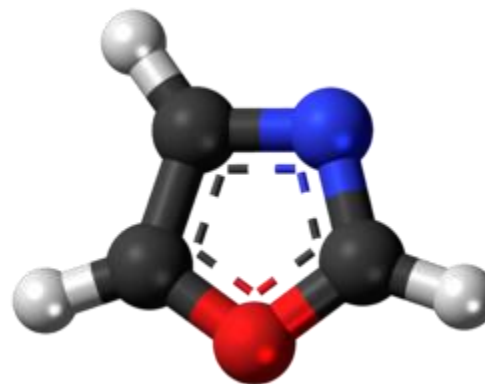


## Reactivities of 1,2 and 1,3-Azoles Part 2

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*Instructor: Dr. Tanatorn Khotavivattana*

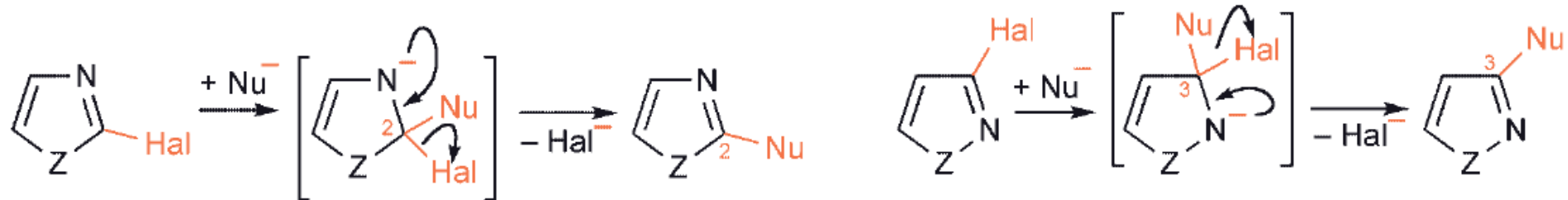
*E-mail: tanatorn.k@chula.ac.th*

**Recommended Textbook:**

*Heterocyclic Chemistry*, 5<sup>th</sup> Edition, J. A. Joule, K. Mills, **2010**, Wiley

### 3) Nucleophiles Substitution

Nucleophilic substitution of halogen follows the **pyridine pattern**

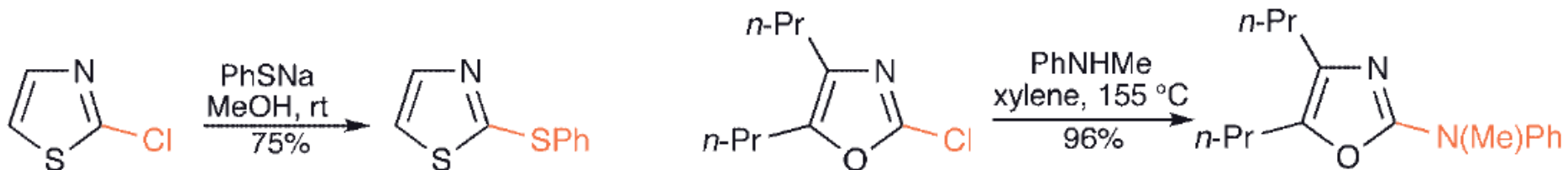


Intermediates for nucleophilic displacements on azoles

it is much faster at the **2-position of 1,3-azoles** and at the **3-position of 1,2-azoles**, than at other ring positions

Resonance contributors to the intermediates for such substitutions make the reason for this plain: the imine nitrogen can act as an electron sink for the attack, only at these positions

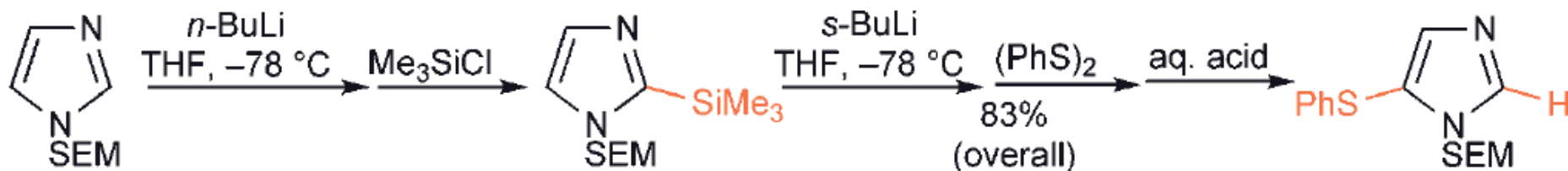
#### Examples



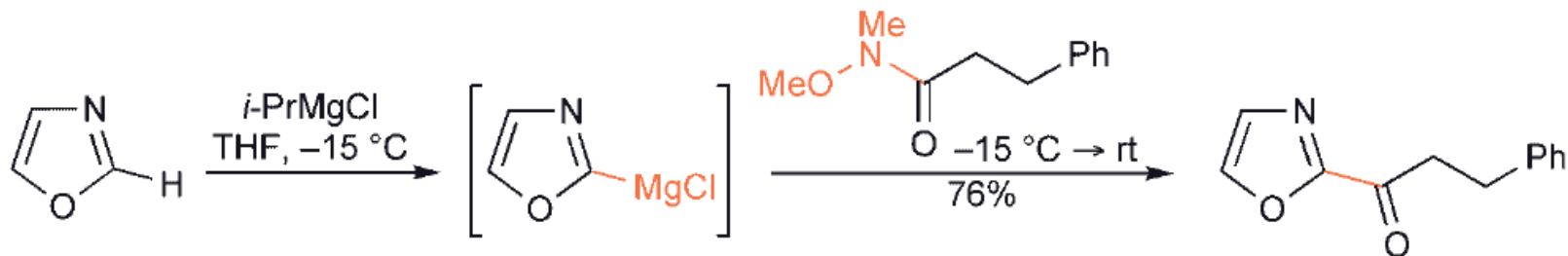
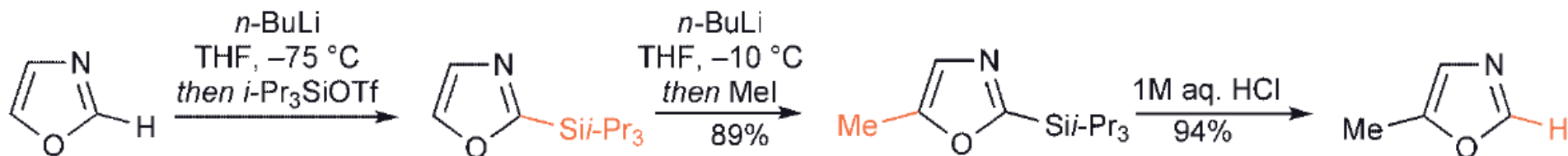
## 4) C-Metallation; 4.1) Direct Ring C–H Metallation

### 1,3-Azoles

Preparative strong-base lithiation of oxazoles, thiazoles and *N*-methylimidazole takes place preferentially at **C-2**, or at C-5 if the former position is substituted



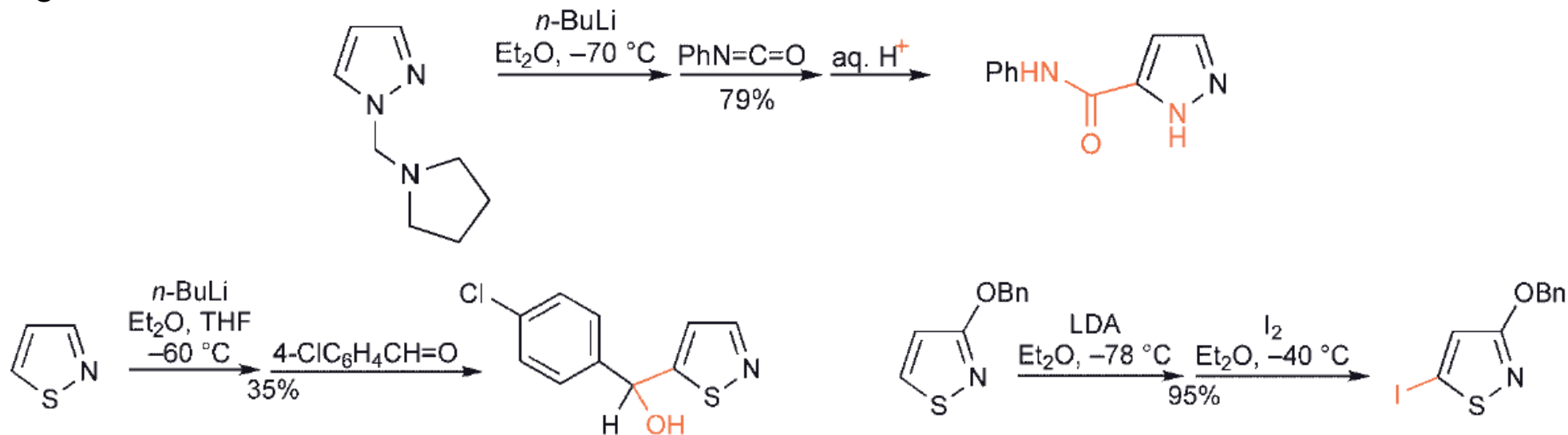
The intrinsic tendency to lithiate at C-2, then C-5, taken with metal–halogen exchange processes for the 4-position, are a powerful combination for elaborations of the 1,3-azoles



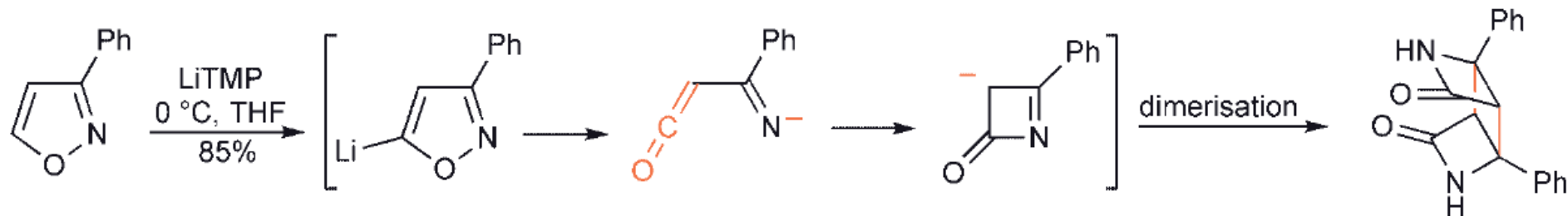
## 4) C-Metallation; 4.1) Direct Ring C–H Metallation

### 1,2-Azoles

The lithiation of 1,2-azoles take place at **C-5**; The C-5-lithiation of pyrazoles requires the absence of the N-hydrogen

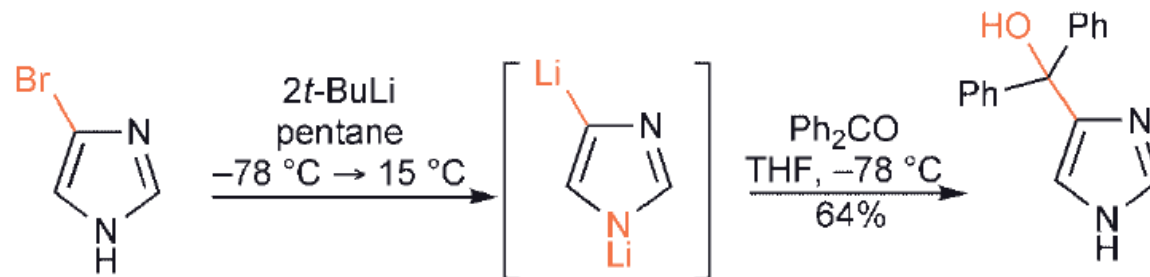
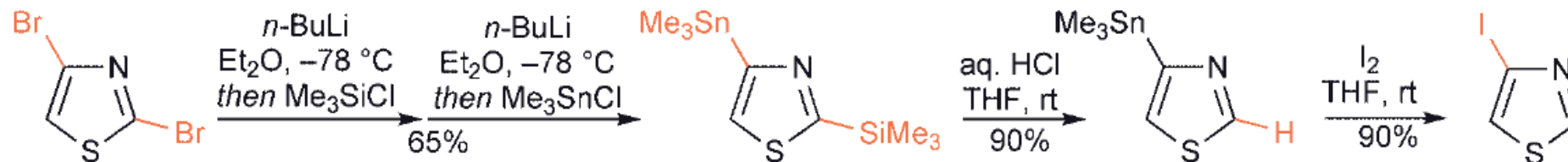


Attempted C-lithiation of isoxazoles with hydrogen at C-3 leads to **ring opening**

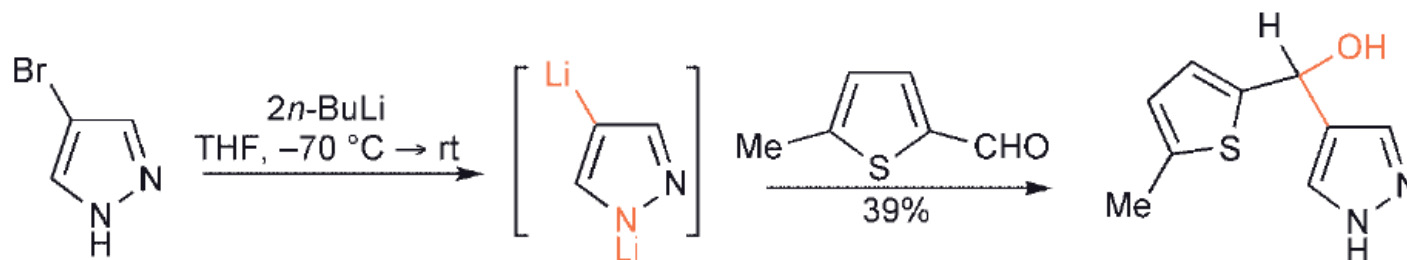


## 4) C-Metallation; 4.2) Metal–Halogen Exchange

**1,3-Azoles** The regioselectivity of metal–halogen exchange processes mirrors the C–H metallations: thus 2,4-dibromothiazole reacts at **C-2** firstly



## 1,2-Azoles

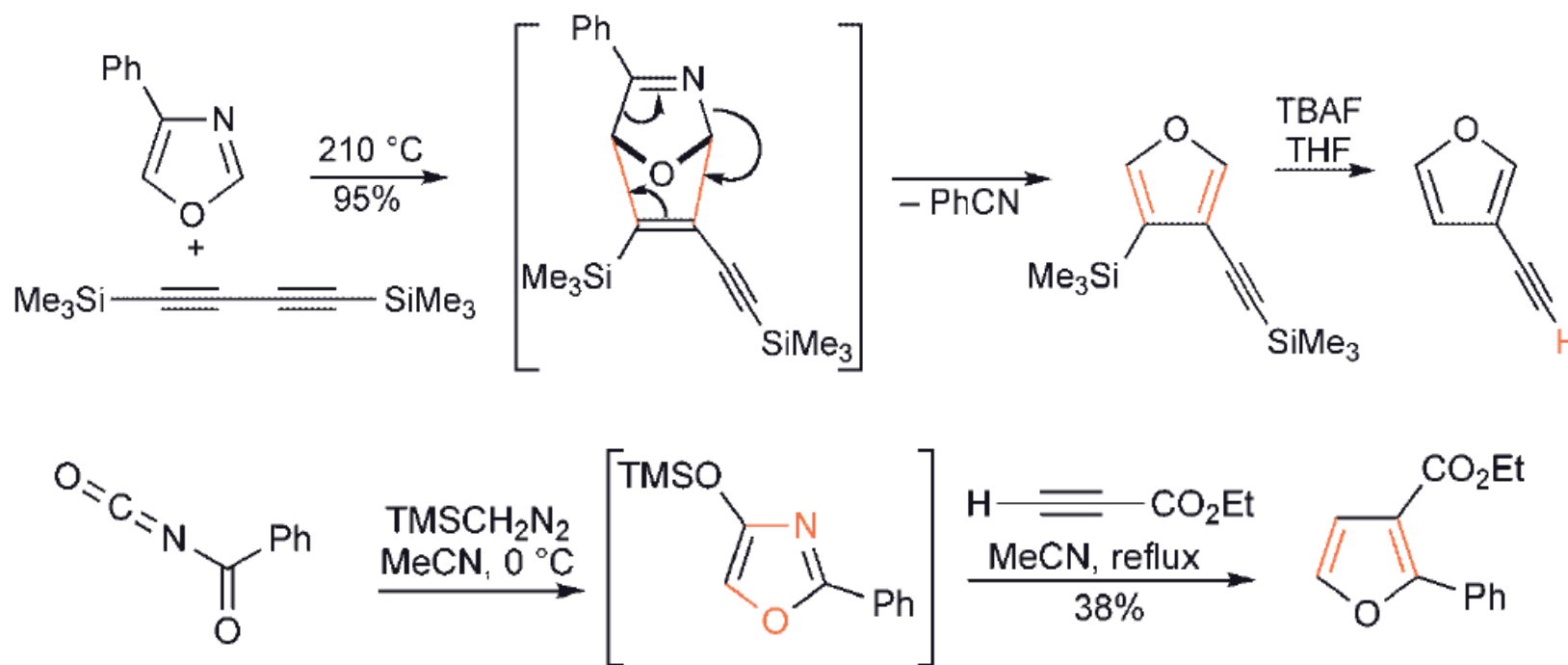


## 5) Electrocyclic Reactions

### 1,3-Azoles

Oxazoles readily undergo Diels–Alder type cycloaddition across the 2,5-positions, in parallel with the behaviour of furans

Oxazole cycloadditions have been reported with **alkyne** dienophiles (tandem Diels–Alder addition and retro Diels–Alder loss of a nitrile leads on to **furans**)



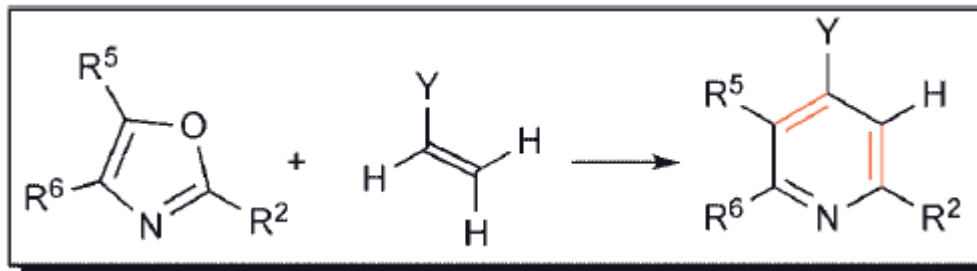
Thiazole and imidazole do not show this mode of reactivity

## 5) Electrocyclic Reactions

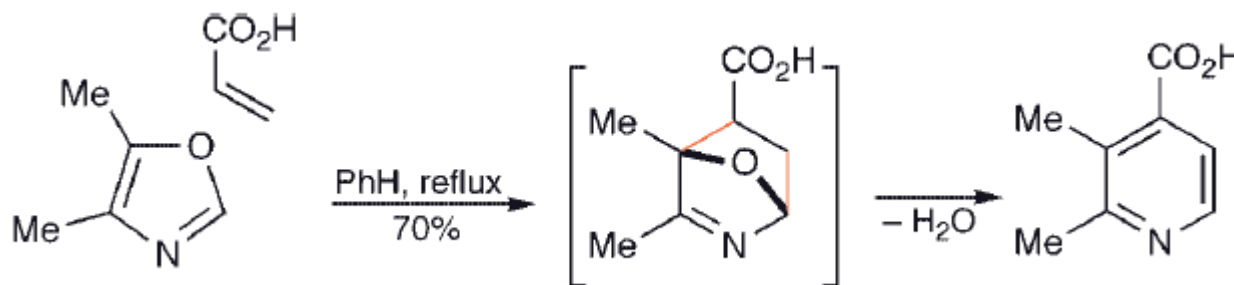
### Ring Synthesis of Pyridines - Recap

#### 4) Via Cycloaddition

##### 4.1) From Oxazoles



- When **acrylic acid** is used as a dienophile, the oxygen is lost as water



- Historically, the first of these was the addition of a dienophile to an oxazole; using **acrylonitrile**, hydrogen cyanide is lost to aromatise and the oxazole oxygen is retained (giving 3-hydroxypyridines)