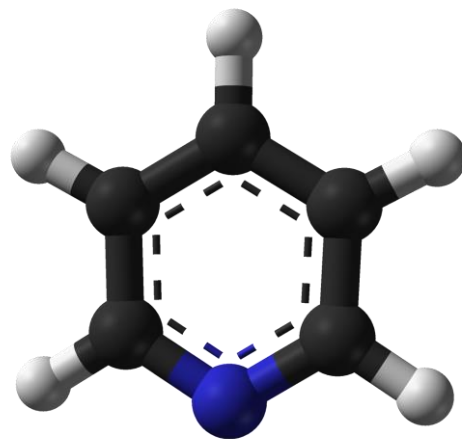


2302687 – Heterocyclic Compounds – Part I

Lecture 3-5

Reactivities of Heteroaromatics – Organometallic



Instructor: Dr. Tanatorn Khotavivattana

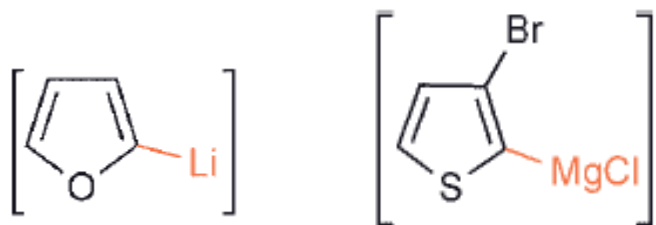
E-mail: tanatorn.k@chula.ac.th

Recommended Textbook:

Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

5) Types of Organometallic Heterocyclic Compounds

- 1) **Nucleophilic and Basic:**
Lithium and Magnesium

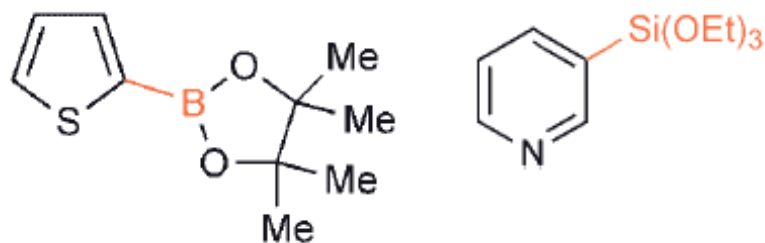


- 2) **Nucleophilic but Non-basic :**
Zinc, Aluminium and Tantalum

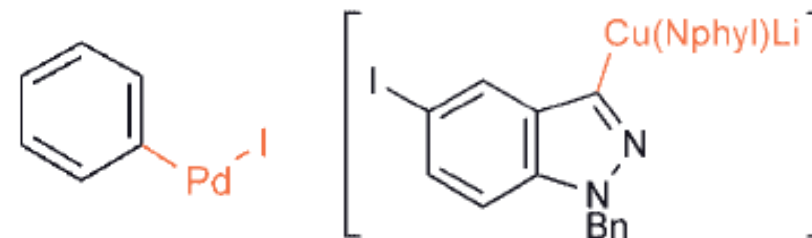


- 3) **Non-nucleophilic:**
(acts as a nucleophilic partner in TM-catalysed coupling reactions)

Boron and Silicon



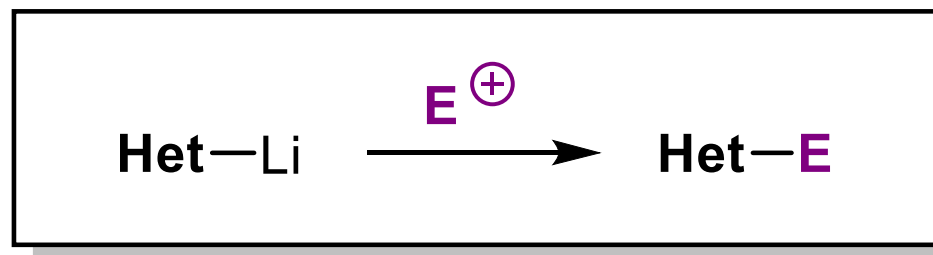
- 4) **Transition Metal Intermediates:**
Palladium, Copper, Rhodium and Nickel



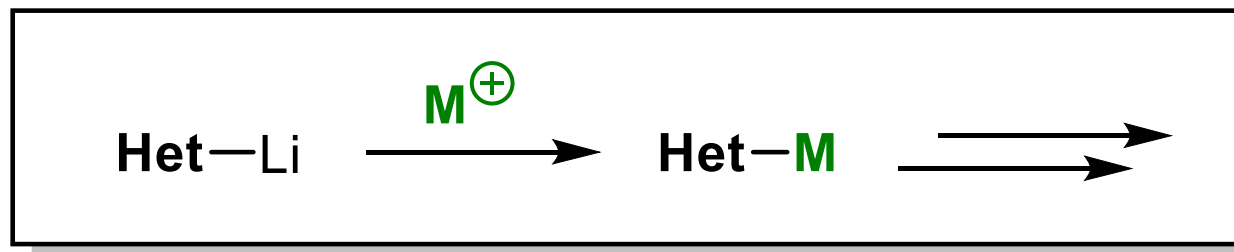
5) Organolithium

Lithio-heterocycles have proved to be the *most useful organometallic derivatives*:

- They **react with the whole range of electrophiles** in a manner exactly comparable to that of aryllithiums (eg. Ph-Li)



- They are often the most convenient source of heterocyclic derivatives of **less electropositive metals**, such as zinc, boron, silicon and tin



5) Organolithium – Preparation

1) Direct Lithiation

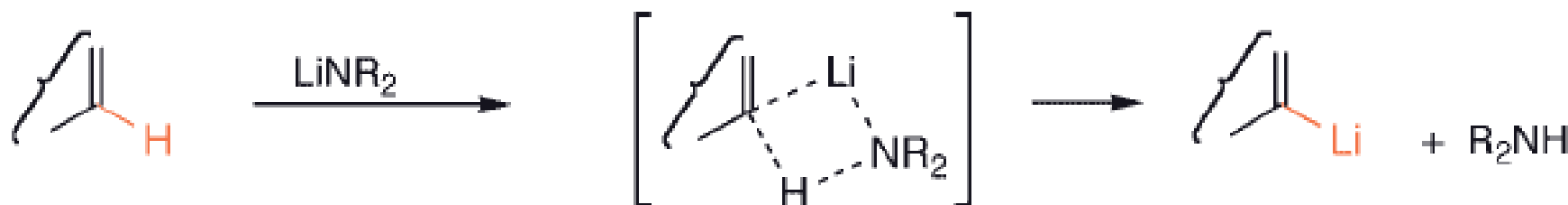
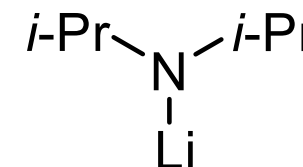
- Many heterocyclic systems react directly with **lithiating agents** to give the lithio-heterocycle via abstraction of a proton

- Lithiating Agents:**

- Alkylolithiums** (*n*-Butyllithium [*n*-BuLi] is the most widely used)

- Lithium amides**

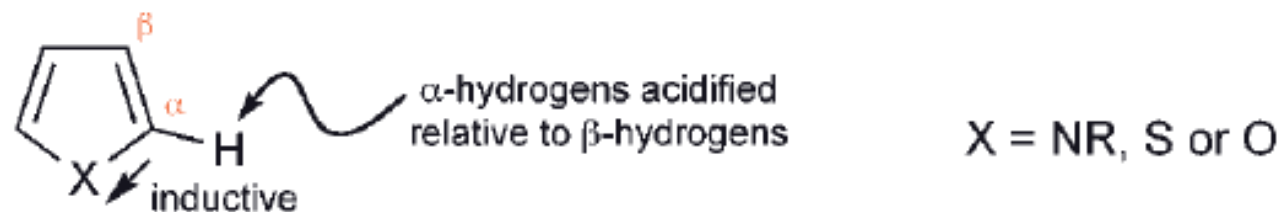
(Lithium diisopropylamide [LDA] is the most widely used)



- The ease of lithiation correlates well with C-hydrogen **acidity** and with the **stability** of the corresponding conjugate base

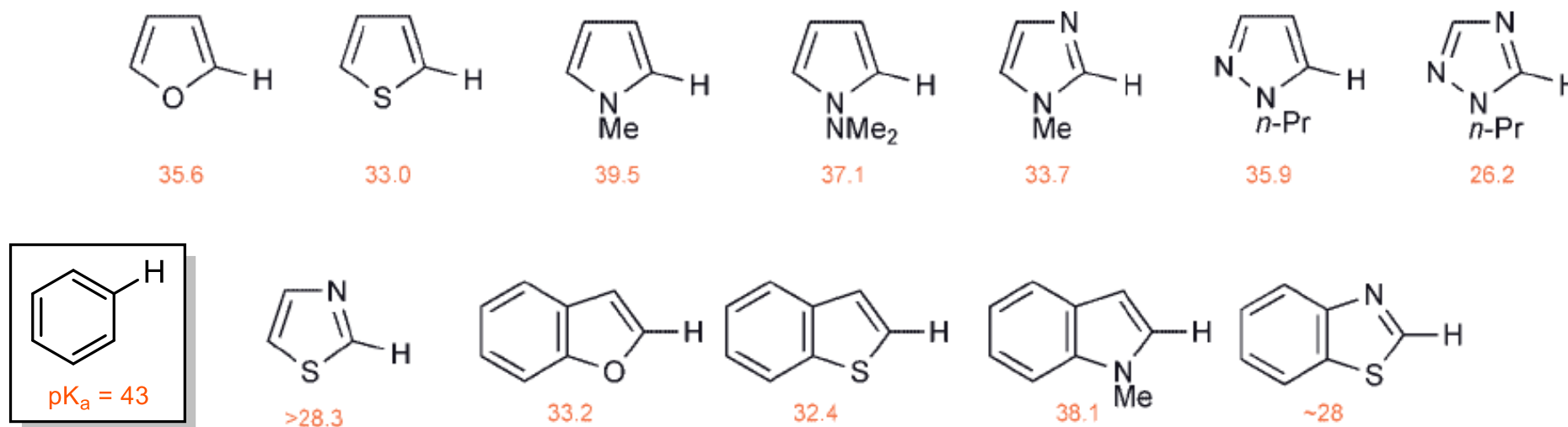
5) Organolithium – Preparation

1) Direct Lithiation – *Five-Membered Heterocycles*



The **inductive effect of the heteroatom** allows direct α -lithiation

Relative Acidities



Equilibrium pK_a values[#] for deprotonation of some five-membered heterocycles in THF

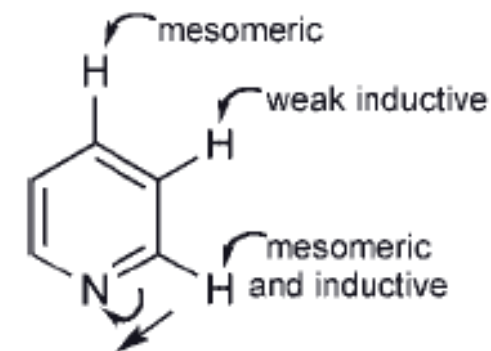
[#] Measured pK_a values vary according to solvent etc.

5) Organolithium – Preparation

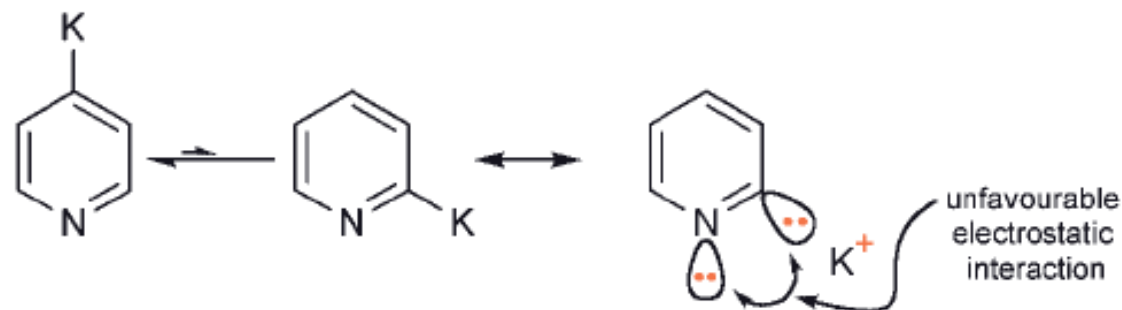
1) Direct Lithiation – *Six-Membered Heterocycles*

In contrast to five-membered rings, the direct metallation of pyridine is quite difficult and complex

The pyridine α - and γ -positions, being more electron-deficient than a β -position, have the kinetically most acidic protons



Generally, negative charge at the γ -position is the more stable, due to **unfavourable repulsion** between the nitrogen lone pair and the α -‘anion’



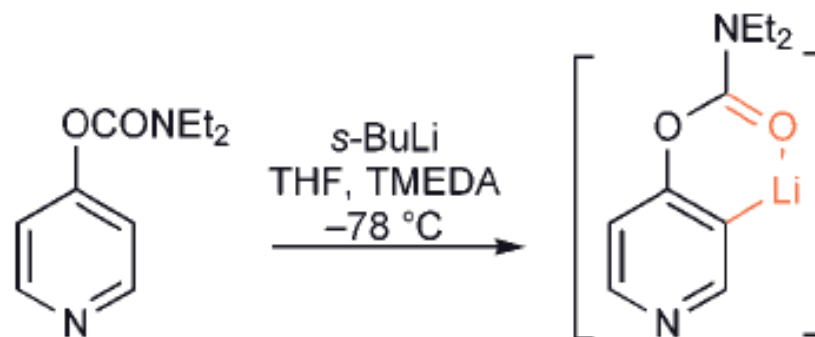
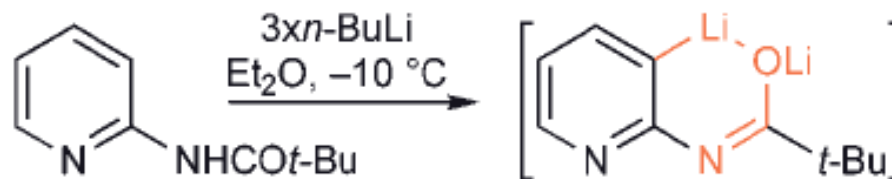
In **non-polar solvents**, stronger coordination of the metal cation with the nitrogen lone pair will reduce this repulsive interaction and thus increase the relative stability of the α -‘anion’

5) Organolithium – Preparation

1) Direct Lithiation – *Six-Membered Heterocycles*

Pyridines carrying **groups which direct metallation ortho**, using chelation and/or inductive influences, can be directly lithiated;

When the group is at a **2-** or **4-**position, lithiation must occur at a **β -carbon**



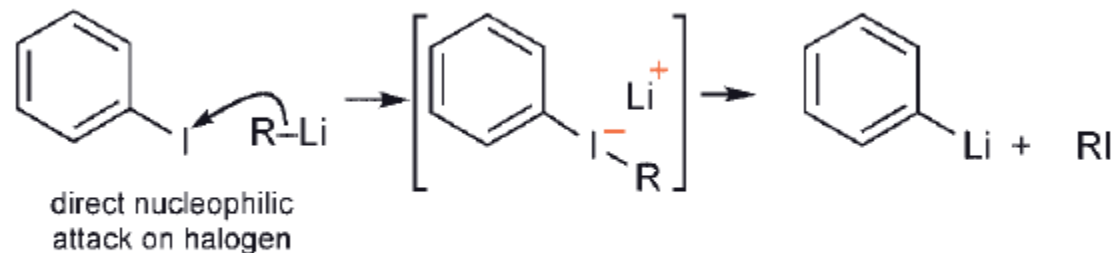
5) Organolithium – Preparation

2) Halogen Exchange

- **Bromo-** and **iodo-**heterocycles react rapidly with **alkyllithiums**, even at temperatures as low as $-100\text{ }^{\circ}\text{C}$, to give the lithio-heterocycle



- The exchange process may involve a four-membered or other **cyclic concerted transition state**, or may possibly proceed via a **direct nucleophilic attack**



Possible mechanisms for metal–halogen exchange

5) Organolithium – Preparation

It is very important to differentiate between

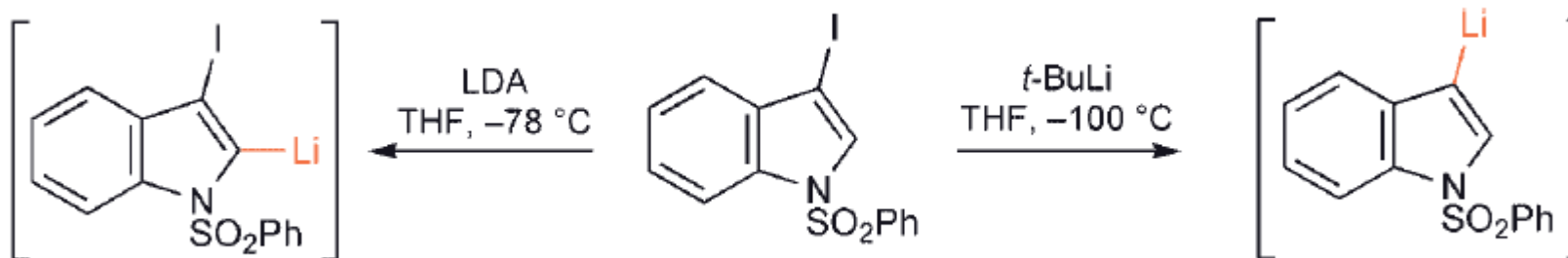
- **pure bases**, such as **lithium diisopropylamide (LDA)**, which act only by deprotonation

and

- **alkyllithiums**, which can act as **bases** or take part in **halogen exchange**

When using alkyllithiums, exchange is favoured over deprotonation by the use of lower temperatures

The reaction of 3-iodo-1-phenylsulfonylindole with the two types of reagent is illustrative



Homework #1

Select 3 papers that demonstrate different types of reactions of heteroaromatic compounds (this could be a part of synthesis route for different types of compounds).

Prepare a video (3-5 minutes) that discuss the key step using the knowledge from this lecture. Post the URL link into the discussion board in the BB system.

Study the videos of your friends and ask questions (as a reply to the URL link).

Prepare for a discussion class in the following zoom meeting.