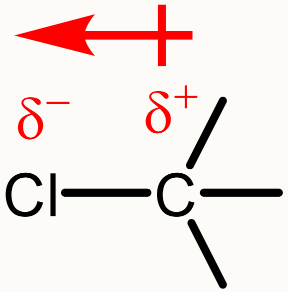
- Identify organometallic reagents;
- Describe their structure and reactivity with electrophiles and proton sources;
- Synthesise organometallic reagents by oxidative addition;
- Identify the features that affect the stability of organometallic reagents.

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
Me_4Sn	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!)

Factors affecting the stability of Organometallics

- The metal (see previous slide)
- The nature of the carbon:

$sp^3 < sp^2 < sp$

$\longrightarrow$

Increasing stability

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

- For sp^3 carbons:

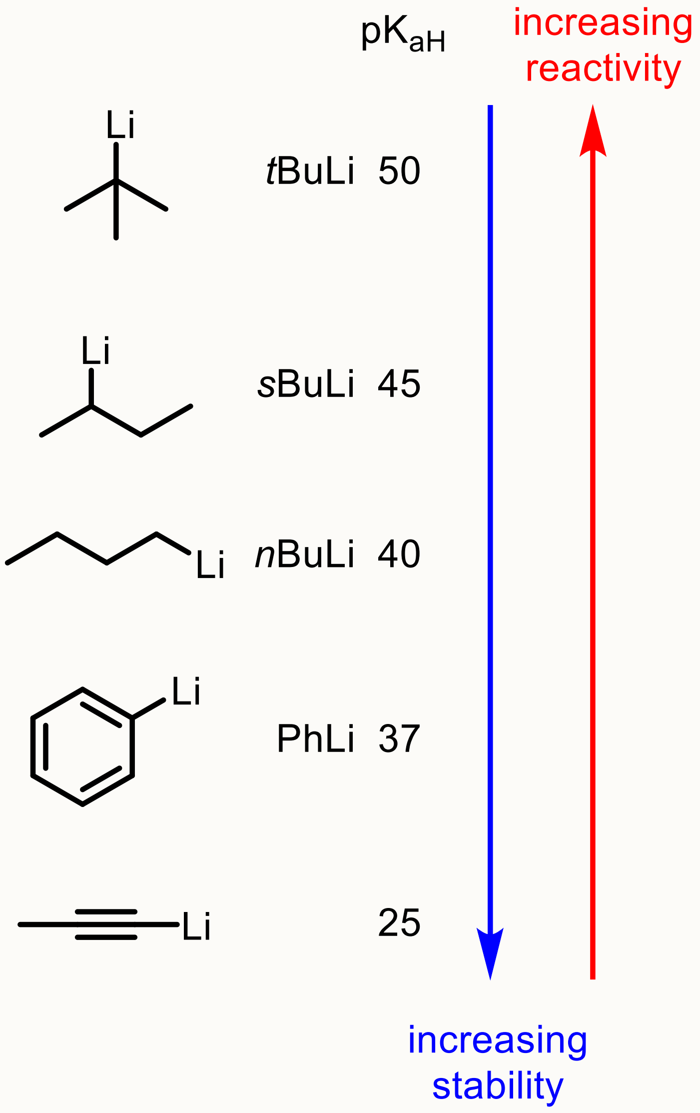
3° < 2° < 1°

$\longrightarrow$

Increasing stability

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

- pK_{aH} can be used as a guide to reactivity/stability:
  The lower the pK_{aH}, the more stable the organometallic.
  (But: most organometallics are highly reactive.)



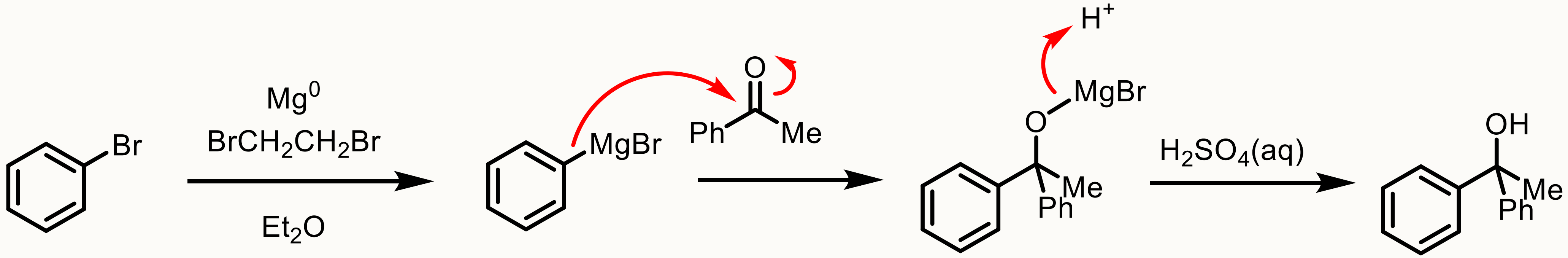
Factors affecting the stability of Organometallics

- Organometallics are highly reactive (very unstable).
- Practical considerations: Organometallics
  - are nucleophilic and basic: need to use aprotic solvents (e.g. THF, Et_2O, Hex)
  - react with O_2: need to use an inert dry atmosphere such as N_2 or Ar.
  - react rapidly and violently with H_2O: 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.

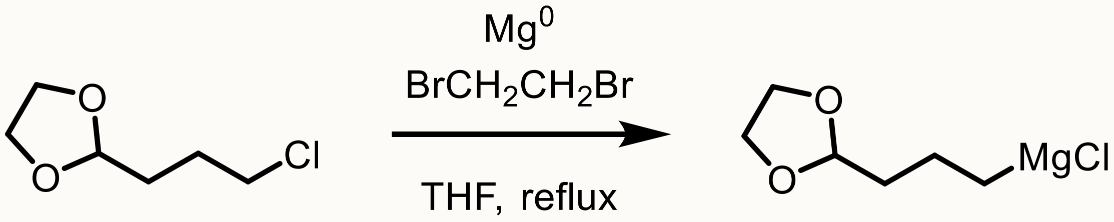
- Revision: reactivity of Grignard reagents:



Organometallic compounds are **nucleophiles**.

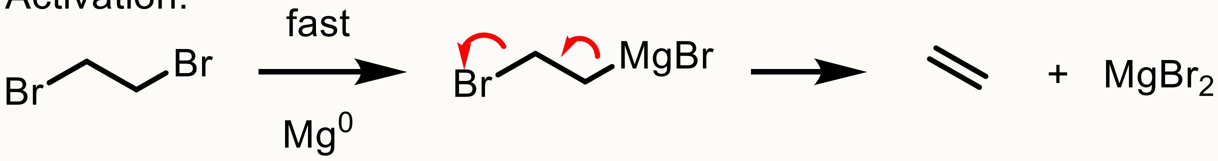
Synthesis of Organometallics: Grignard reagents

- 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:



Grignard reagent

Activation:



Synthesis of Organometallics: Grignard reagents

- Order of reactivity towards oxidative addition:

$$R{-}X \xrightarrow[\text{THF, reflux}]{Mg^0,\ I_2} R{-}Mg{-}X$$

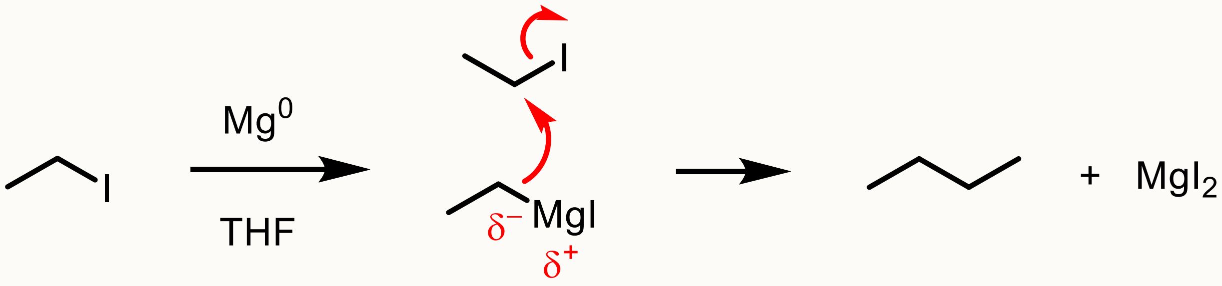
Grignard reagent

R–I > R–Br > R–Cl

← increasing reactivity

- But: chlorides (R–Cl) are often cheap, and the by-product ($MgCl_2$) is insoluble and therefore easy to remove.

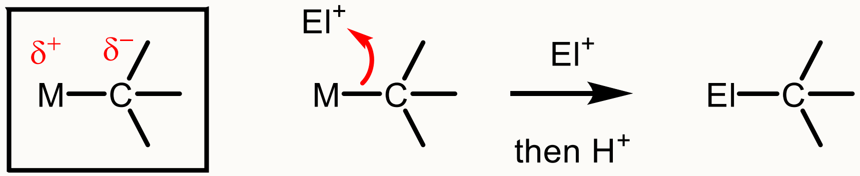
- Alkyl iodides sometimes undergo an unwanted side-reaction (Wurtz coupling):



Summary

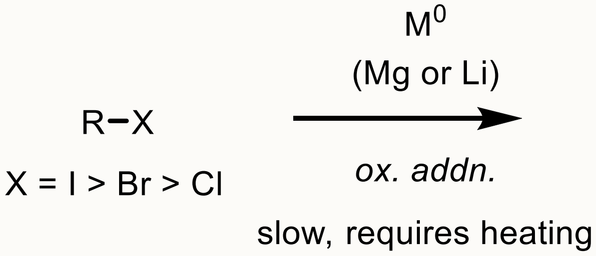
In this lecture, you learnt

- 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.

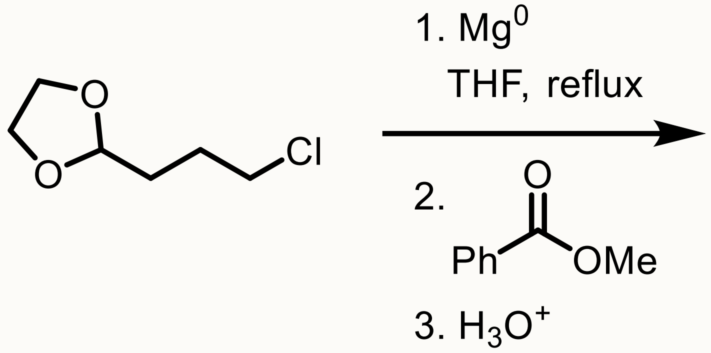
The negative charge on carbon is stabilised by:
– $sp > sp^2 > sp^3$
– sp^3: 1° > 2° > 3°
– conjugation, coordinating heteroatoms, α-heteroatoms

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 2: Synthesis and reactivity of organometallics

Transmetallation, organocuprates, *ortho*-lithiation

Learning outcomes

In this lecture, you will learn:

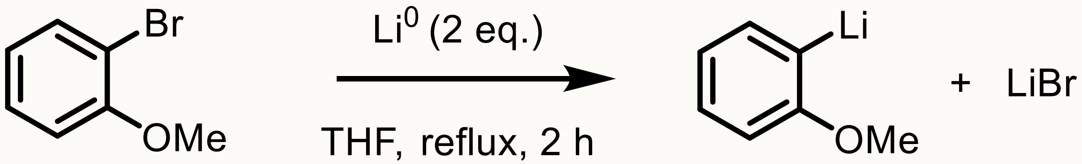
- how to synthesise organolithium reagents by halogen-lithium exchange
- how to synthesise organolithium reagents by deprotonation (*ortho*-lithiation).

Recommended Reading: Clayden, Organic Chemistry, Chapter 9

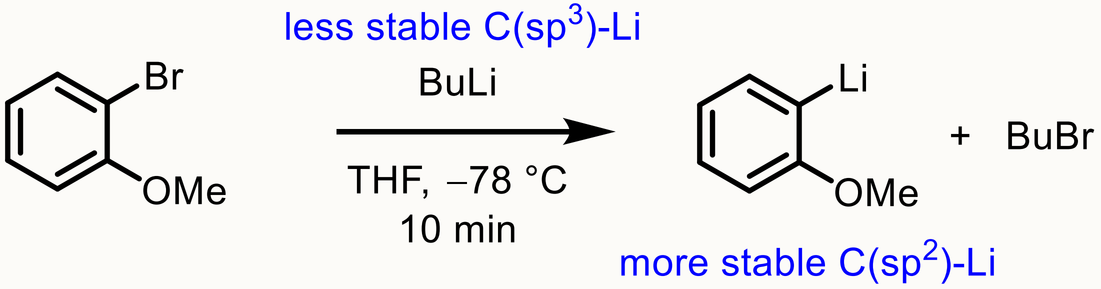
Synthesis of Organometallics: Halogen-Lithium exchange

- 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

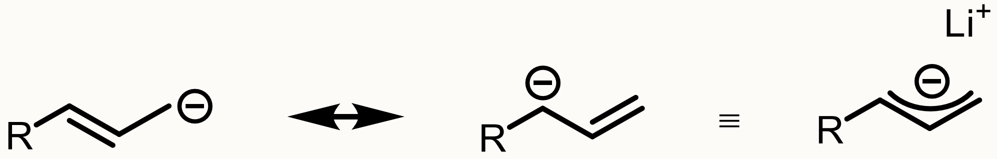

less stable $C(sp^3)$-Li

more stable $C(sp^2)$-Li

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° > 2° > 3°
- Conjugation increases stability:

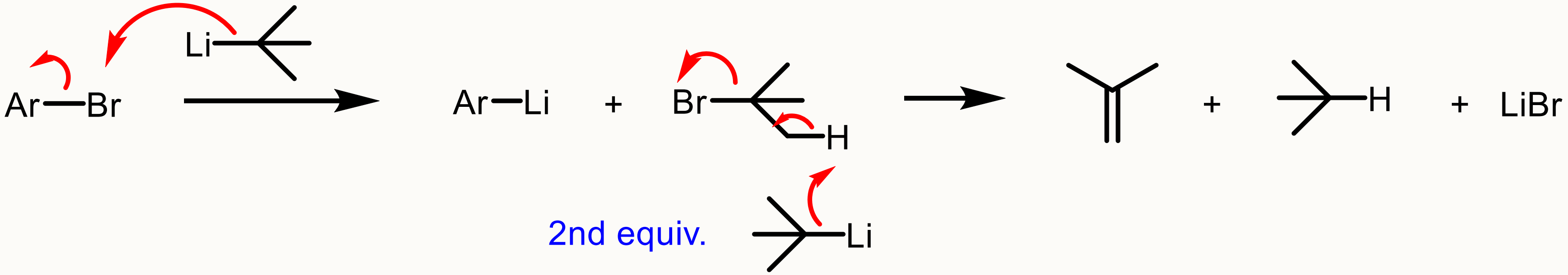


- Internal heteroatom co-ordination increases stability:

- α-heteroatom stabilization:

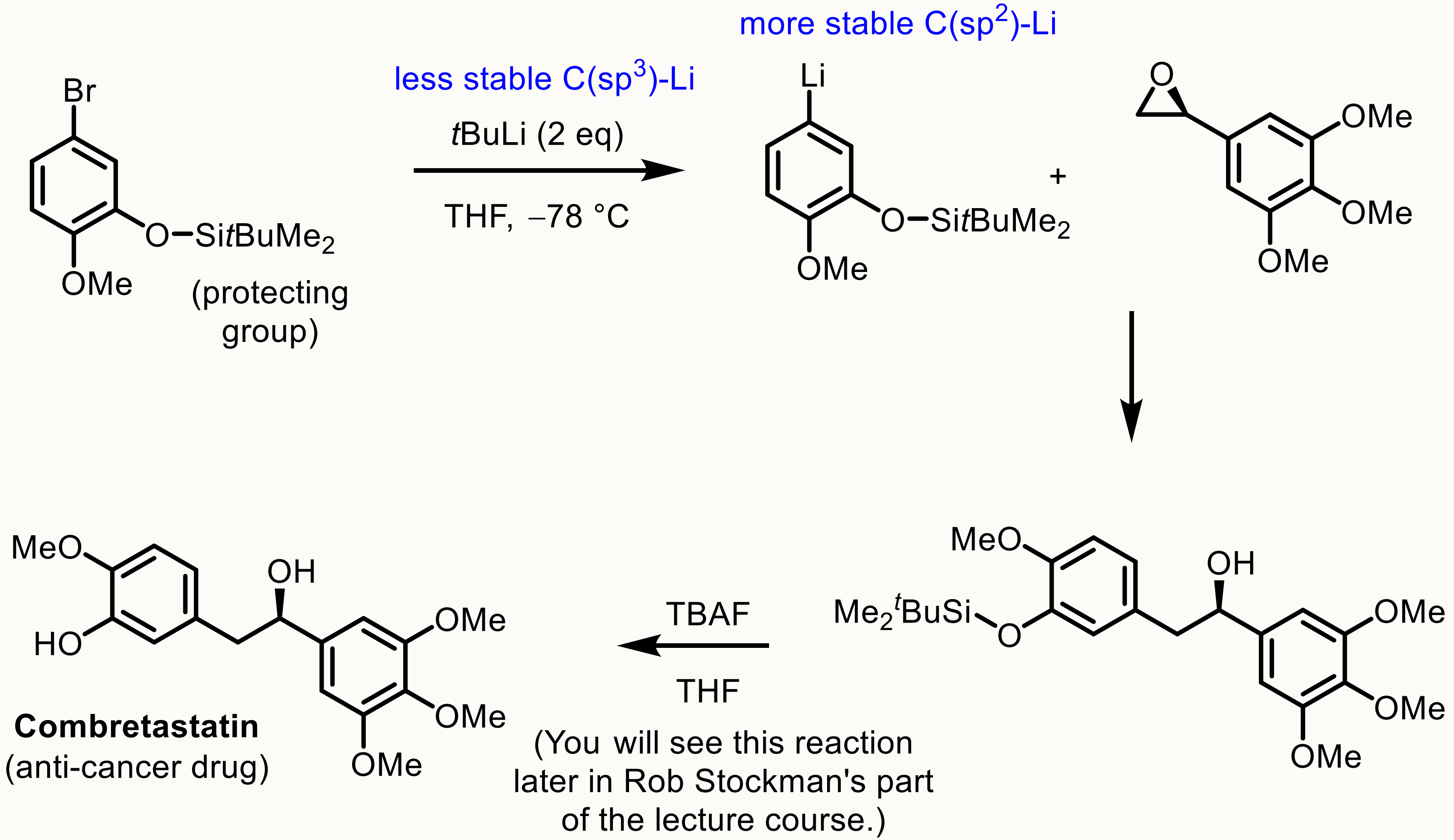
How much BuLi is necessary?

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



less stable C(sp^3)-Li

*t*BuLi (2 eq)

THF, –78 °C

more stable C(sp^2)-Li

(protecting group)

TBAF

THF

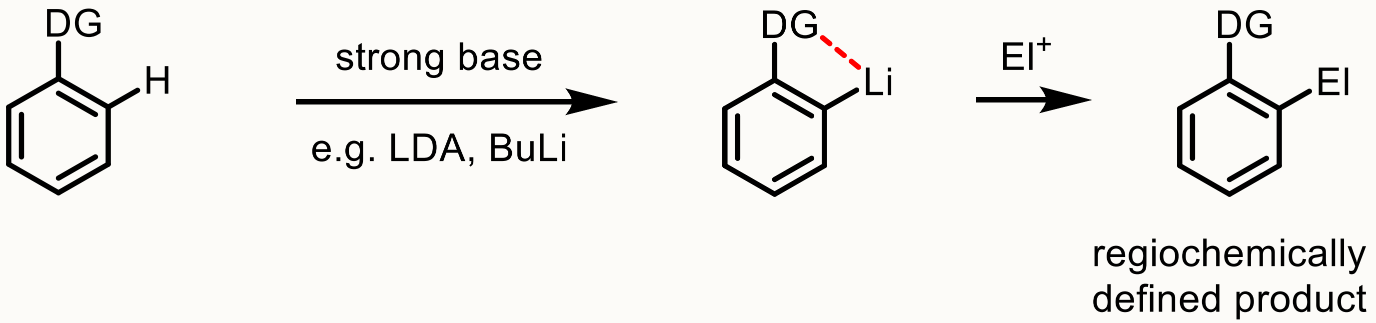
(You will see this reaction later in Rob Stockman's part of the lecture course.)

Combretastatin
(anti-cancer drug)

Ortho-lithiation (deprotonation) of aryl rings

- We can also make organolithium reagents by deprotonation of C – H bonds. A strong base (BuLi or LDA) is necessary.

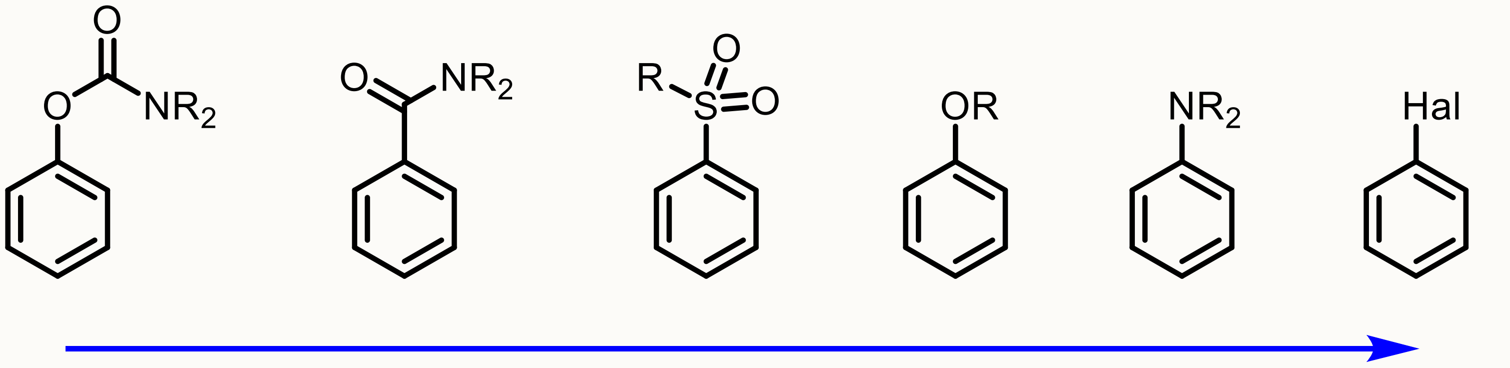
- Directing groups (DG) enable regioselective ortho-lithiation (deprotonation of aromatic C–H bonds):



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:



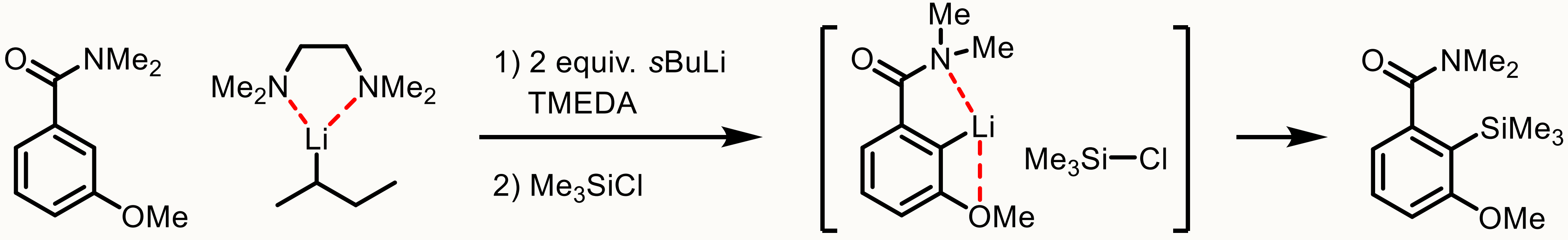
decreasing directing groups ability / strength

Hal: need to use
LDA to avoid
Hal-Li exchange

- We cannot use functional groups that would react with BuLi (esters, ketones, etc.)

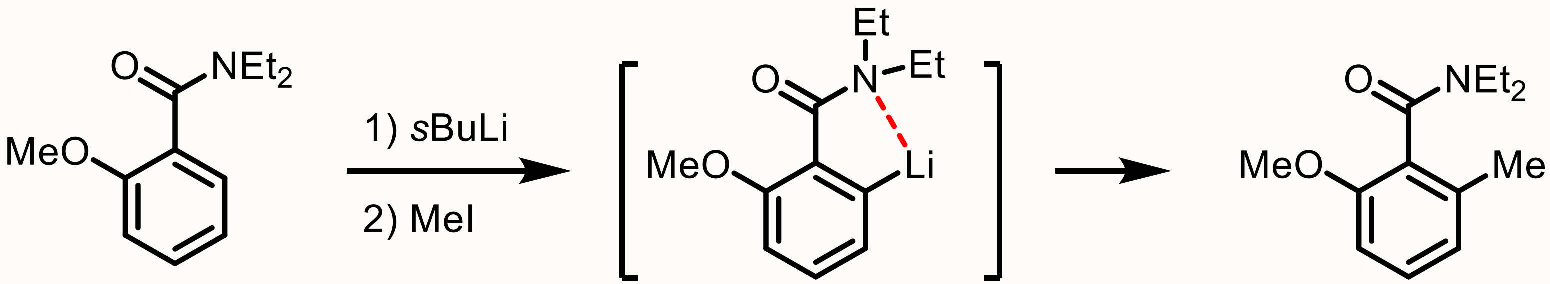
Two directing groups in *ortho*-lithiation

- Reinforcing: both groups direct to the same position



TMEDA makes BuLi
more basic

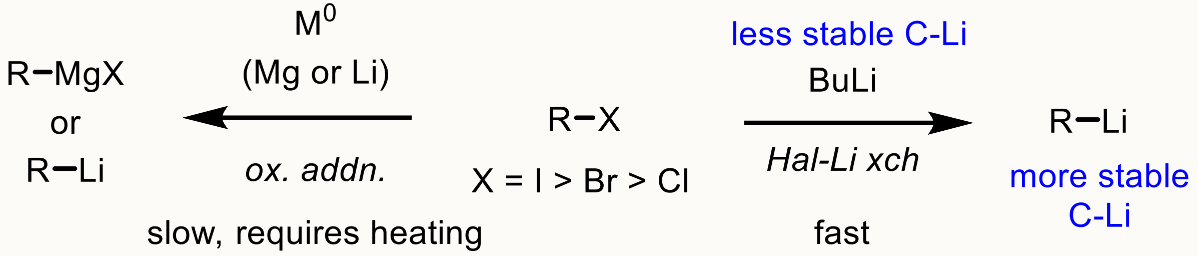
- Competing: the stronger directing group 'wins'



Summary

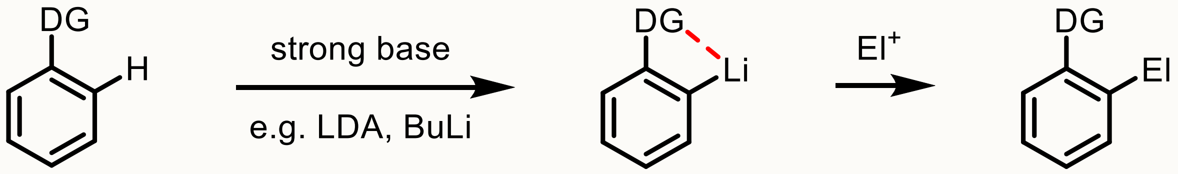
In this lecture, you learnt:

- how to synthesise organolithium reagents by Hal–Li exchange;



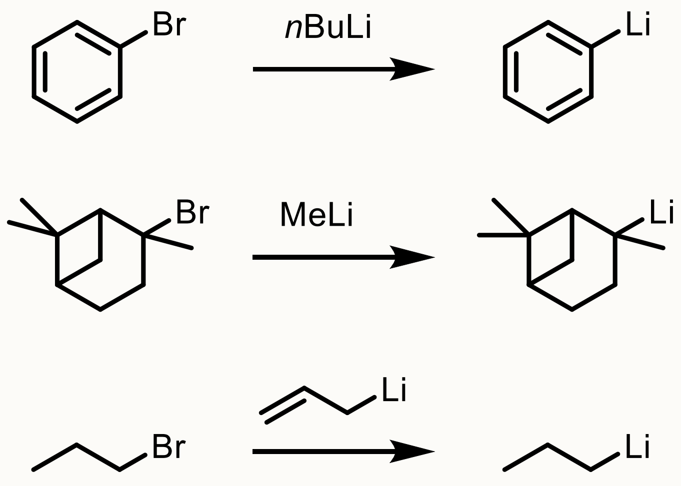
Driving force: formation of a more stable C–Li species from a less stable C–Li species.

- how to synthesise organolithium reagents in a regioselective manner by deprotonation of aromatic C – H bonds (*ortho*-lithiation).

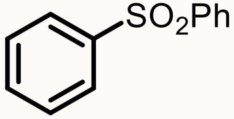


Practice questions

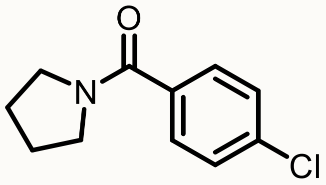
1. Predict whether the following transformations will proceed:



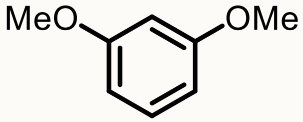
2. Predict the products of the reactions of **A**, **B** and **C** with BuLi and CO_2:



A



B



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Lecture 3: Synthesis of organolithium reagents II

Organolithium synthesis by deprotonation (part 2)

Learning outcomes

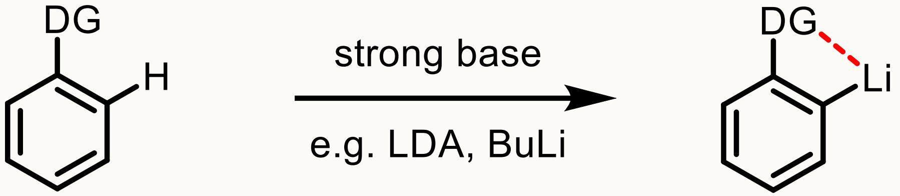
In this lecture, you will learn:

- 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.

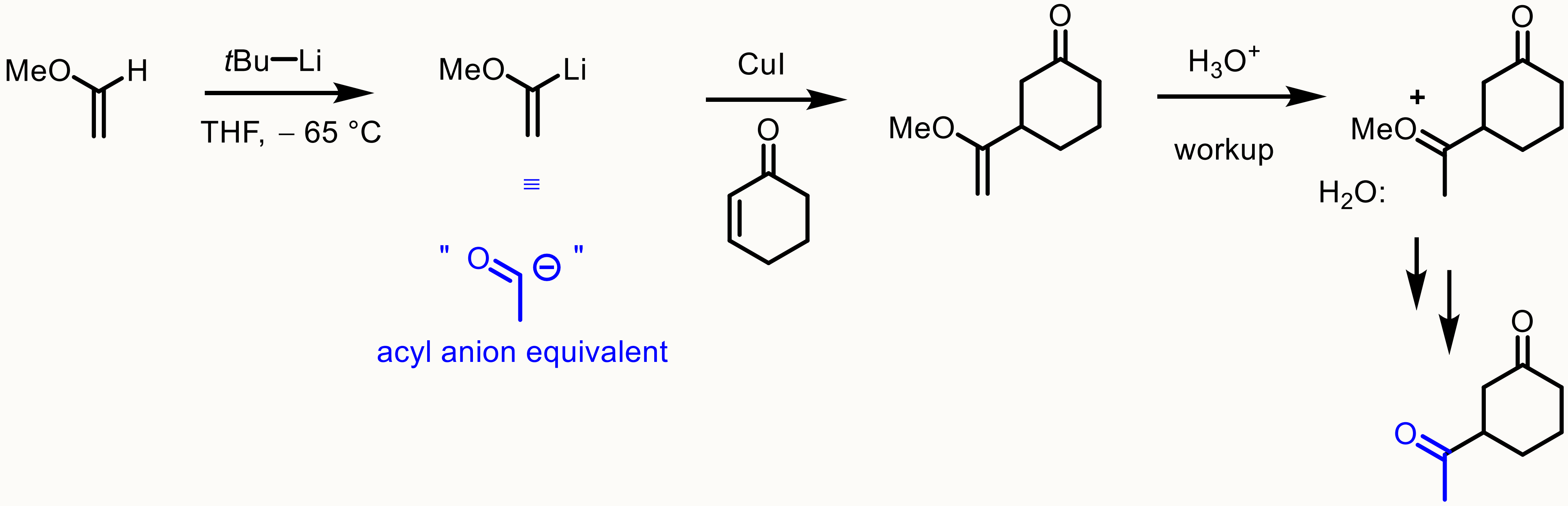
Recommended Reading: Clayden, Organic Chemistry

Lithiation α to Heteroatoms: Oxygen

- We have seen directed lithiation of aromatics:

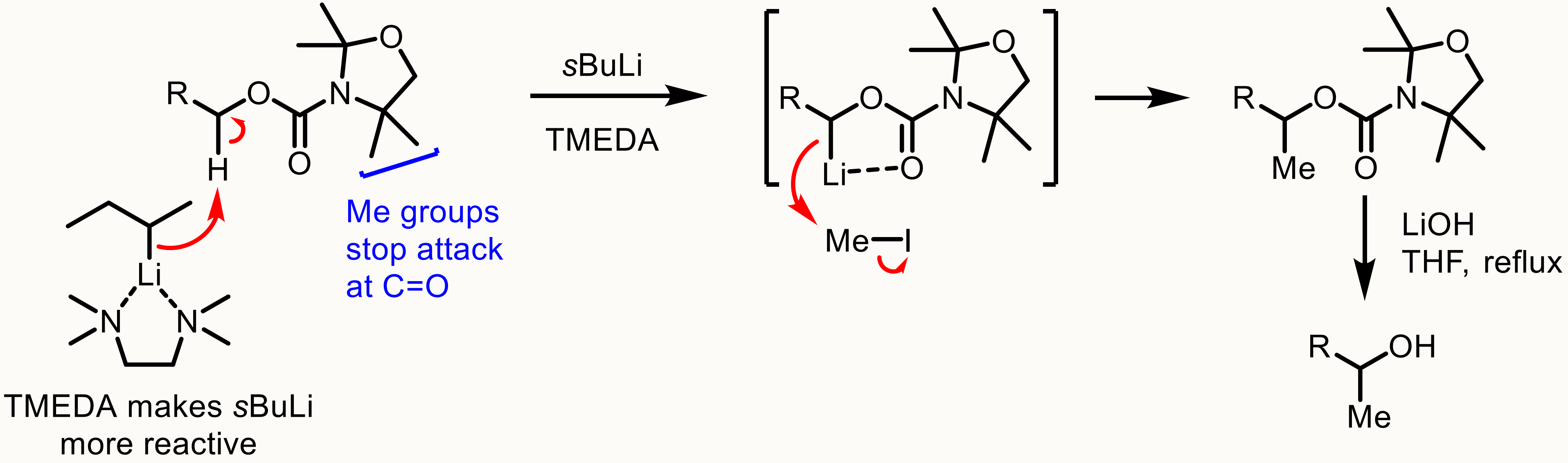


- Similar reactivity can be observed at other C(sp^2)–H bonds, e.g. alkenes:



Lithiation α to Heteroatoms: Hoppe Lithiation

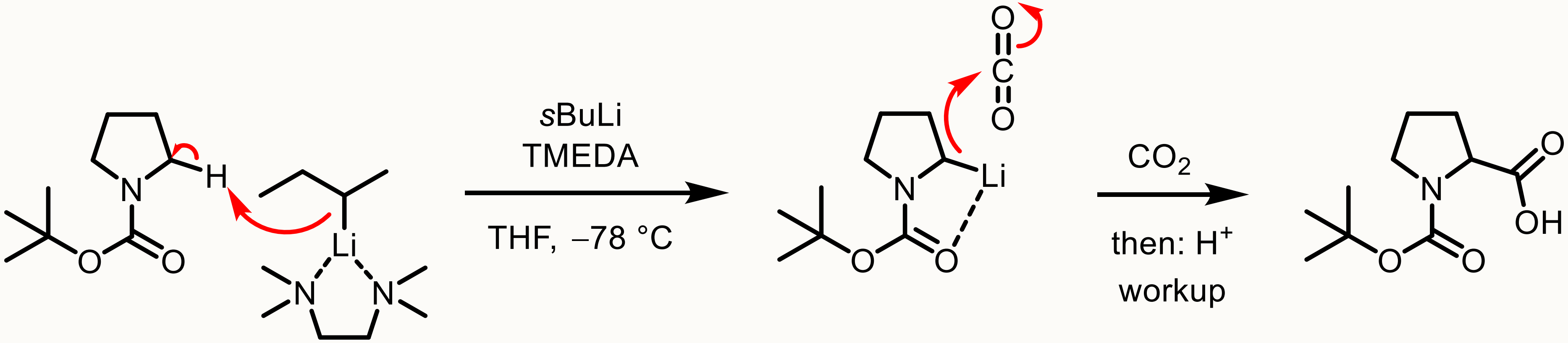
- We can even deprotonate an sp^3 C–H *alpha* to oxygen if there is an electron-withdrawing group on the oxygen:



TMEDA makes *s*BuLi more reactive

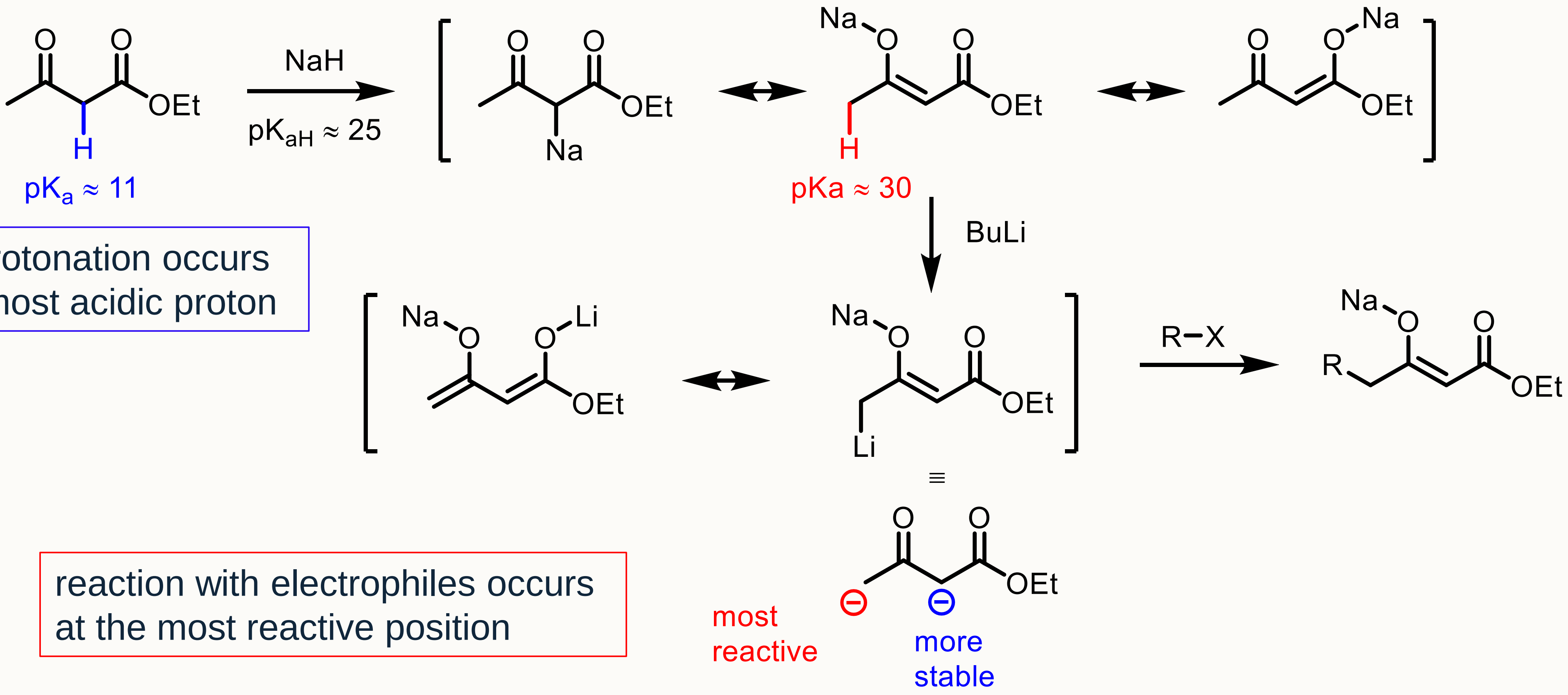
Lithiation α to Heteroatoms: Nitrogen

- 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:



Formation of R–Li: Dienolates

- We can also deprotonate other acidic hydrogens – *e.g.* enolate formation:

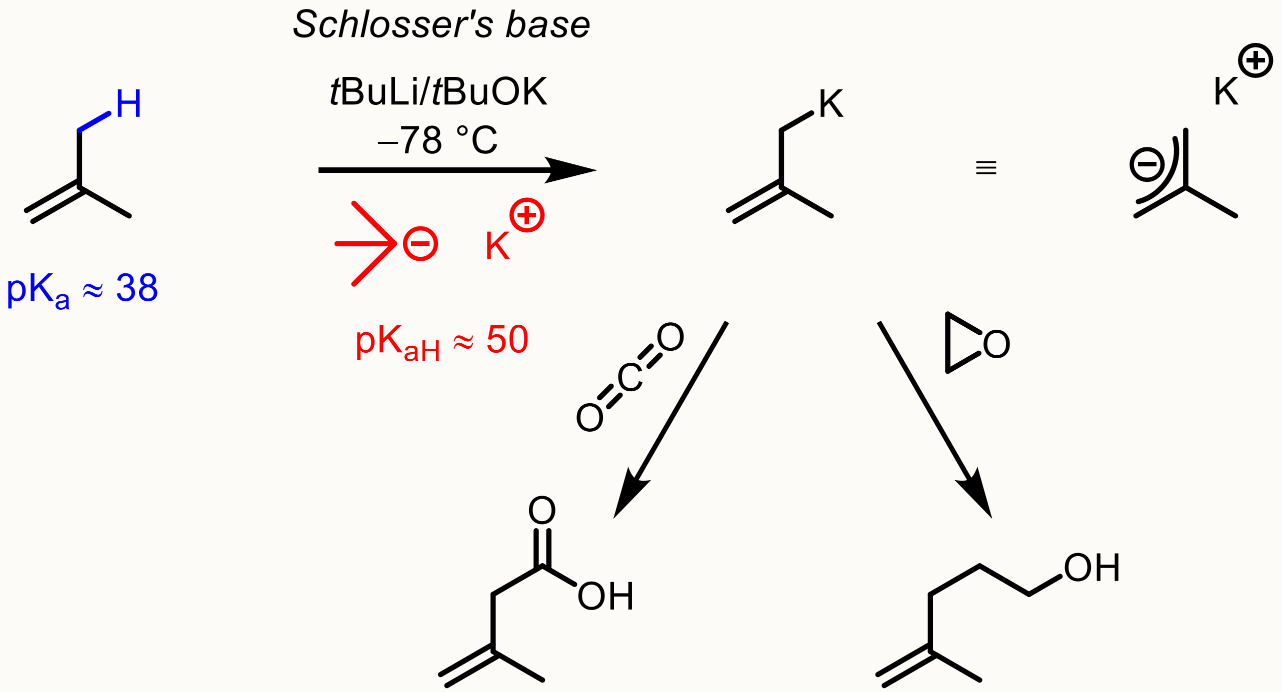


1st deprotonation occurs at the most acidic proton

reaction with electrophiles occurs at the most reactive position

Schlosser’s base: “Superbase”

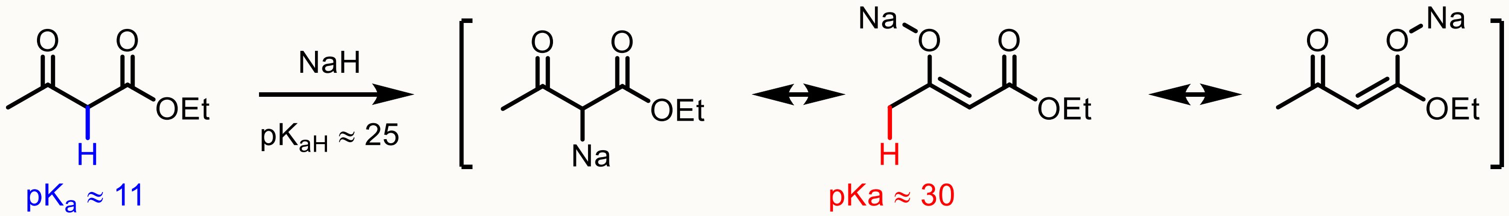
- The combination of two bases (an alkyllithium base and a group I metal alkoxide) gives rise to very powerful “superbases” that enable deprotonation at very weakly acidic positions.
- *E.g.* Schlosser’s base, one of the most powerful bases known, will abstract protons from allylic or benzylic positions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



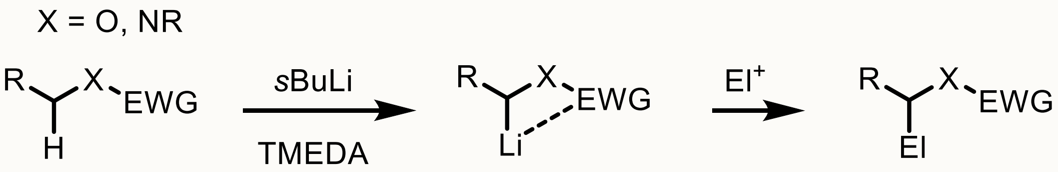
Summary

In this lecture, you learnt:

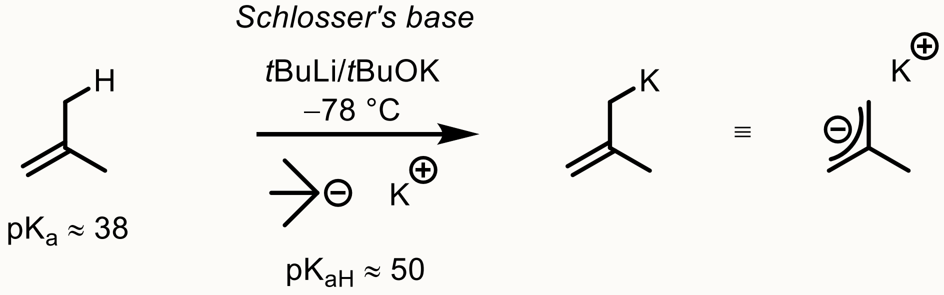
- how to make organolithiums by deprotonating acidic protons, *e.g.*
  - enolates:



  - *alpha* to heteroatoms:

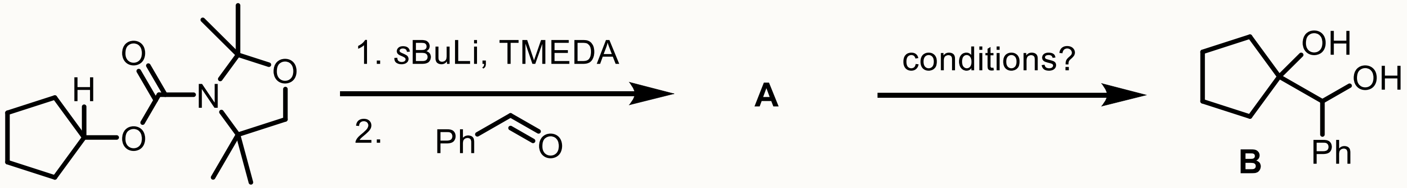


- how to combine an alkyllithium base and a group I metal alkoxide to generate “superbases” for the deprotonation of weakly acidic protons:



Practice questions

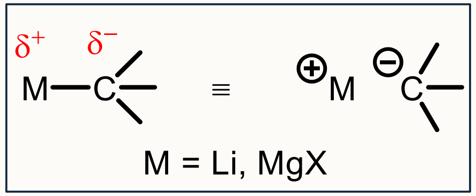
1. Provide curly arrow reactions mechanisms for the formation of product **A**, and suggest a structure for **A**.
2. Suggest reaction conditions and draw a curly arrow reaction mechanism for the formation of **B** from **A**.



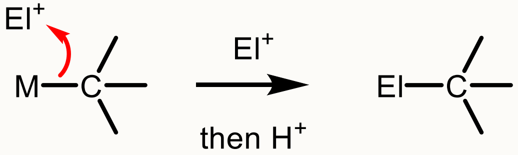
Recap: R–Li and R–MgBr

Previously, you learnt that:

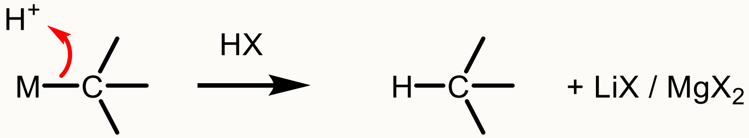
- organometallic reagents with electropositive metals have significant ionic character; they are highly reactive and unstable above cryogenic temperatures.



- they are nucleophilic on carbon and react with electrophiles:



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



Lecture 4: Organocuprate Chemistry

Organocuprate (copper) chemistry

Learning outcomes

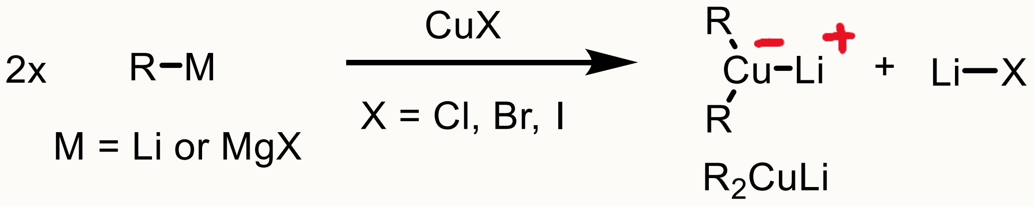
In this lecture, you will learn:

- 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

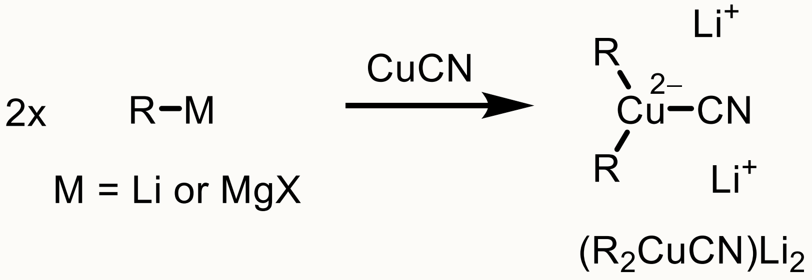
- Organocuprates (organocopper reagents) can be made by transmetallation from an organolithium (or Grignard) and a copper salt.
- There are two types of organocuprates:
  - Lower-order cuprates (Gillman reagents)



When making organocuprates, consider:

- Need to use aprotic solvents (THF or Et_2O).
- Unstable > 0 °C.
- Prepared and used “in situ”.

  - Higher-order cuprates (Lipshutz reagents)

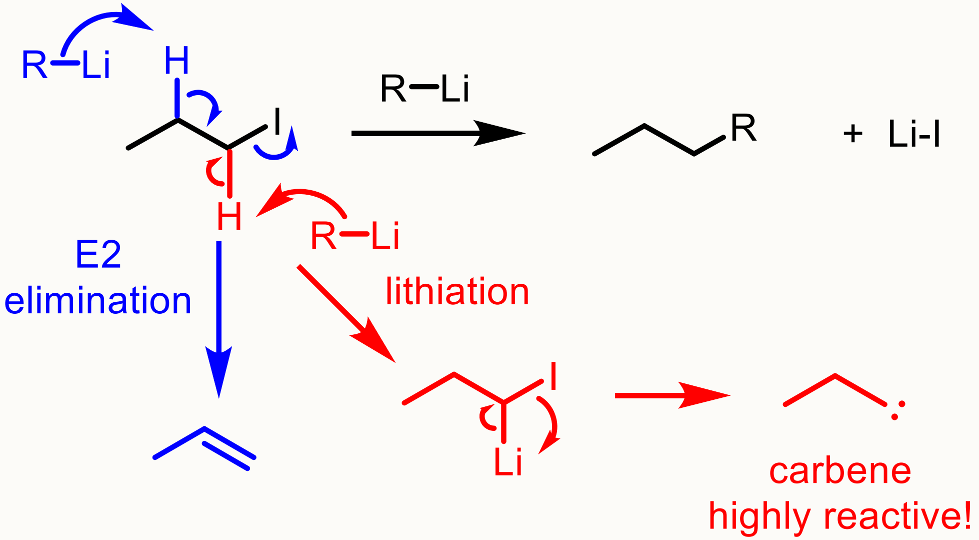


- Organocuprates are “**softer**” nucleophiles and **less basic** than Grignard or organolithium reagents. This results in different reactivity.

Cuprate reactivity: Substitution reactions

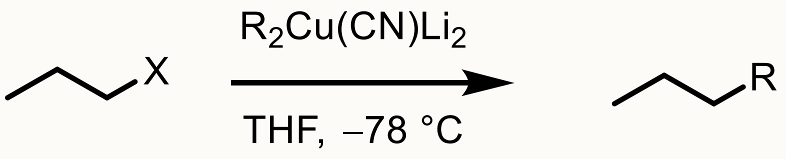
1. Cuprates **are less basic** than Grignard (R–MgBr) and organolithium (R–Li) reagents

- Problem: Because Grignard and organolithium reagents are strong bases, they do not cleanly undergo S_N2 reactions with alkyl halides because of competing elimination reactions:



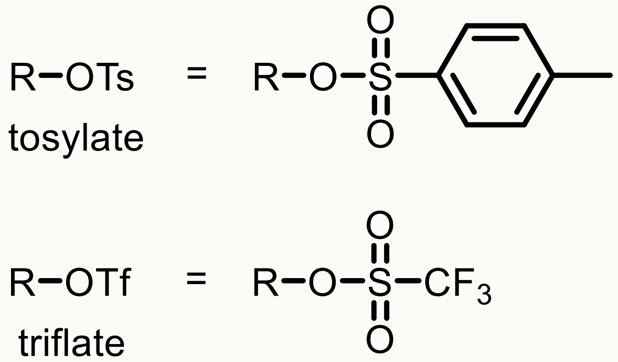
Cuprate reactivity: Substitution reactions

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

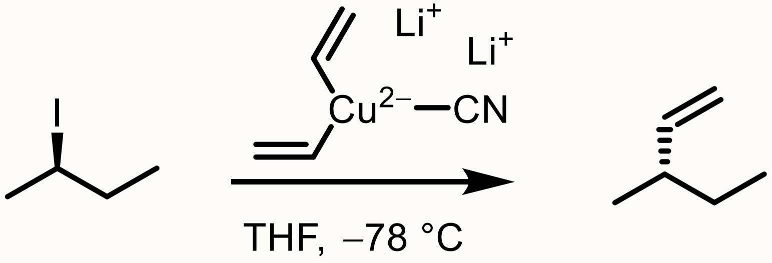


X = I, Cl, Br, OTs, OTf

pseudohalides:



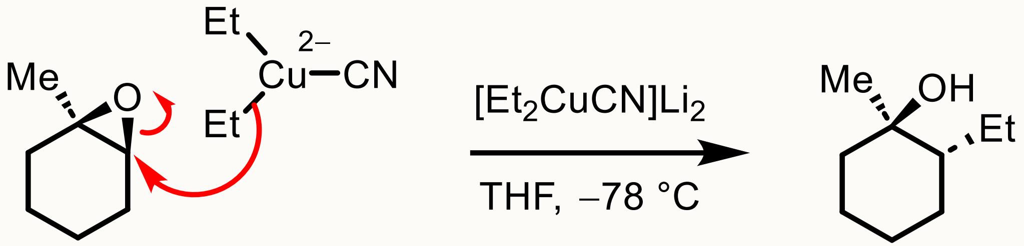
e.g.



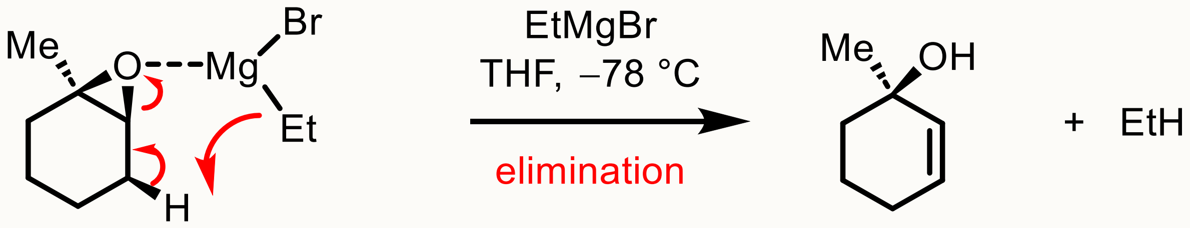
- Only one R-group is transferred. CN group always stays on Cu.
- S_N2: inversion of stereochemistry.

Cuprate reactivity: Ring-opening of epoxides

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

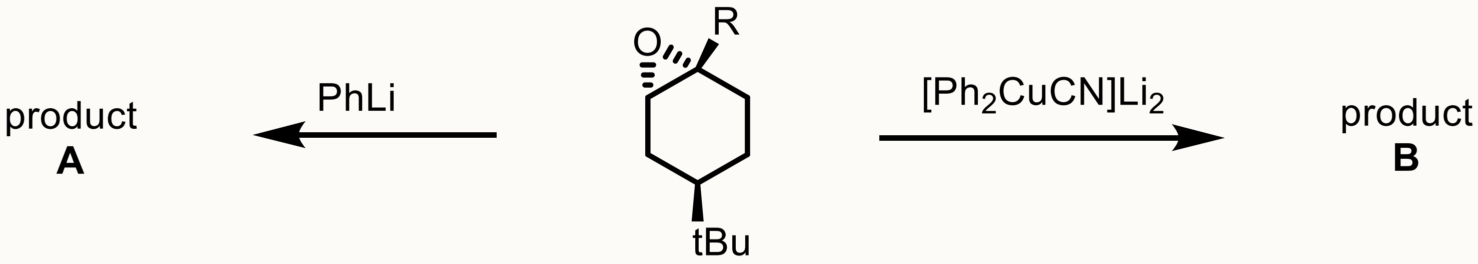


Epoxide opening is selective for the less hindered position (sterics).



Question

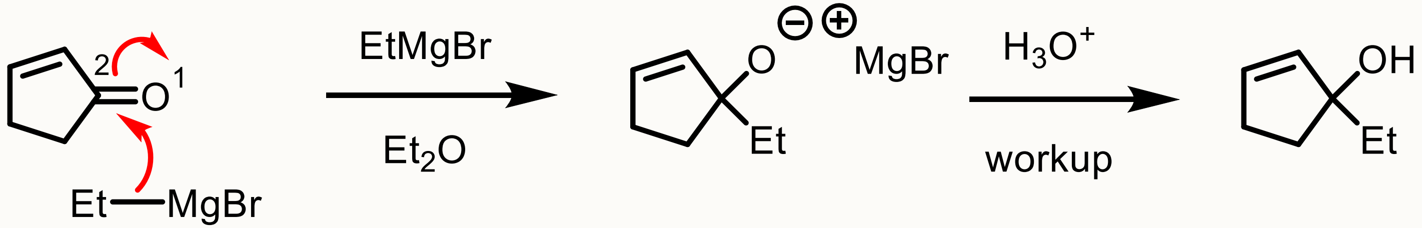
Predict the products (**A** and **B**) of the following two reactions:



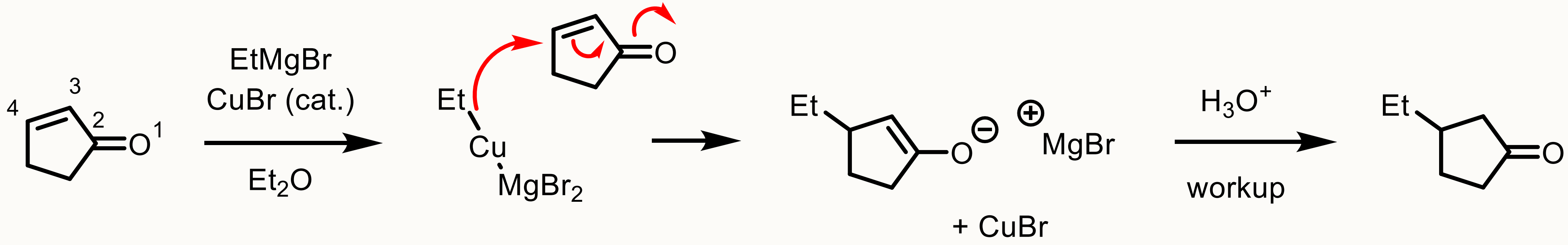
Cuprate reactivity: Conjugate addition

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

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



- 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^-, $R_2C=O$, MeLi, MeMgBr

→ reactivity dominated by electrostatic interactions

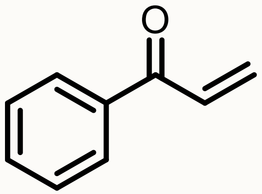
- Soft nucleophiles / electrophiles: delocalised charge in large, ‘diffuse’ orbitals
  e.g. RS^-, I^-, R_3P, α,β-unsaturated ketones and other conjugated alkenes, Me_2CuLi

→ reactivity dominated by HOMO–LUMO interactions

Clayden, Chapter 15

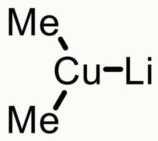
Question

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?

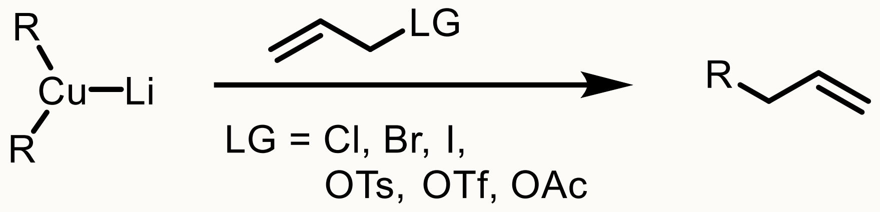
$F^{\ominus}$ $\quad$ $\mathrm{Ph{-}SH}$ $\quad$ $\mathrm{Me{-}Li}$



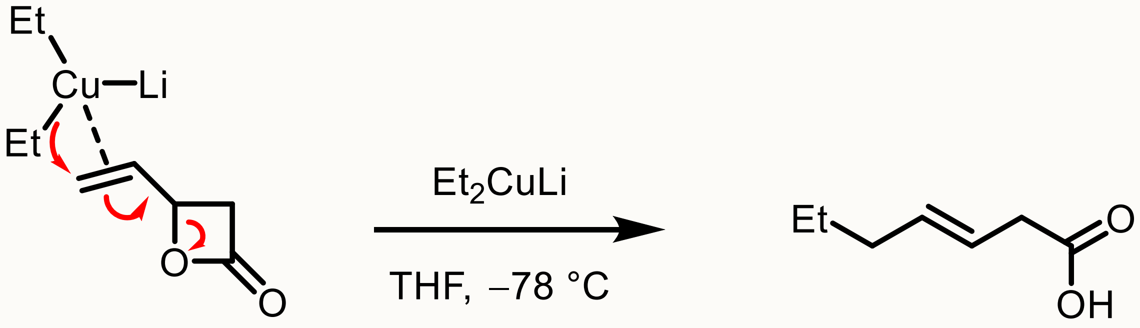
$\mathrm{Me_2Cu{-}Li}$

Cuprate reactivity: Conjugate addition

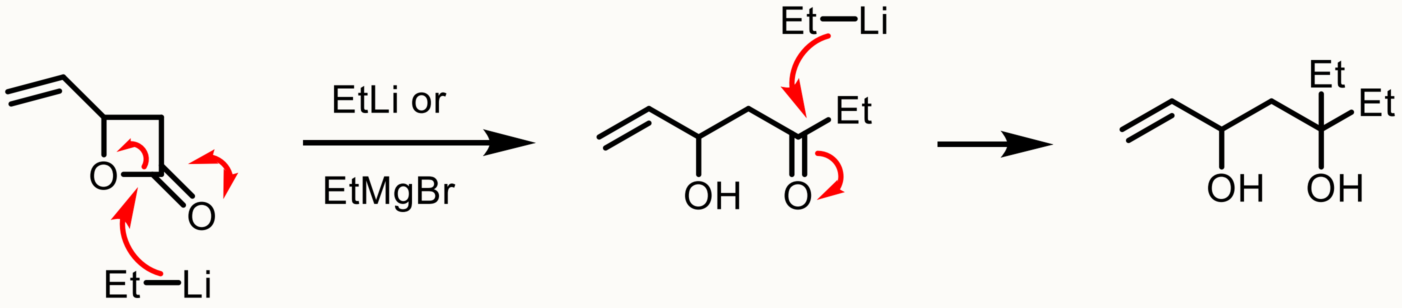
- Cuprates will cleanly displace a wide range of allyl substituted leaving groups.
- Soft nucleophiles: S_N2' reactions



e.g.



soft reacts with soft

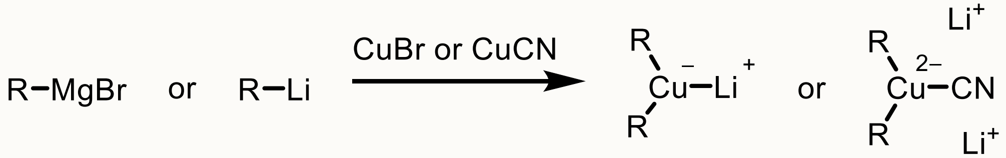


hard reacts with hard

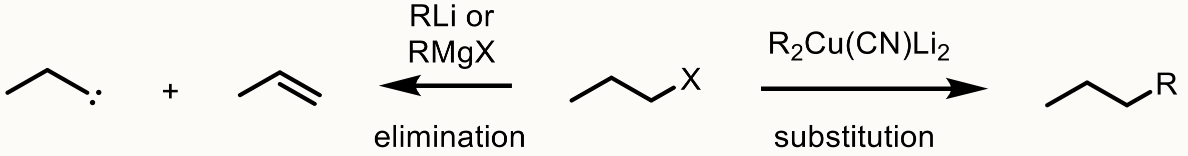
Summary

In this lecture, you learnt:

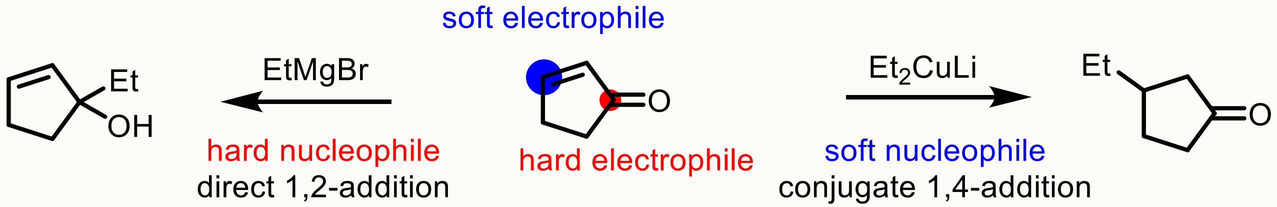
- how to make organocuprates by transmetallation from R–Li or R–MgBr



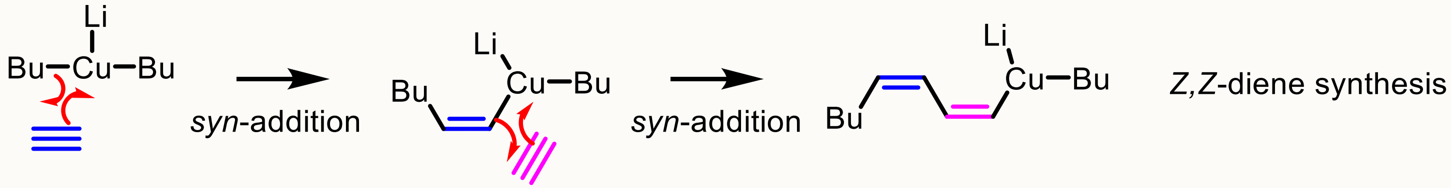
- how the reactivity of organocuprates differs from R–Li and R–MgBr:
  - they are less basic and therefore less prone to elimination reactions:



  - they are soft nucleophiles and react with soft electrophiles:



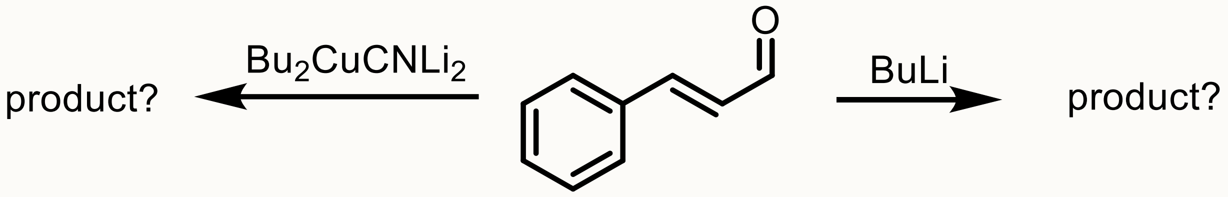
  - they undergo syn-selective carbocupration reactions with alkenes:



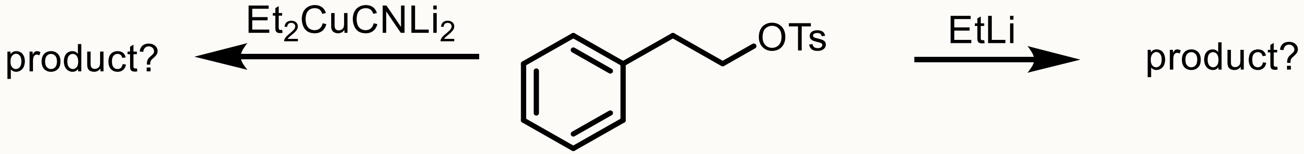
Practice questions

1. Predict the outcome of the following reactions:

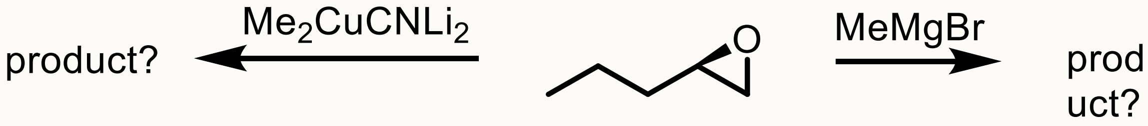
(a)



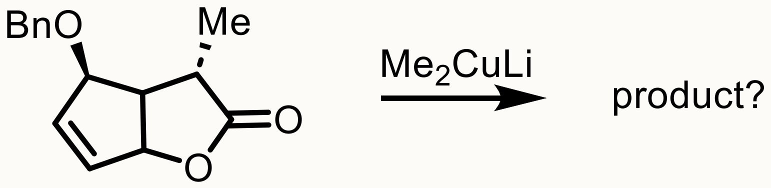
(b)



(c)



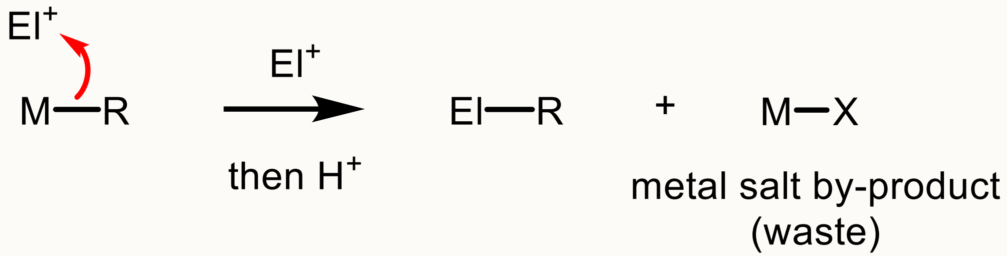
(d)



Course Overview

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

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

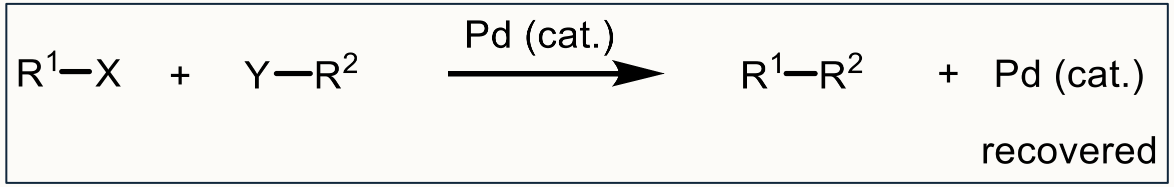


$$M{-}R \xrightarrow[\text{then } H^+]{El^+} El{-}R + M{-}X$$

metal salt by-product (waste)

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

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



$$R^1{-}X + Y{-}R^2 \xrightarrow{\text{Pd (cat.)}} R^1{-}R^2 + \text{Pd (cat.)}$$

recovered

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:

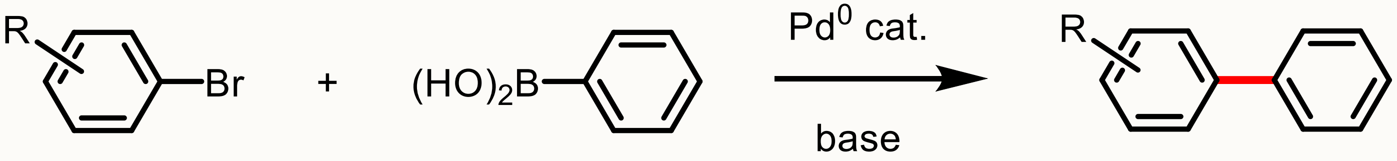
2001	Asymmetric synthesis (Rh, Ru, Ti)
2005	Metathesis (Mo, Ru) [Stockman lectures]
2010	Cross-coupling (Pd) [**these lectures**]
2022	Click chemistry (Cu)

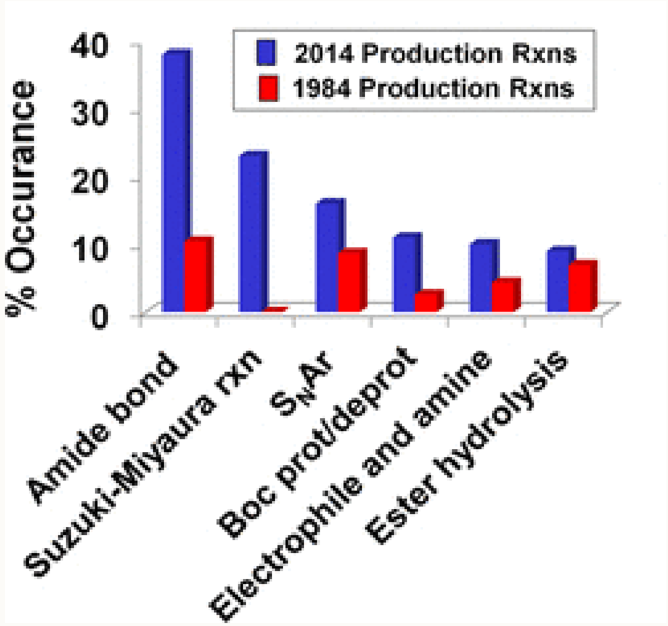
- This course will focus on palladium-catalysed cross-coupling reactions. These reactions are powerful transformations for C–C bond formation:

$$R^1{-}X \quad + \quad Y{-}R^2 \quad \xrightarrow{\text{Pd (cat.)}} \quad R^1{-}R^2 \quad + \quad \underset{\text{recovered}}{\text{Pd (cat.)}}$$

Introduction to Pd cross-coupling chemistry: The Suzuki reaction

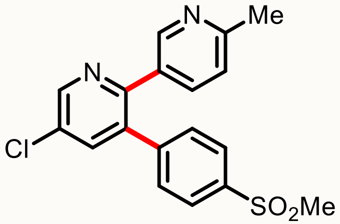
The Suzuki reaction is the second most common reaction in medicinal chemistry.



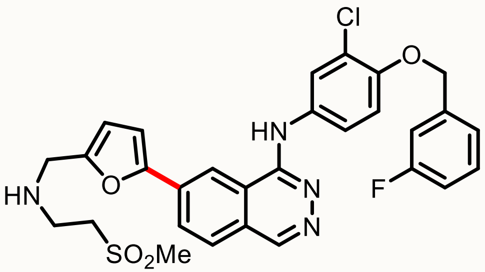


Source: *J. Med. Chem.* **2016**, *59*, 4443

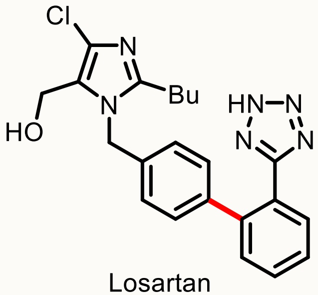
Examples of pharmaceuticals made via Suzuki reactions:



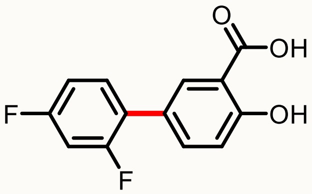
Etoricoxib
(anti-inflammatory)



Lapatinib
(anti-cancer)

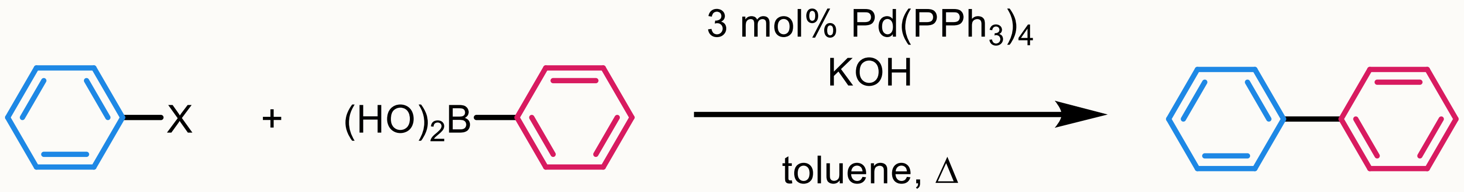


Losartan
(high blood pressure)



Diflunisal
(anti-inflammatory)
Aspirin derivative

Pd cross-coupling reactions: Mechanism of the Suzuki reaction



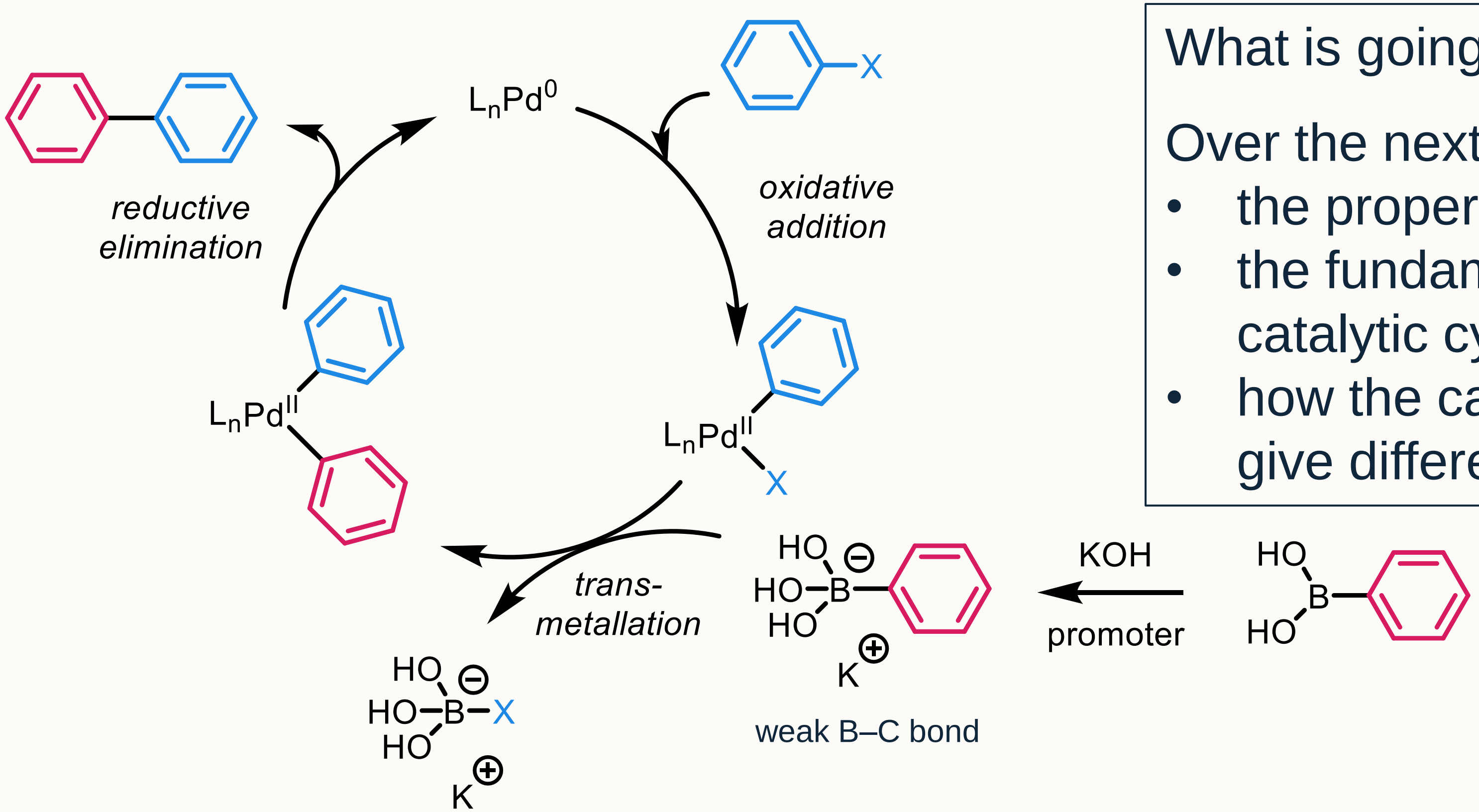
X = halide (I, Br, Cl)
or pseudohalide (OTf)

weak C–X bond

weak C–B bond

strong C–C bond
(+ strong B–X bond)

Driving force:
thermodynamics



weak B–C bond

strong B–X bond

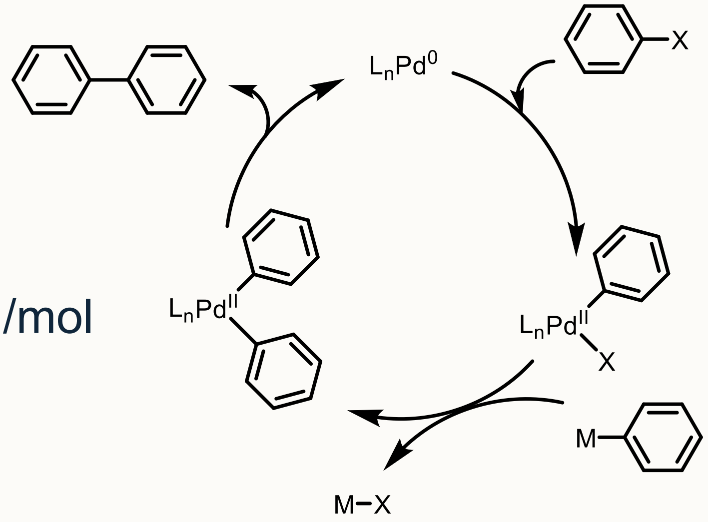
What is going on here?

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



C–C bonds ≈ 100 kcal/mol

C–Halogen bonds ≈ 55–100 kcal/mol
(C–I 55 < C–Br 65 = C–OTf 65 < C–Cl 100)

Pd–C bonds ≈ 50 kcal/mol
Pd–Hal bonds ≈ 70 kcal/mol

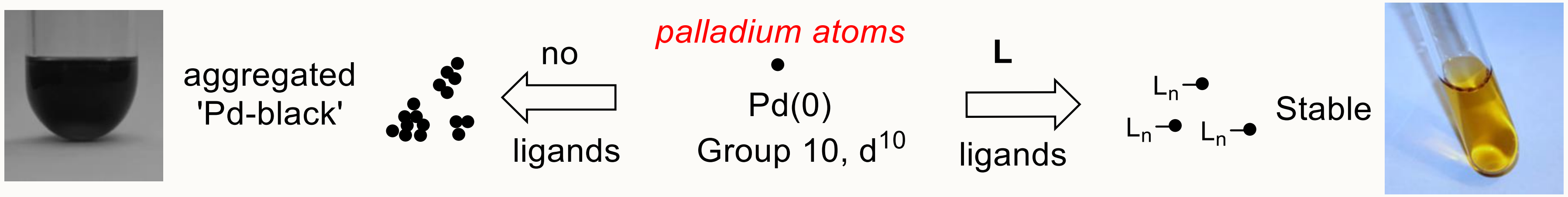
Pd–C bonds ≈ 50 kcal/mol

M–C bonds ≈ 50 kcal/mol

M–Hal bonds ≈ 100 kcal/mol

The metal catalyst

- Ligands are required to stabilise the metal catalyst:



aggregated 'Pd-black'

no ligands

palladium atoms

Pd(0)

Group 10, d^{10}

L

ligands

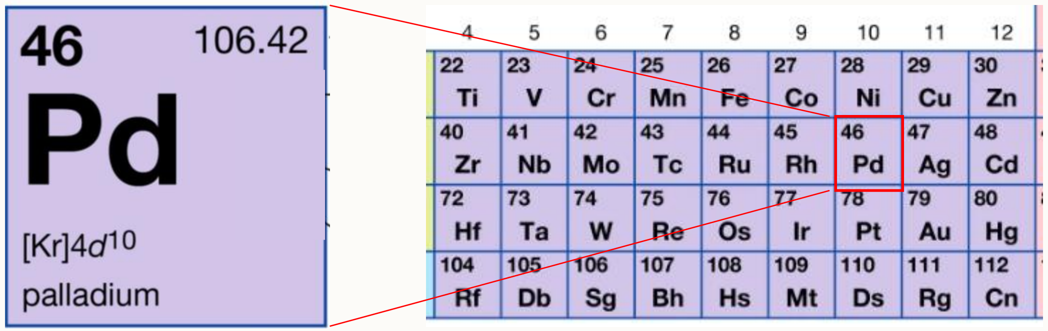
L_n–●

Stable

- 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.



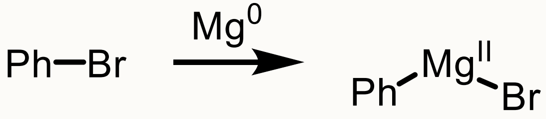
4	5	6	7	8	9	10	11	12
22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn
40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd
72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg
104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn

oxidation state = 0 – (formal charge of ligands)

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

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

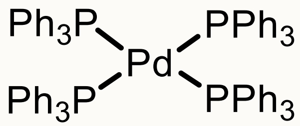
Note: We've (briefly) seen oxidation states before:



The metal catalyst

OS = 0 – (ligand charge)
e^- = (10 – OS) + (ligand e^-)

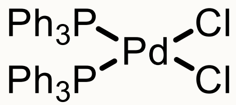
- Consider some common palladium pre-catalysts:



formal charge: 0

electrons: 2

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



formal charge: 0
electrons: 2

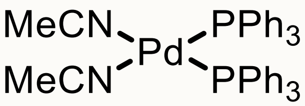
formal charge: –1
electrons: 2

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

- 18- and 16-electron complexes are coordinatively 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:



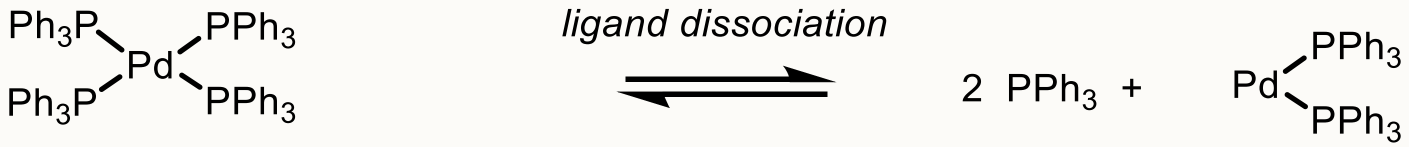
OS = 0 – (ligand charge)
e^- = (10 – OS) + (ligand e^-)

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	–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



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 (d^{10}) 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
electrons: 2

formal charge: –1
electrons: 2

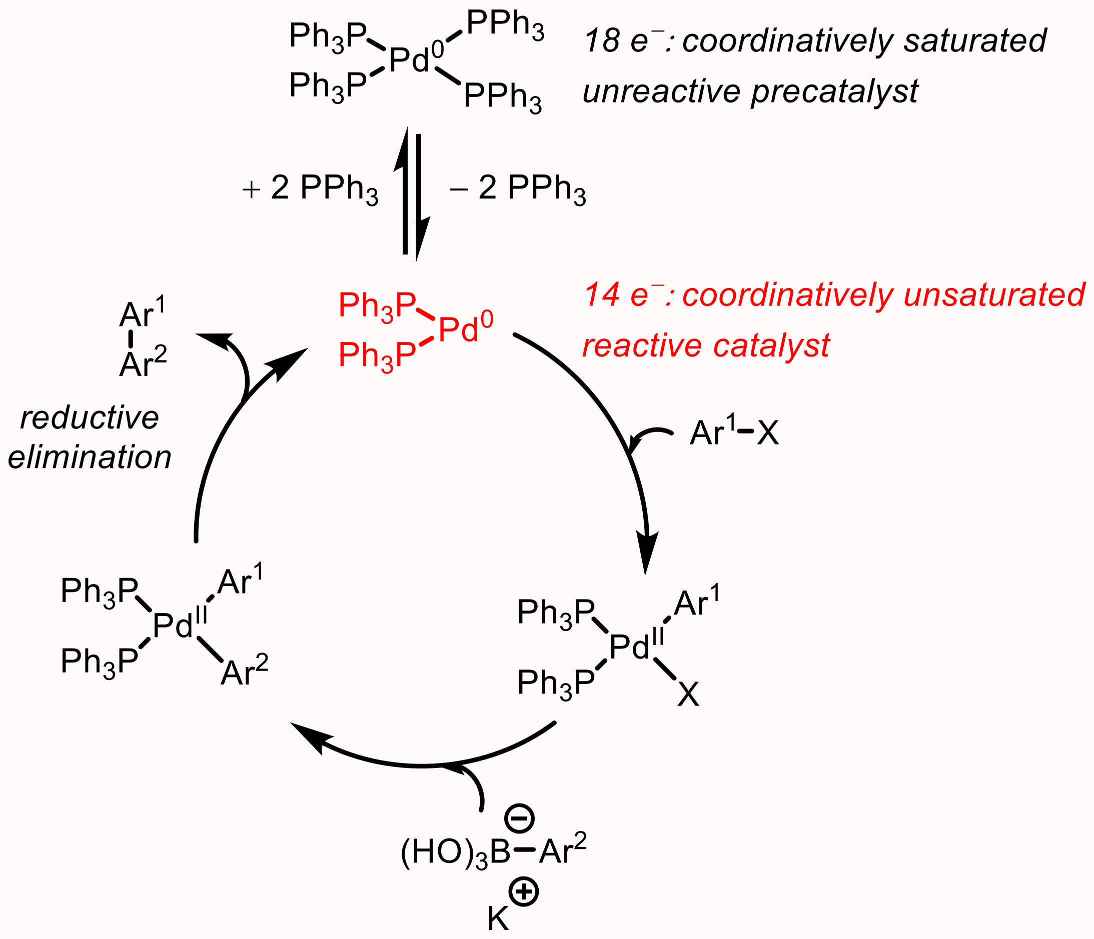
oxidation state = 0 – (2x –1) = 2 Pd(II)
electrons: (10 – 2) + (4 x 2) = 16 e$^-$
coordinatively saturated: unreactive

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

- Pd(II) complexes (d^8) are electron-poor and highly **electrophilic**.

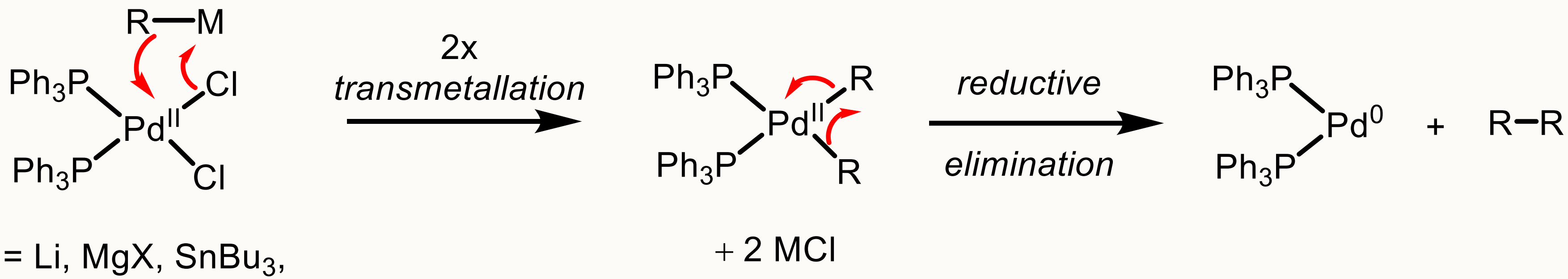
The metal catalyst

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



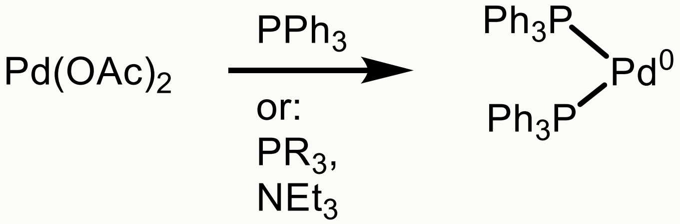
Other ways of generating active Pd(0) catalysts

- A reactive Pd(0) catalyst can also be generated from Pd(II) pre-catalysts:
- Option 1: Reduction of L_nPdX_2 (X = halide or pseudohalide) with an organometallic (M–R is often the coupling partner in cross-coupling reactions, present in excess):



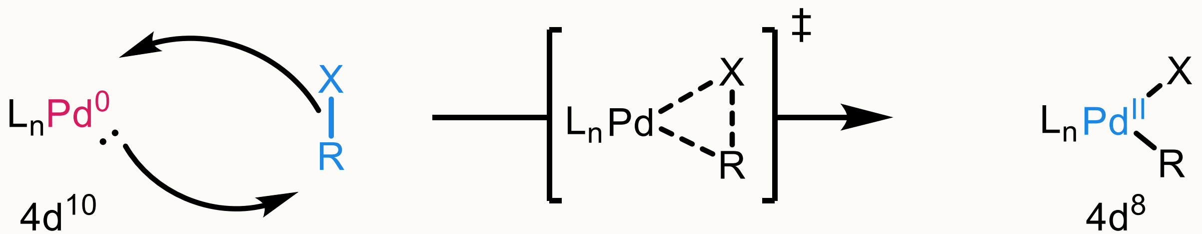
M = Li, MgX, $SnBu_3$,
ZnX, $^{-}B(OH)_3$

- Option 2: Reduction of $Pd(OAc)_2$ with phosphines:



Fundamental reactions: Oxidative addition

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

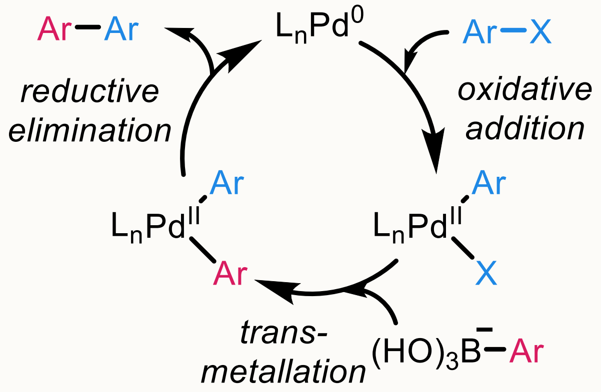


$4d^{10}$ electron rich nucleophilic

electrophilic

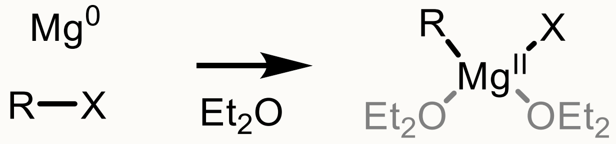
X = I > Br > Cl

$4d^8$ electron poor electrophilic product



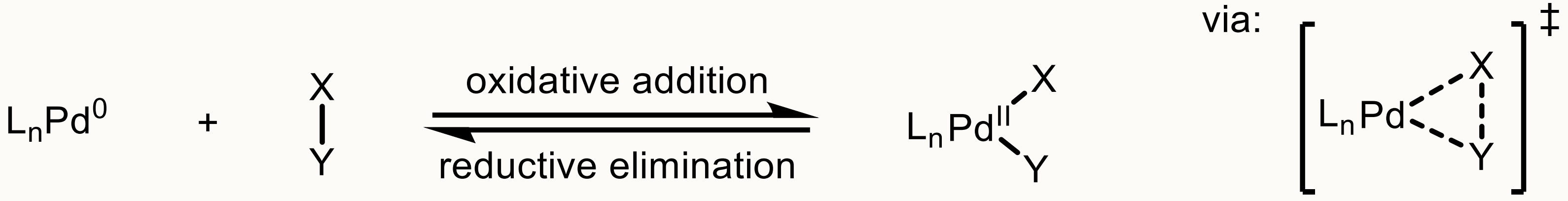
  - The reaction requires two free coordination sites on Pd.
  - Selective *cis*-addition of X and R to the metal centre (concerted reaction).
  - The metal is oxidised from Pd(0) to Pd(II), hence the name *oxidative* addition.
  - It is difficult to show transition metal reactivity with curly arrows.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

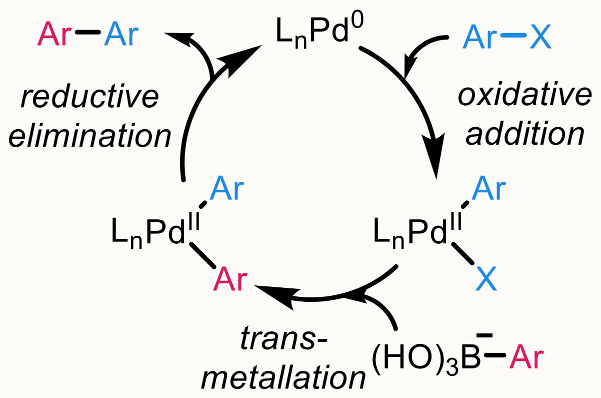
- We have seen oxidative addition before: Grignard reagents (lecture 1).



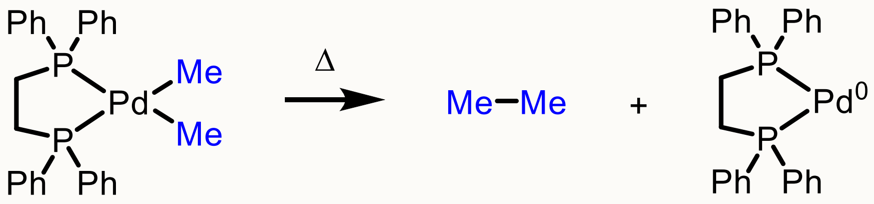
Fundamental reactions: Reductive elimination

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

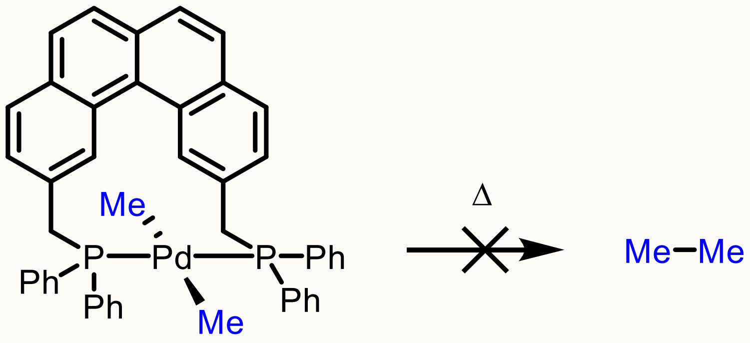




- Reductive elimination removes (eliminates) metal atoms and forms new single bonds (X–Y). The metal is reduced from Pd(II) to Pd(0) in the process.
- The substituents undergoing reductive elimination (X and Y) need to be *cis* to each other:



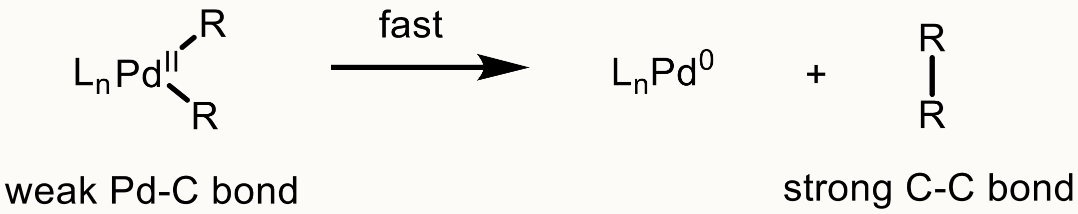
ligands *cis*:
reductive elimination occurs.



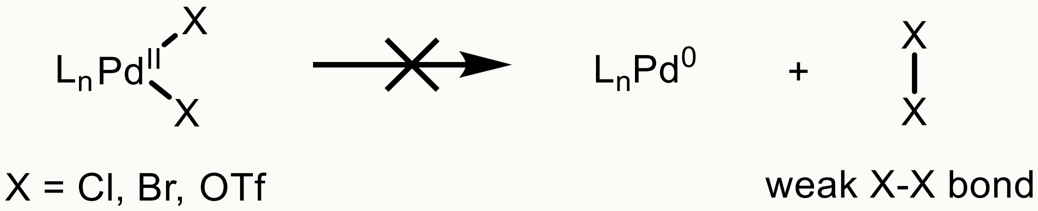
ligands *trans*:
reductive elimination does not occur.

Fundamental reactions: Reductive elimination

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

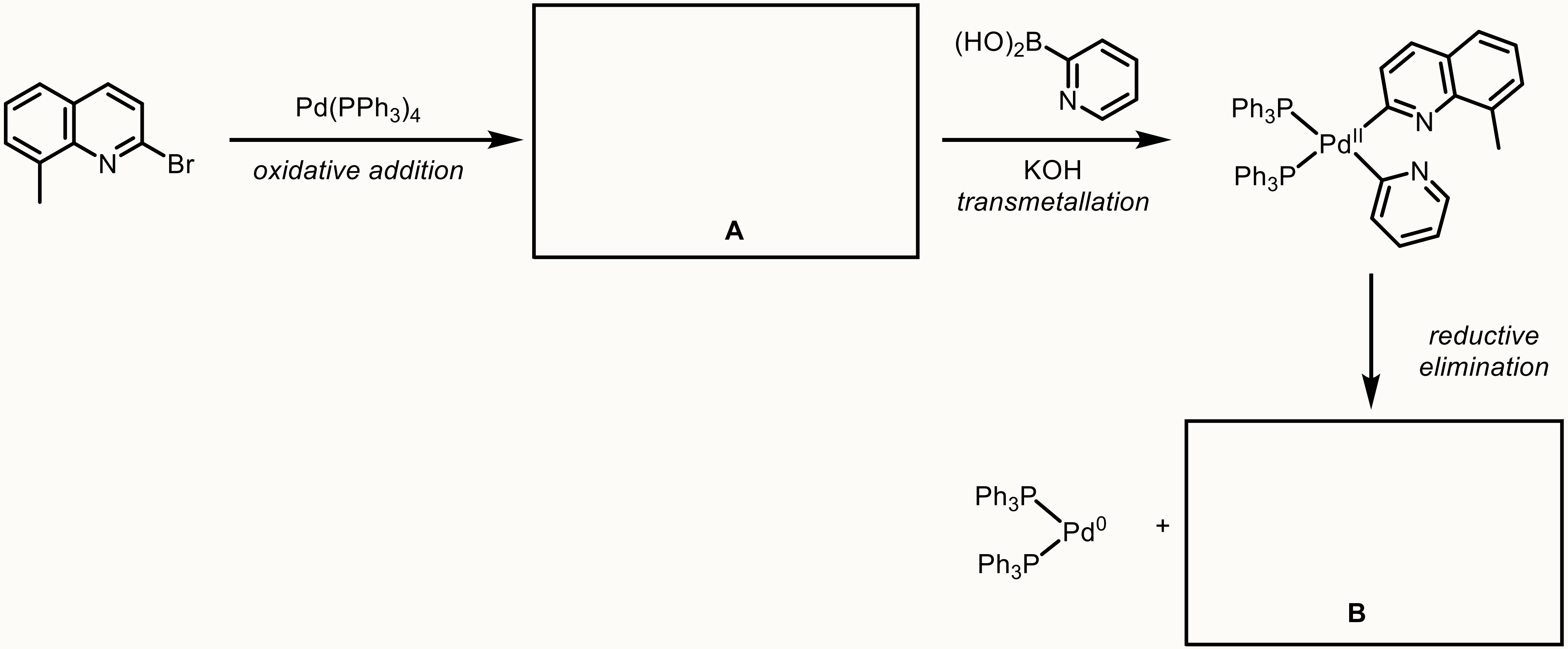


  - It does not occur if the new bond would be weak:

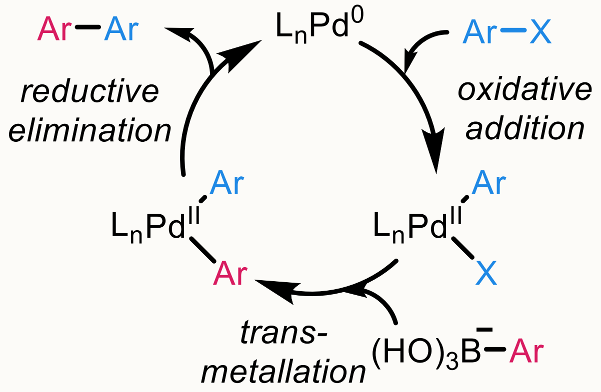


Question

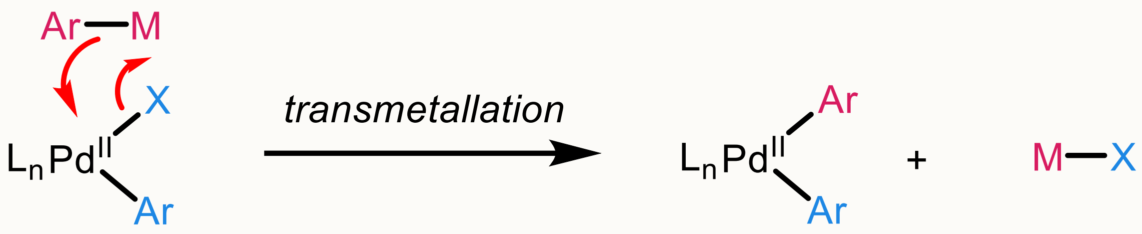
Draw the missing intermediates / products **A** and **B**:



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).

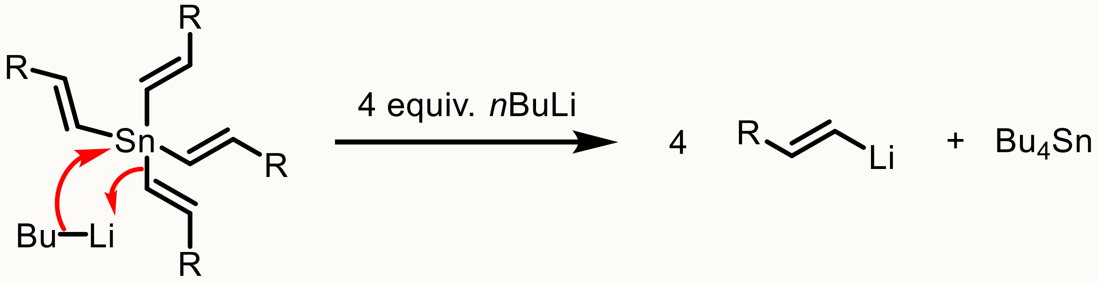


M = ZnX, $SnBu_3$, $^-B(OH)_3$, etc.

driving force:
strong M-X bond

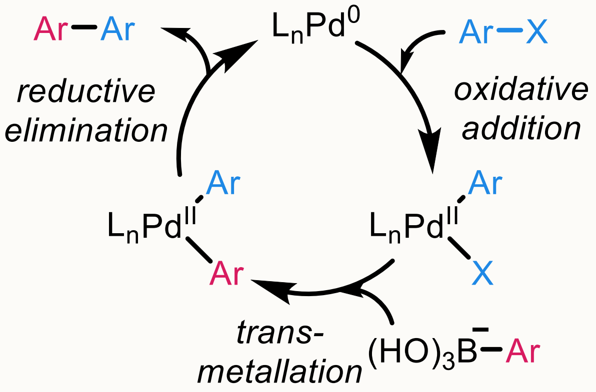
- This step is important, because it allows the transfer of different groups onto palladium which can then be coupled together in the reductive elimination step.

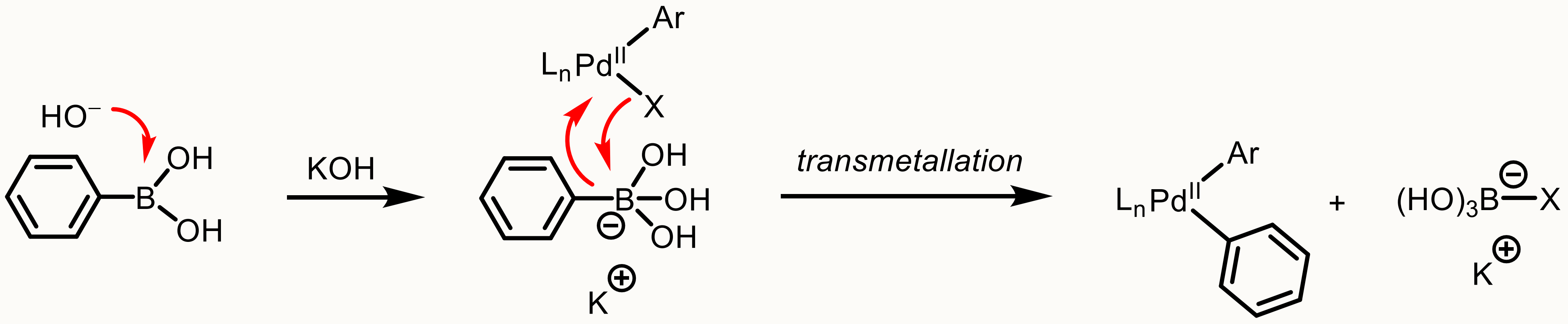
- We have seen transmetallation before: tin-lithium exchange (lecture 2).



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:

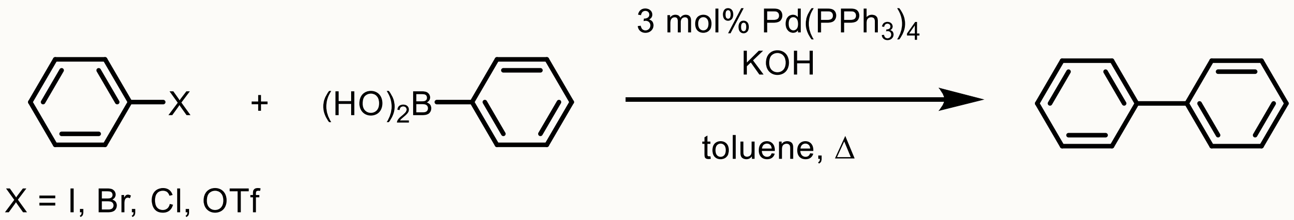


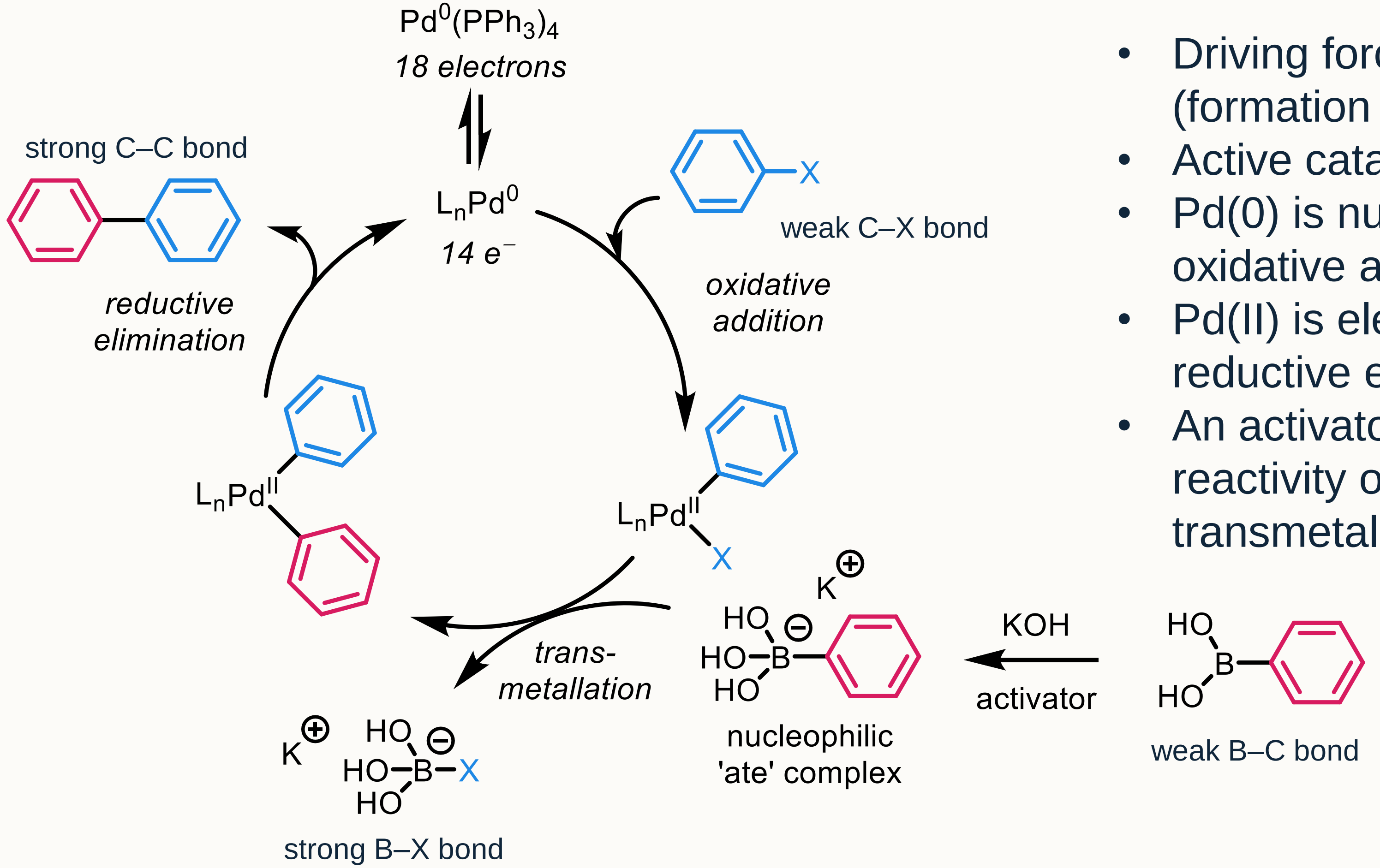


more nucleophilic 'ate' (borate) complex

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

Summary: The Suzuki reaction





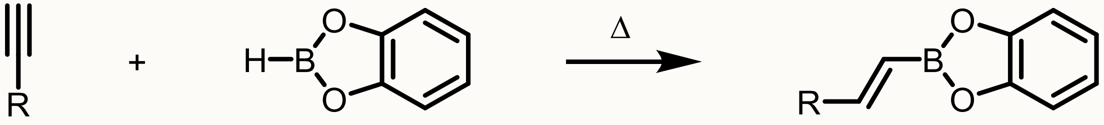
- Driving force: thermodynamics (formation of strong C–C and B–X bonds).
- Active catalyst is coordinatively unsaturated.
- Pd(0) is nucleophilic (electron-rich) and undergoes oxidative addition.
- Pd(II) is electrophilic (electron-poor) and undergoes reductive elimination.
- An activator (HO$^-$ or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

Boronic acids: the coupling partners in Suzuki reactions

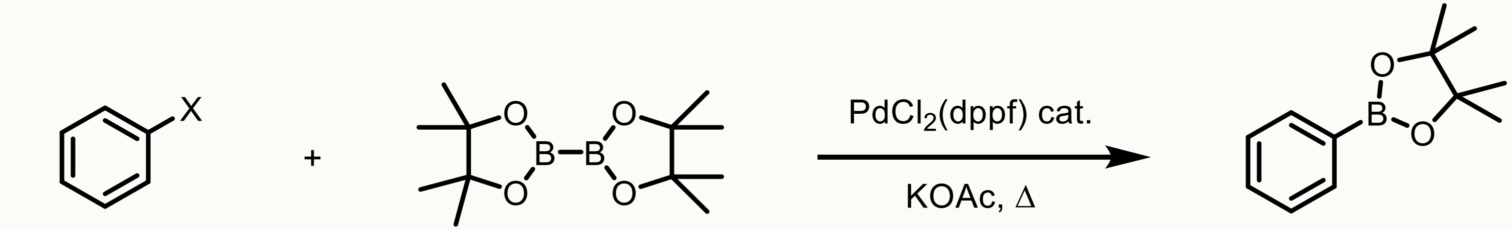
- Boronic acids and esters are readily available reagents that can be made in different ways.
  - Transmetallation from organolithium reagents:

$$R{-}Li \xrightarrow[\textit{transmetallation}]{B(OMe)_3} R{-}B(OMe)_2 \xrightarrow[\textit{fast hydrolysis}]{H_3O^+} R{-}B(OH)_2$$

  - Hydroboration of alkynes and alkenes:



  - Pd cross-coupling (Miayura borylation):



X = Br, I, OTf

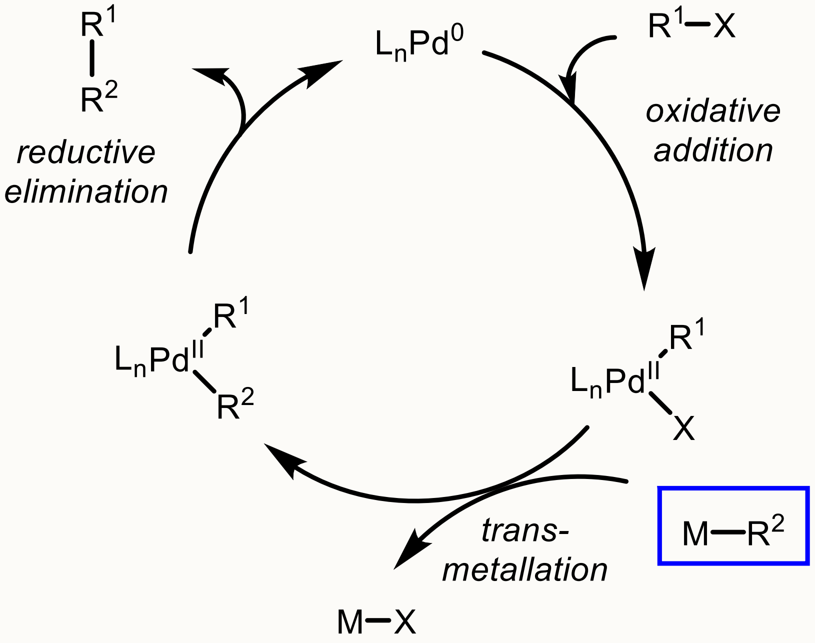
B_2pin_2

Ph-Bpin

- 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:

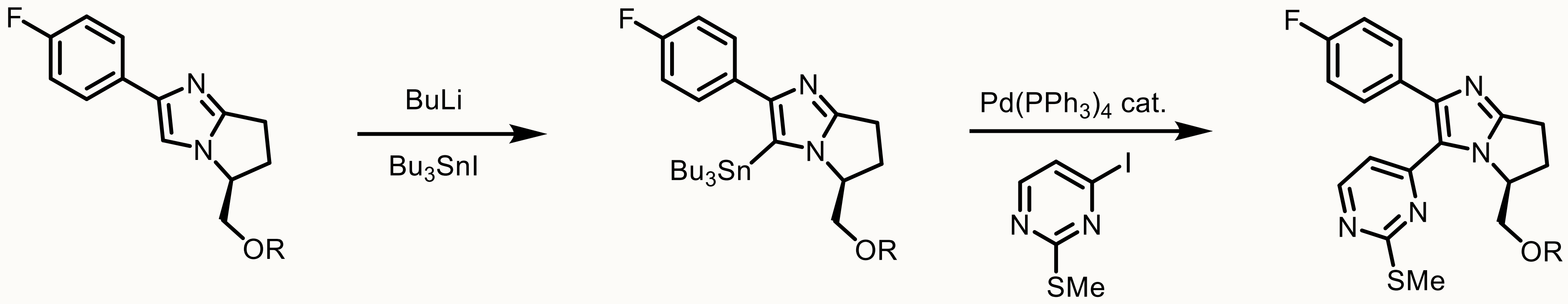


M = $SnBu_3$	Stille reaction
M = ZnX	Negishi reaction
M = Li	Murahashi reaction
M = $SiMe_3$	Hiyama reaction

Alternative coupling partners

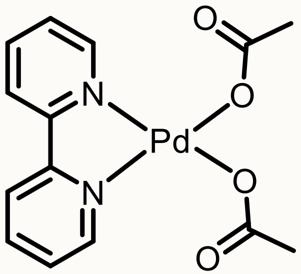
	Advantages	**Disadvantages**
Suzuki (M = $B(OH)_2$)	Very reliable, good substrate scope. Boronic acids readily available.	Activation necessary.
Hiyama (M = $SiMe_3$)		Similar reactivity to $R–B(OH)_2$: activation necessary.
Stille (M = $SnBu_3$)	Good functional group compatibility. More reactive than $R–B(OH)_2$: no activator necessary.	Very toxic!
Negishi (M = ZnX)	Good functional group compatibility. More reactive than $R–B(OH)_2$: no activator necessary.	Oganozinc 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

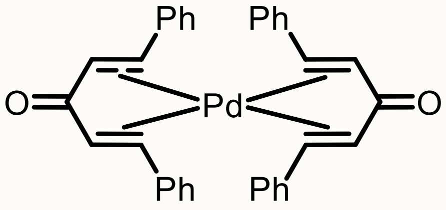


Practice questions

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

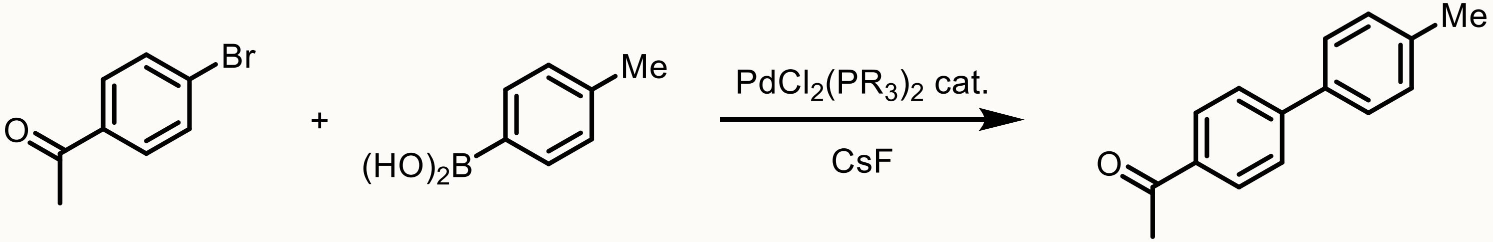


(bipy)Pd(OAc)$_2$



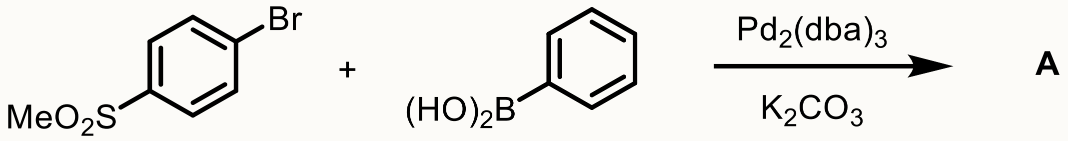
Pd(dba)$_2$

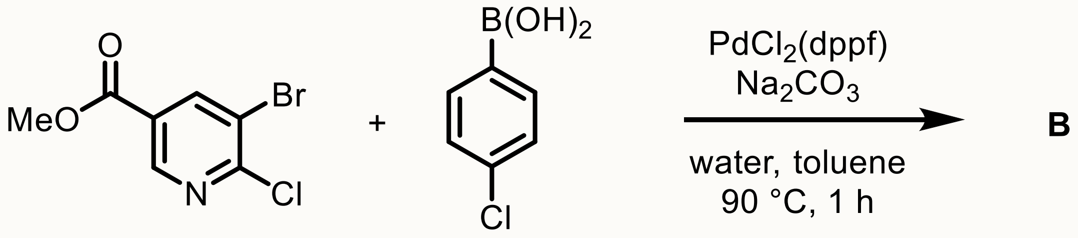
2. Draw a catalytic cycle for the following Suzuki reaction:

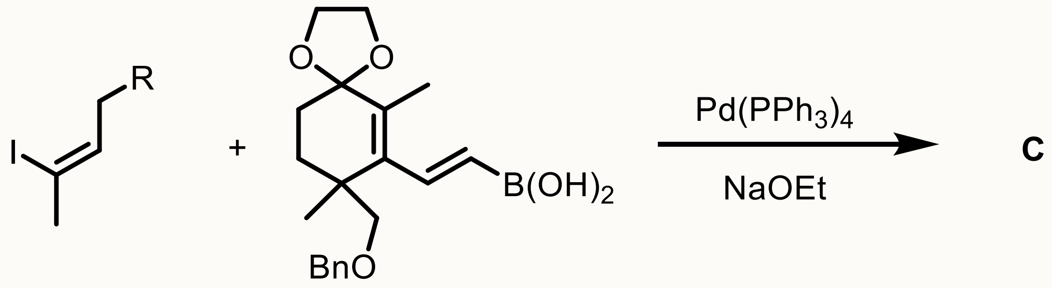


Practice questions

3. Draw the product of the following Suzuki reactions:

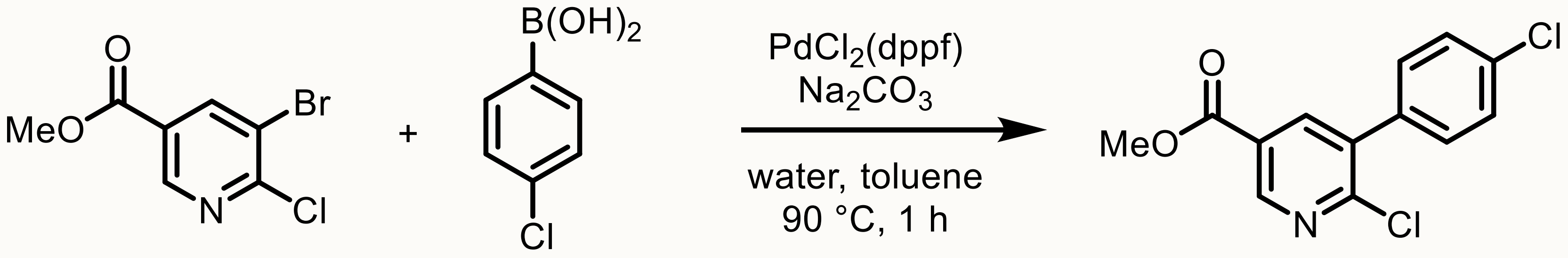






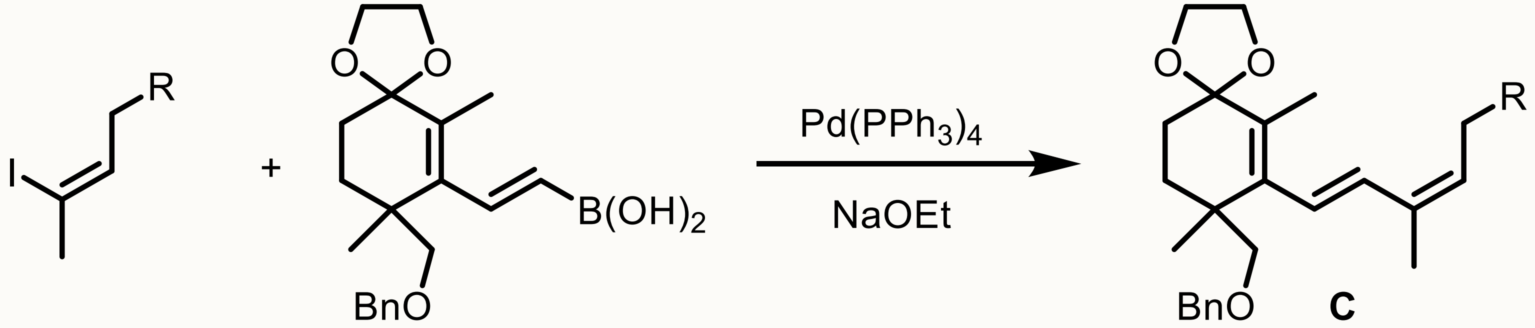
Lectures 5+6: Practice question 3

Draw the product of the following Suzuki reactions:



B

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



C

Alkenes can also be coupled in Suzuki reactions.

<u>But</u>: <u>Alkyl</u> halides are not generally successful coupling partners in Suzuki reactions.

Lecture 7: The Heck reaction

The Heck reaction

Learning outcomes

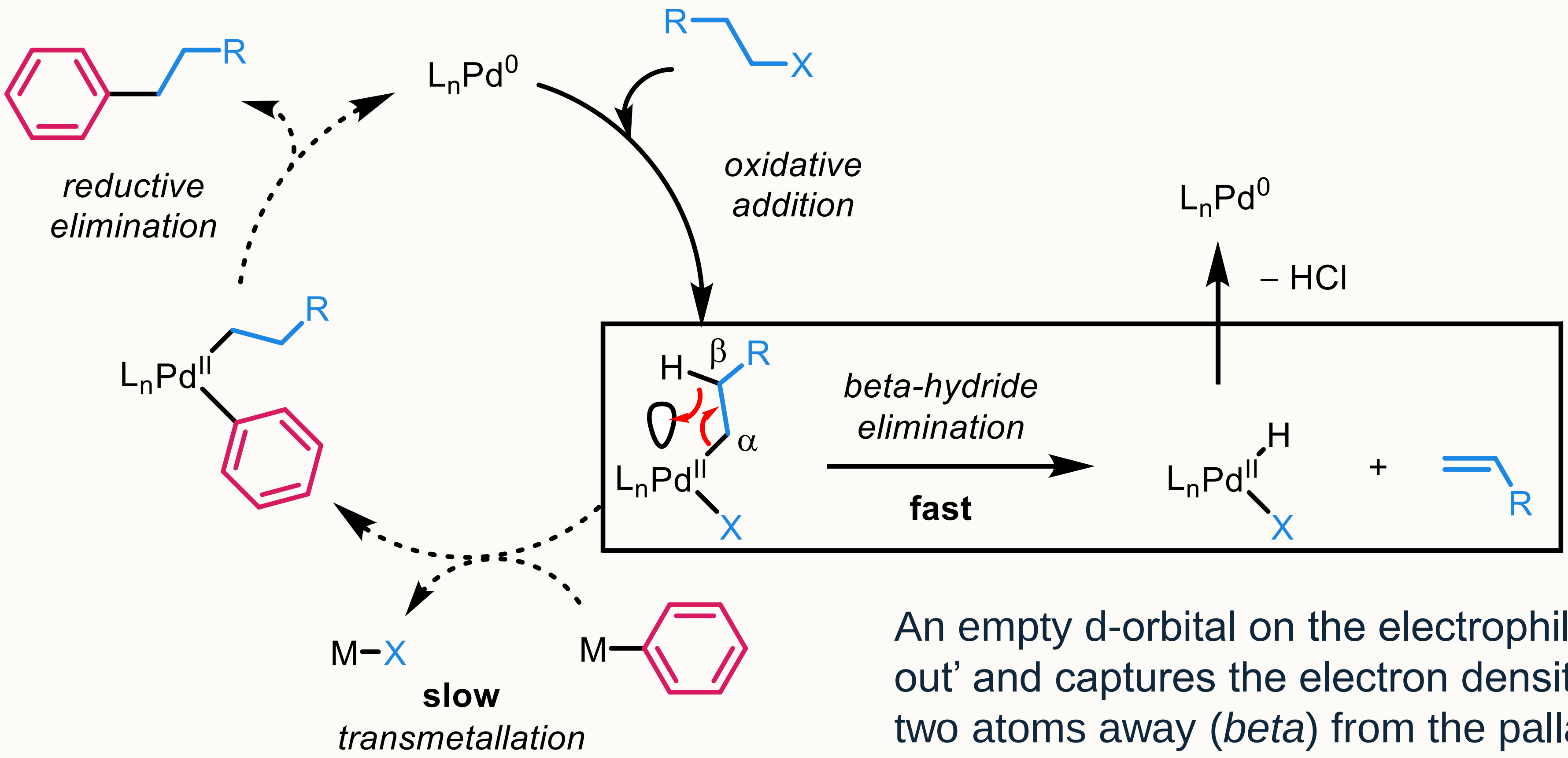
In this lecture, you will learn about:

- two more fundamental reactions in palladium catalysis: *beta*-hydride elimination and ligand migration / carbometallation;
- their role in the Heck reaction.

Recommended Reading: Clayden, Organic Chemistry, Chapter 40

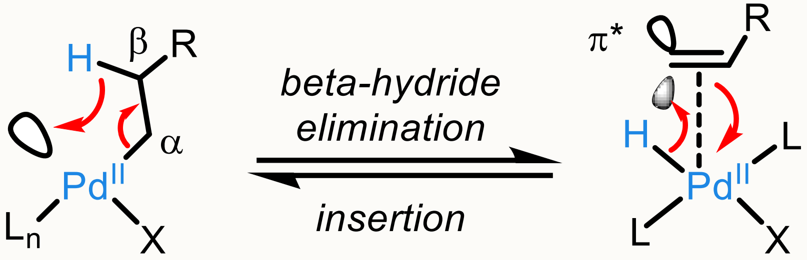
Fundamental reactions: β-Hydride elimination

- 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:



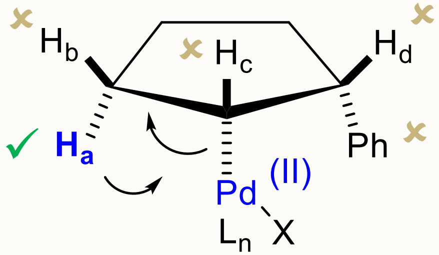
An empty d-orbital on the electrophilic Pd(II) ‘reaches out’ and captures the electron density in a C–H bond two atoms away (*beta*) from the palladium.

Fundamental reactions: β-Hydride elimination



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

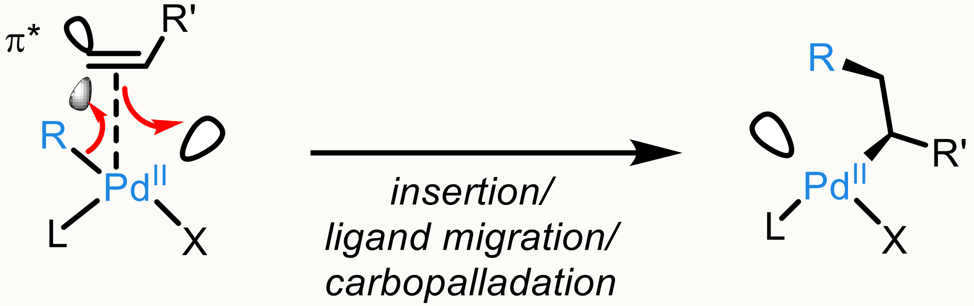
- A *cis* free coordination site on palladium is required.
- Palladium is not oxidised or reduced in this process.
- β-Hydride elimination is **syn** specific, *i.e.* only H_a is eliminated in this complex:



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

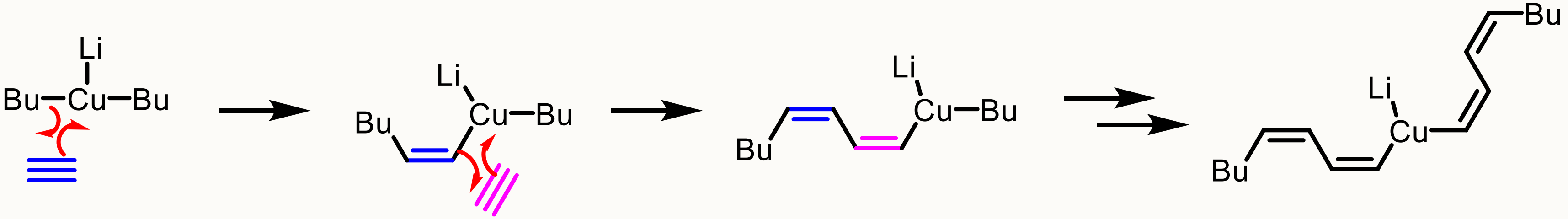
Fundamental reactions: Insertion, Carbometallation / Ligand migration

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



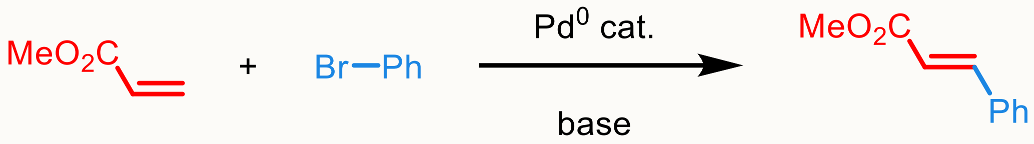
  - Pd is not oxidised or reduced.
  - The reaction is **syn**-specific (R and Pd add to the same face of the alkene).
  - Regioselectivity: R attaches to the less substituted end of the double bond (to avoid steric clash with the substituents on the alkene).
  - The reverse process does not occur readily.

- We have seen carbometallation before: carbocupration (lecture 4).



The Heck Reaction

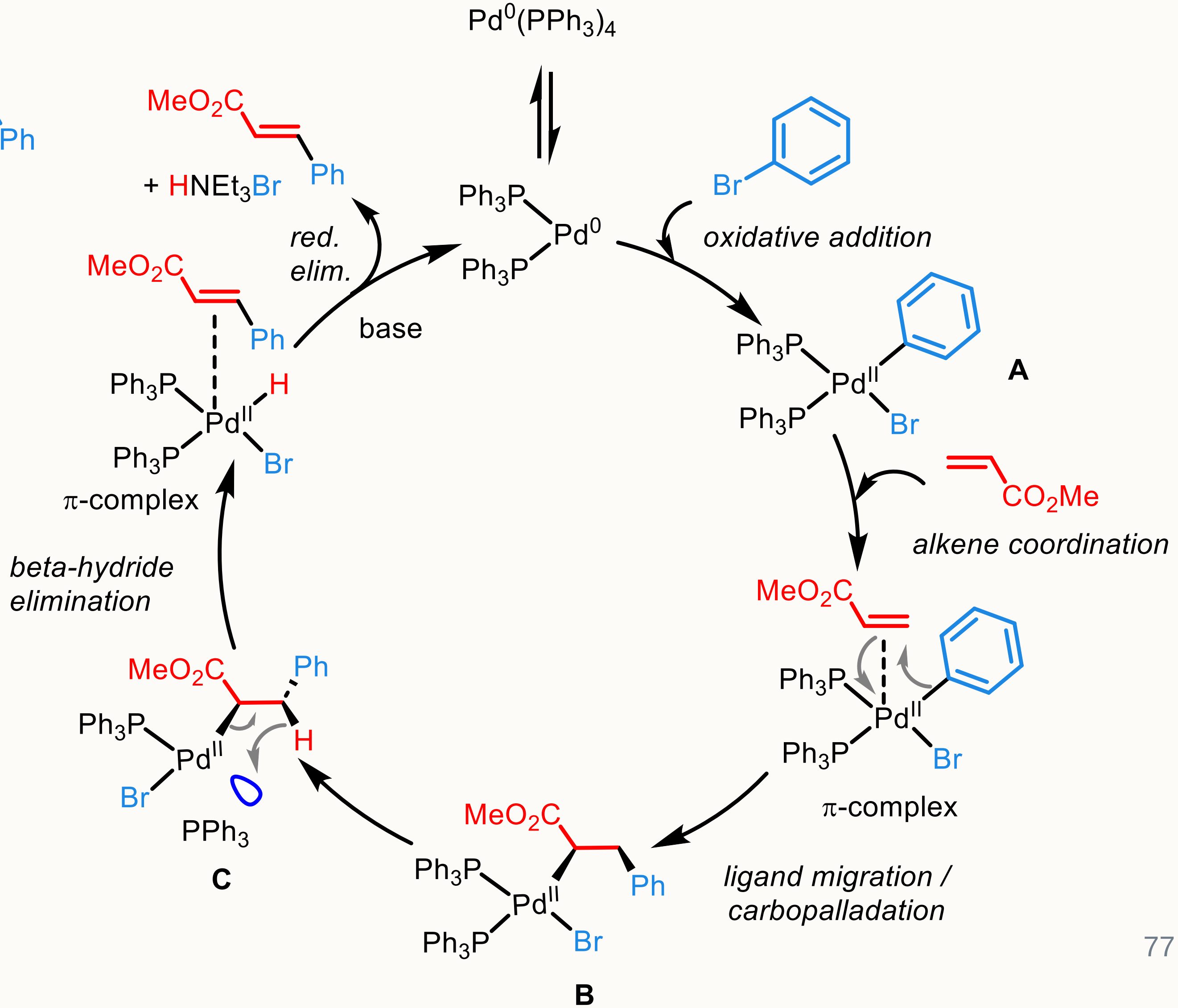
- β-Hydride elimination and carbopalladation are important steps in the Heck reaction:



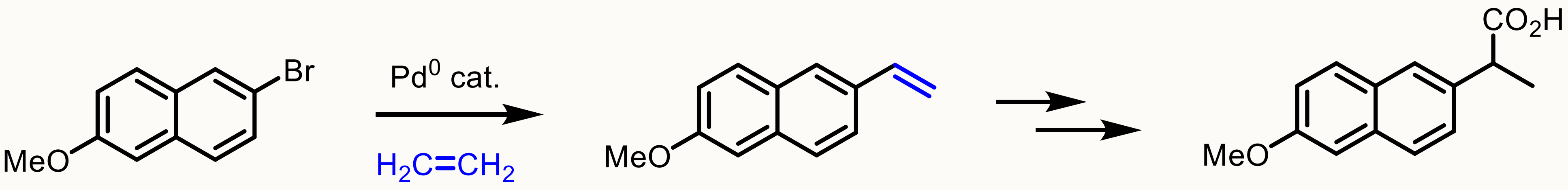
A: Pd^{II} is electrophilic: coordinates to electron-rich alkene.

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 PPh_3 gives a free coordination site (empty d orbital) on Pd required for β-H elimination.



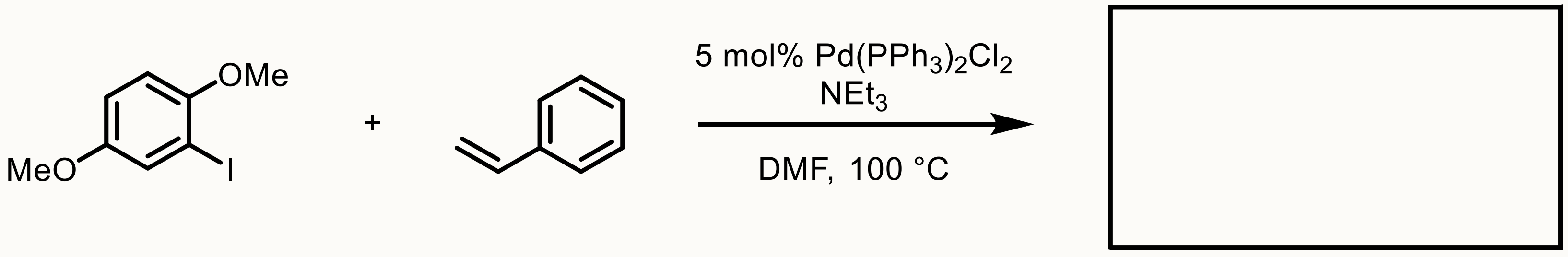
The Heck reaction: An example from medicinal chemistry



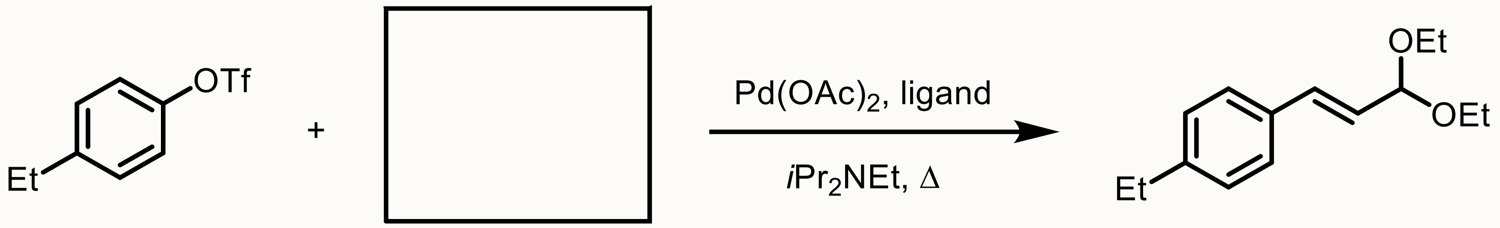
Naproxen
non-steroidal
anti-inflammatory

Questions

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



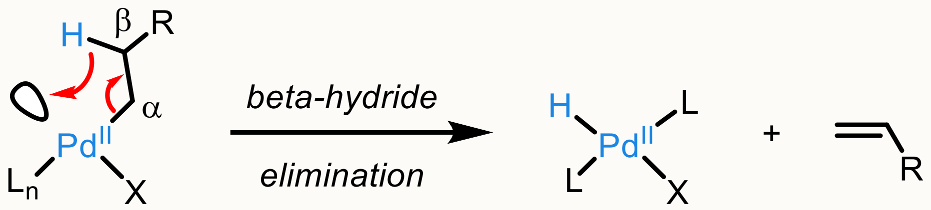
2. Propose a reagent for the following Heck reaction:



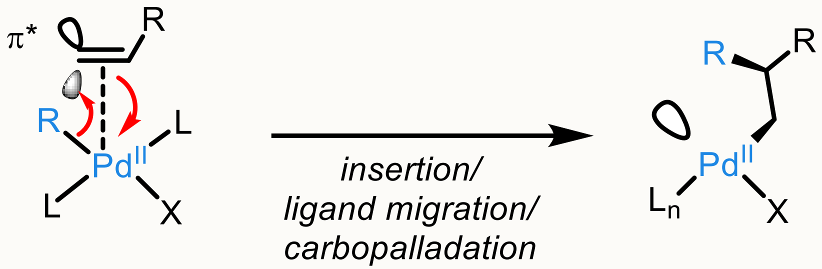
Summary

In this lecture, you learnt:

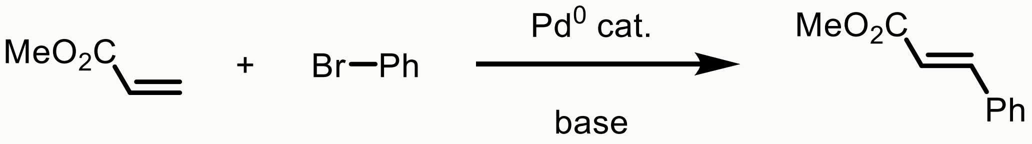
- that Pd(II) σ–alkyl complexes undergo rapid *beta*-hydride elimination:



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

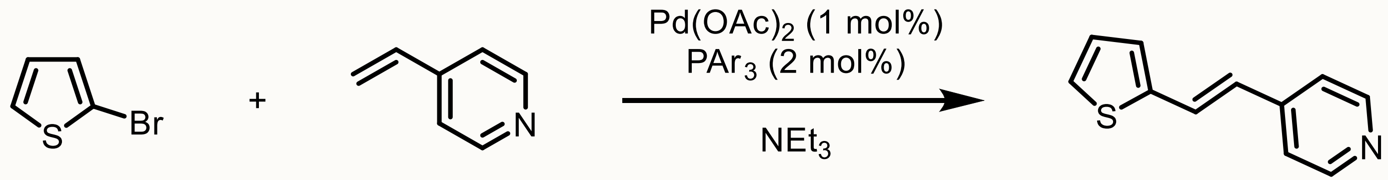


- how these two processes play a key role in the Heck cross-coupling reaction:



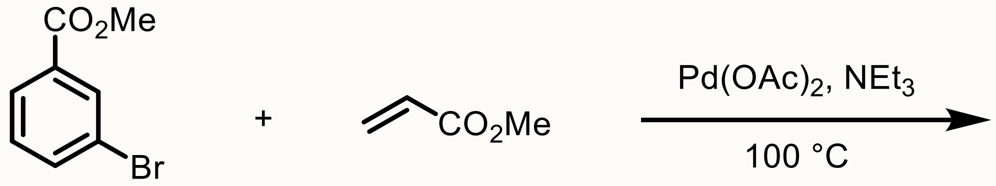
Practice questions

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

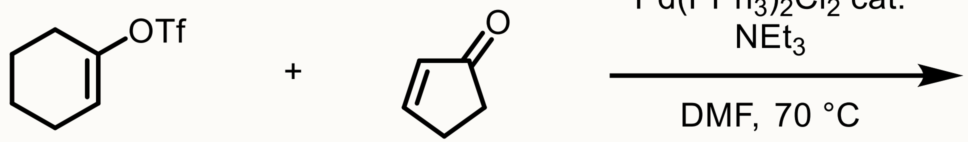


2. Identify the products of the following Heck reactions:

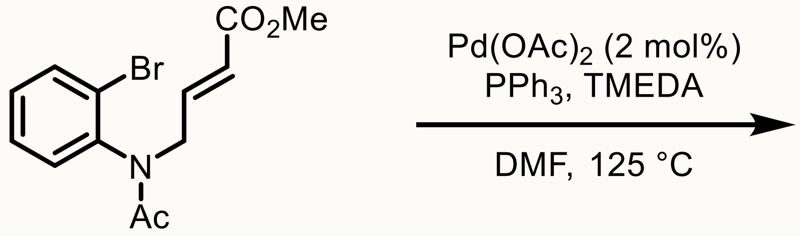
a)



b)



c)



Lecture 8: The Buchwald-Hartwig reaction

The Buchwald-Hartwig reaction

Learning outcomes

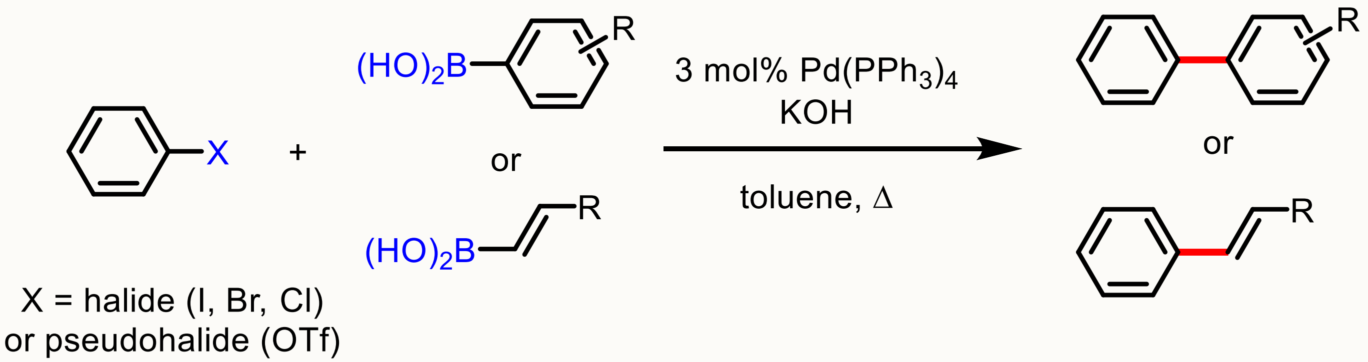
In this lecture, you will learn:

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

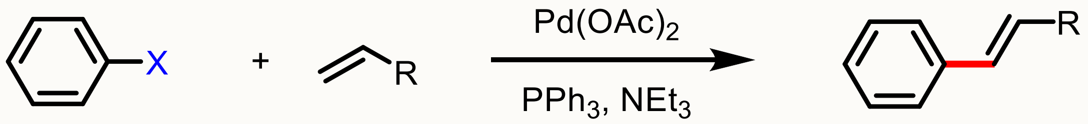
Recommended Reading: Clayden, Organic Chemistry, Chapter 40

Recap: Pd catalysed cross-coupling reactions

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

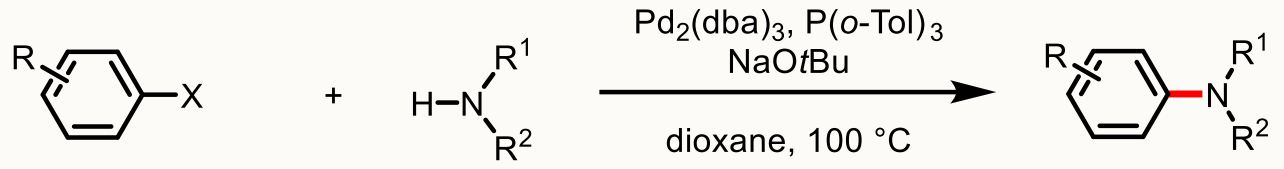


  - Heck reaction:



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

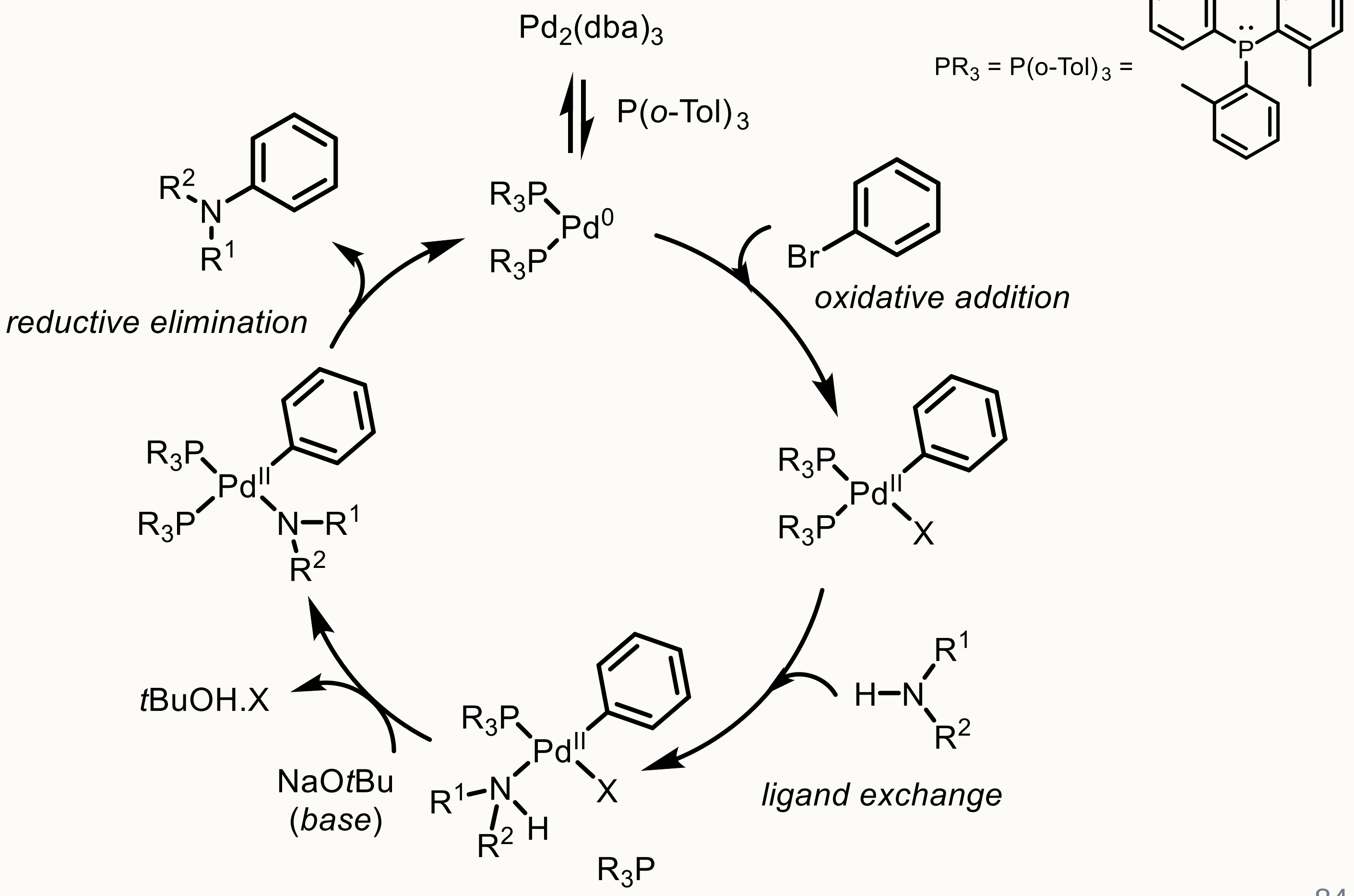
The Buchwald-Hartwig reaction: C–N formation



X = halide (I, Br, Cl)
or pseudohalide (OTf)

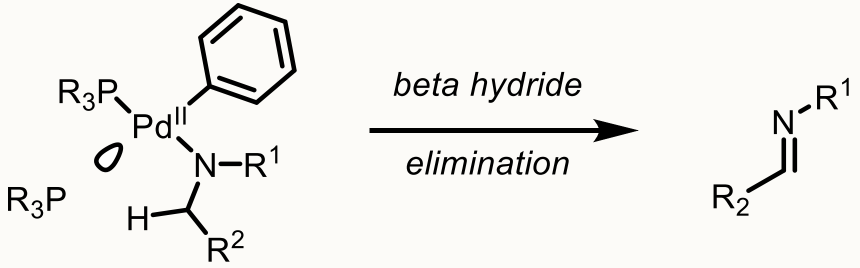
primary or
secondary
amines

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

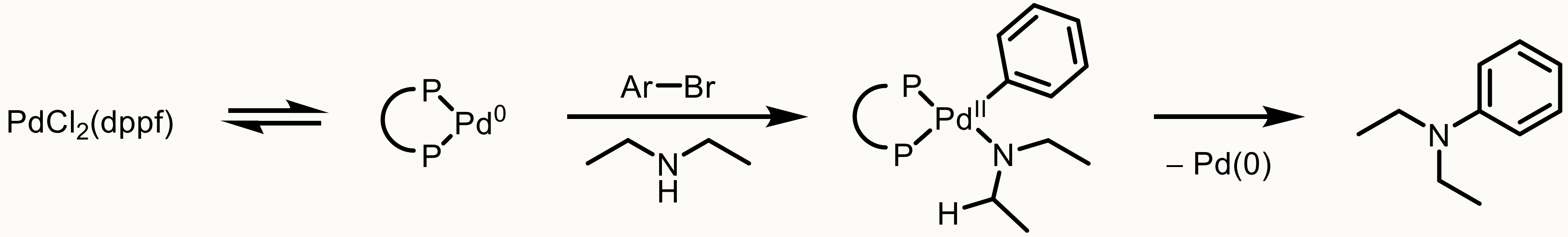


The Buchwald-Hartwig reaction: C–N formation

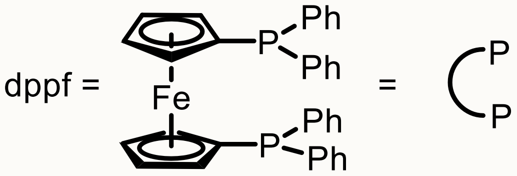
- When alkyl amines are used in this reaction, competing *beta*-hydride elimination can lead to unwanted by-products:



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

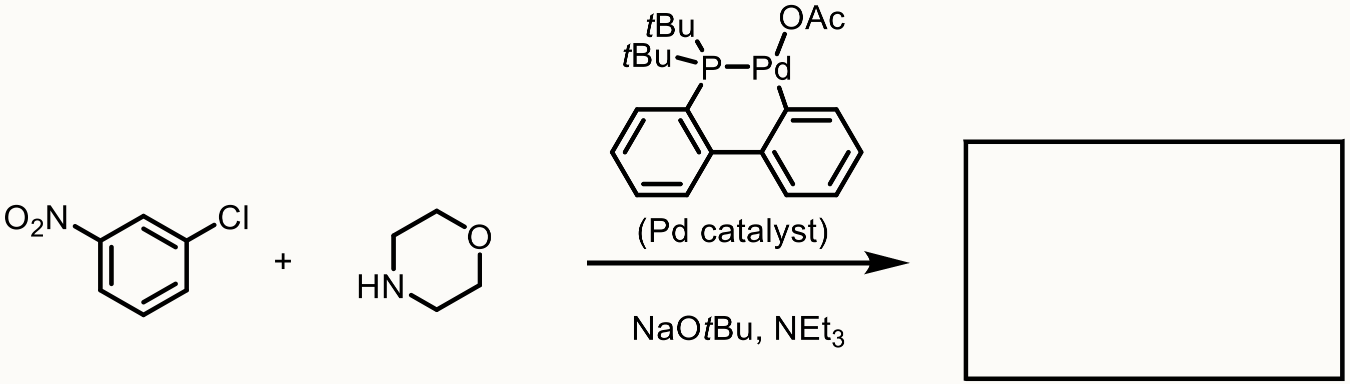


no free coordination site on Pd:
no beta-hydride elimination

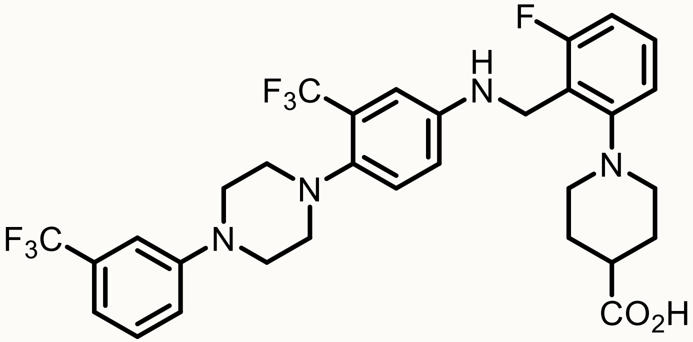


Question

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

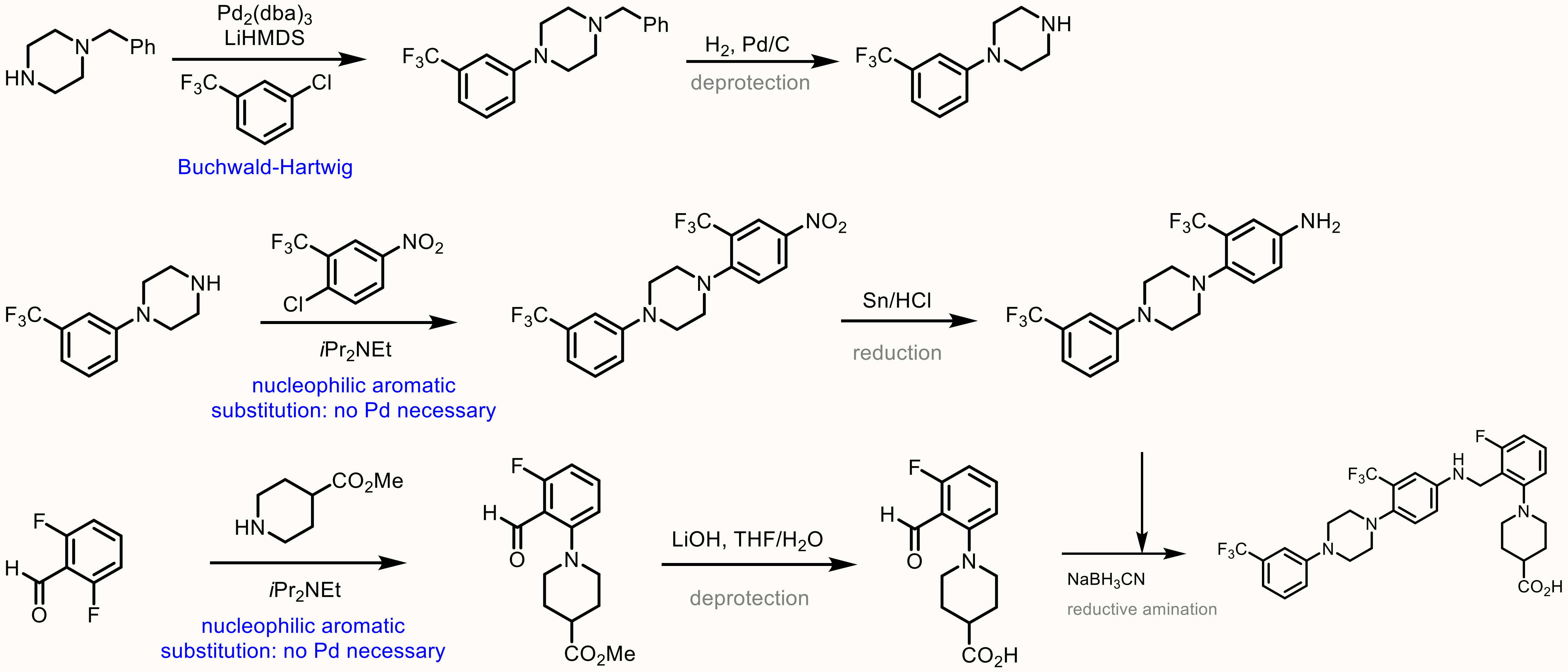


The molecule below is a drug to control blood clotting. Identify the bonds that could be made via Buchwald-Hartwig cross coupling.



Application in medicinal chemistry

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



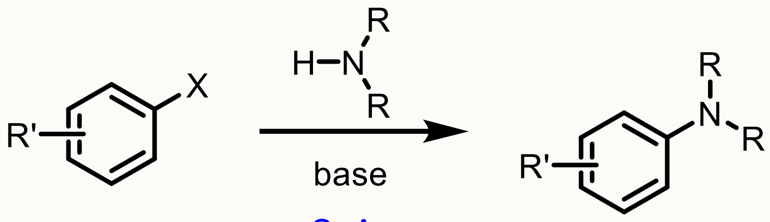
Buchwald-Hartwig

nucleophilic aromatic substitution: no Pd necessary

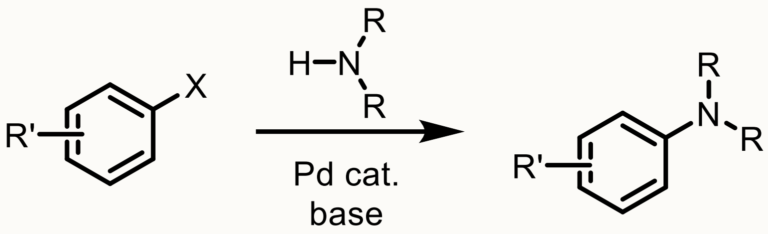
nucleophilic aromatic substitution: no Pd necessary

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?



S_NAr



Buchwald-Hartwig

Nucleophilic aromatic substitution:

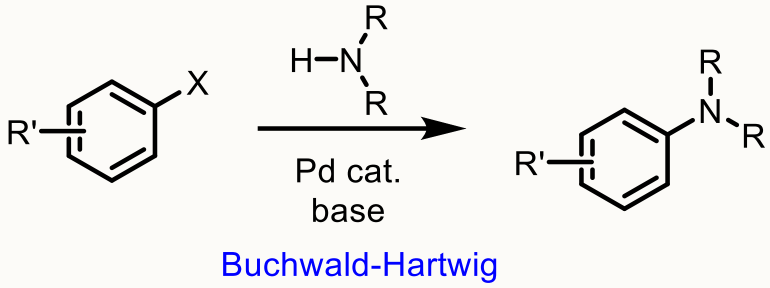
- Leaving group: F > Cl > Br > I
- Regiochemistry: There must be an electron-withdrawing group (R' = F, NO_2, CF_3, etc.) *ortho* or *para* to the leaving group
- No expensive Pd catalyst required.

Buchwald-Hartwig reaction:

- Leaving group: I > Br > Cl >> 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.

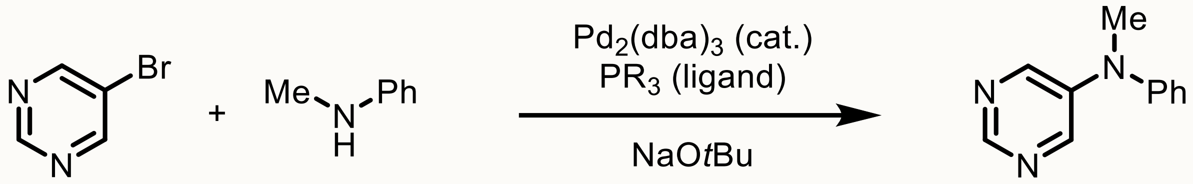


Next lecture: **workshop**.

Next week, we will work through the practice questions together, and I will answer any questions you have on the material.

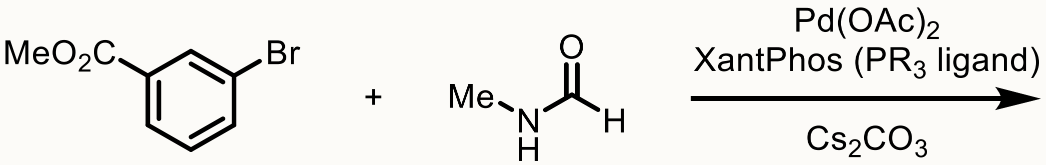
Practice questions

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

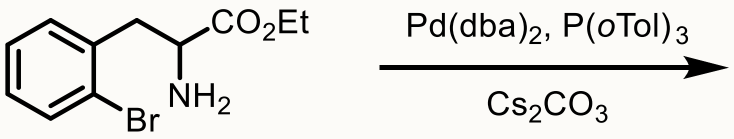


2. Identify the products of the following Heck reactions:

a)



b)



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.

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

b) Why is it not possible to use an S_NAr strategy for the synthesis of this molecule?