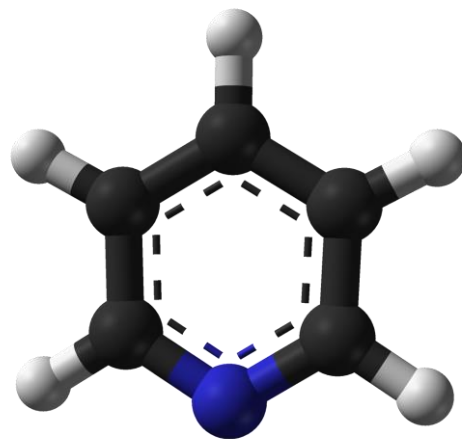


Reactivities of Heteroaromatic – Electrophilic Substitution



Instructor: Dr. Tanatorn Khotavivattana

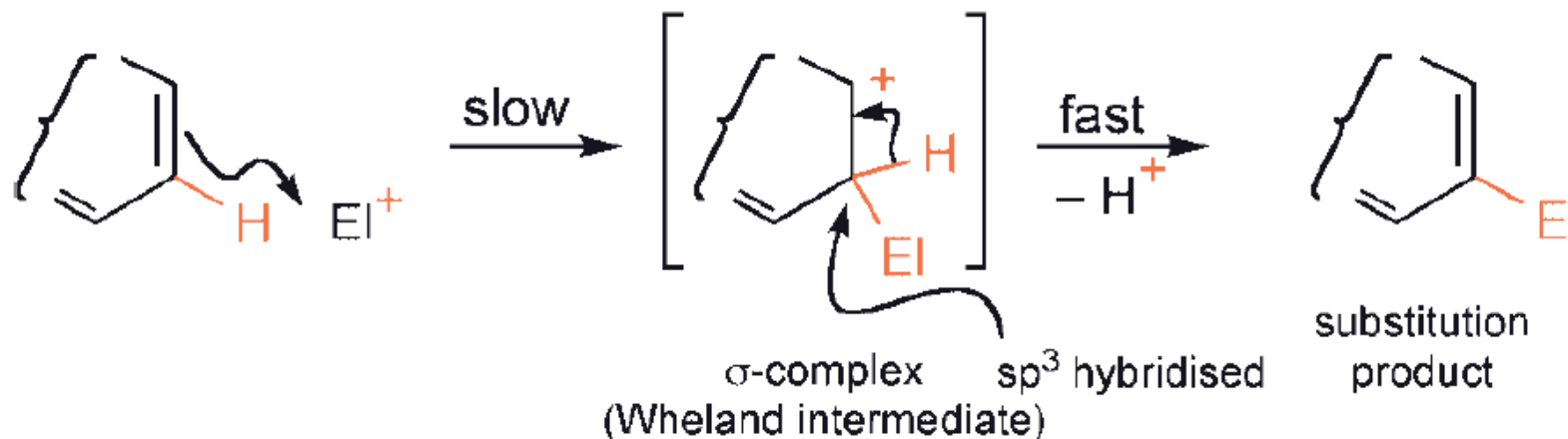
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Recommended Textbook:

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

2) Substitution Reactions – Electrophilic

- **Mechanism** : proceeds via a two-step sequence
 - 1) **Addition** (of E^+) giving a positively charged intermediate (usually **rate determining step**)
 - 2) **Elimination** (normally of H^+)



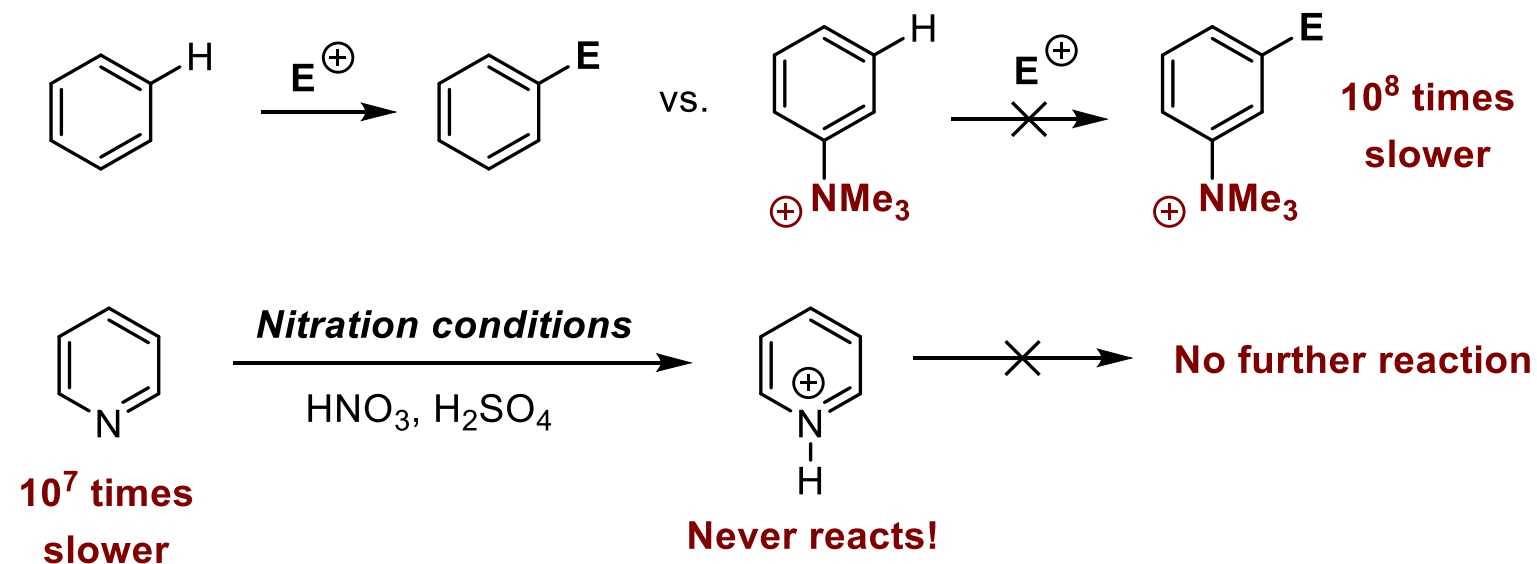
- Under most circumstances such substitutions are **irreversible** and the product ratio is determined by **kinetic control**

2) Substitution Reactions – Electrophilic

2.1) Six-membered heterocycles

- For the heterocycles that are **basic** (eg. pyridine), the interaction of the nitrogen lone pair with the **electrophilic species** in the reaction mixture (*protons in a nitrating mixture, or aluminium chloride in a Friedel–Crafts combination*), will take place far faster than any C-substitution
- The substrate is converted into a **positively charged salt** and therefore enormously reducing its nucleophilicity;

c.f. benzene vs. *N,N,N*-trimethylanilinium cation

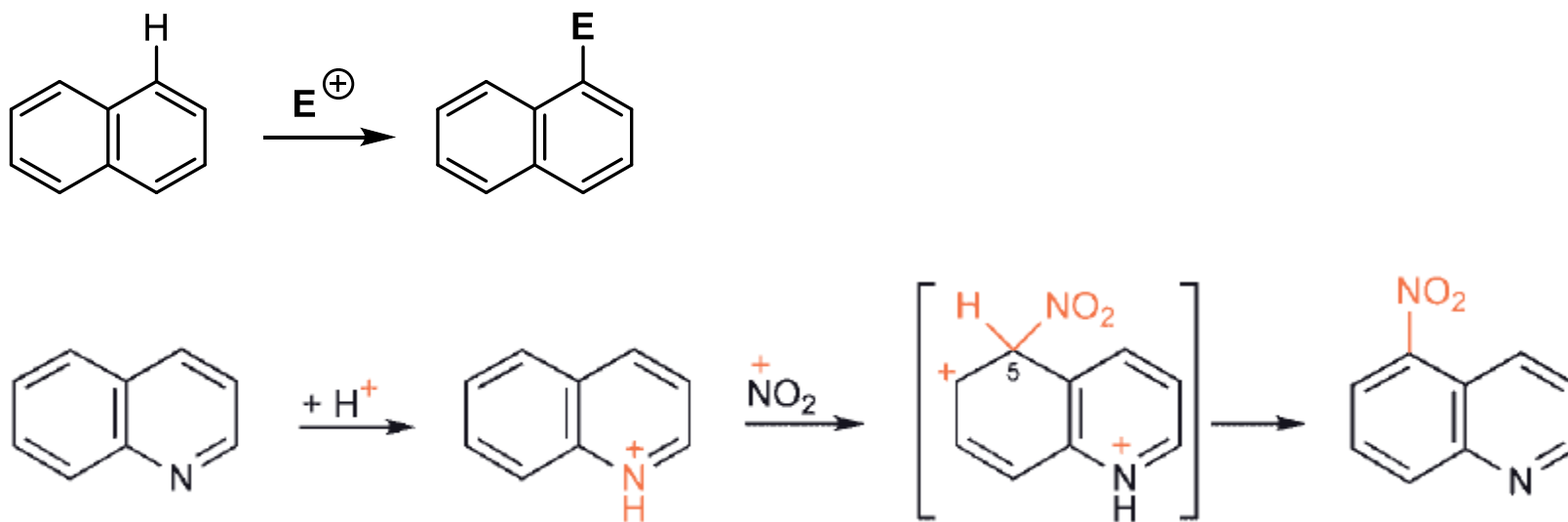


2) Substitution Reactions – Electrophilic

2.1) Six-membered heterocycles

- All heterocycles with a pyridine-type nitrogen do not easily undergo electrophilic substitution **unless** :

1) *The molecule has another, **fused benzene** ring in which substitution can take place*



**10^{10} times
slower**

2) Substitution Reactions – Electrophilic

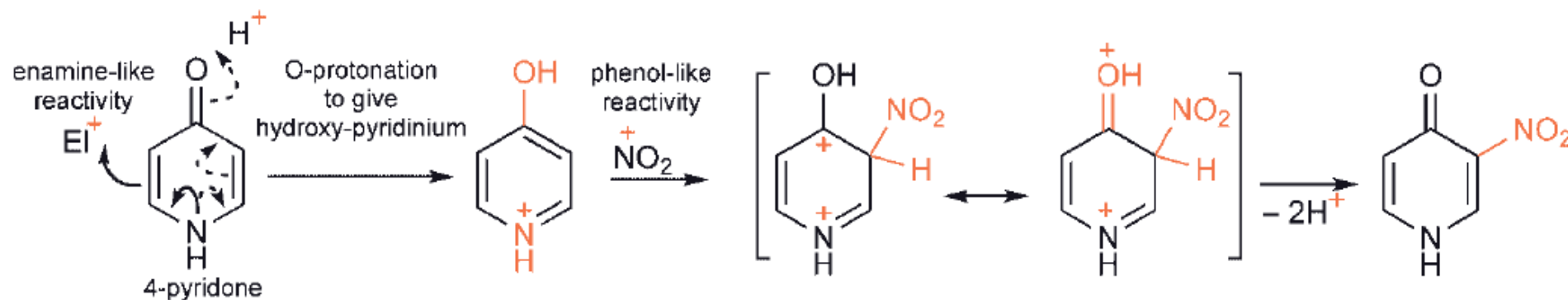
2.1) Six-membered heterocycles

- All heterocycles with a pyridine-type nitrogen do not easily undergo electrophilic substitution **unless** :

2) *There are other substituents on the ring which ‘**activate**’ the ring*

- ‘Activating’ substituents, i.e. groups that can release electrons either **inductively** or especially **mesomerically**, make the electrophilic substitution of pyridine rings to which they are attached faster

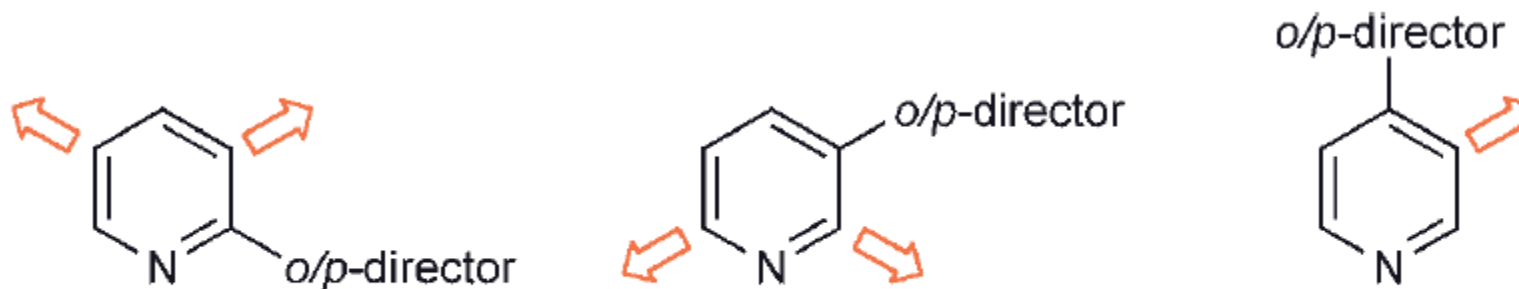
- For example, **4-pyridone** nitrates at the 3-position via the O-protonated salt (*Mesomeric effect*)



2) Substitution Reactions – Electrophilic

2.1) Six-membered heterocycles

- Pyridines carrying activating substituents at C-2 are attacked at C-3/C-5
- Those with such groups at C-3 are attacked at C - 2/C - 6, and not at C-4
- Those with substituents at C-4 undergo attack at C-3

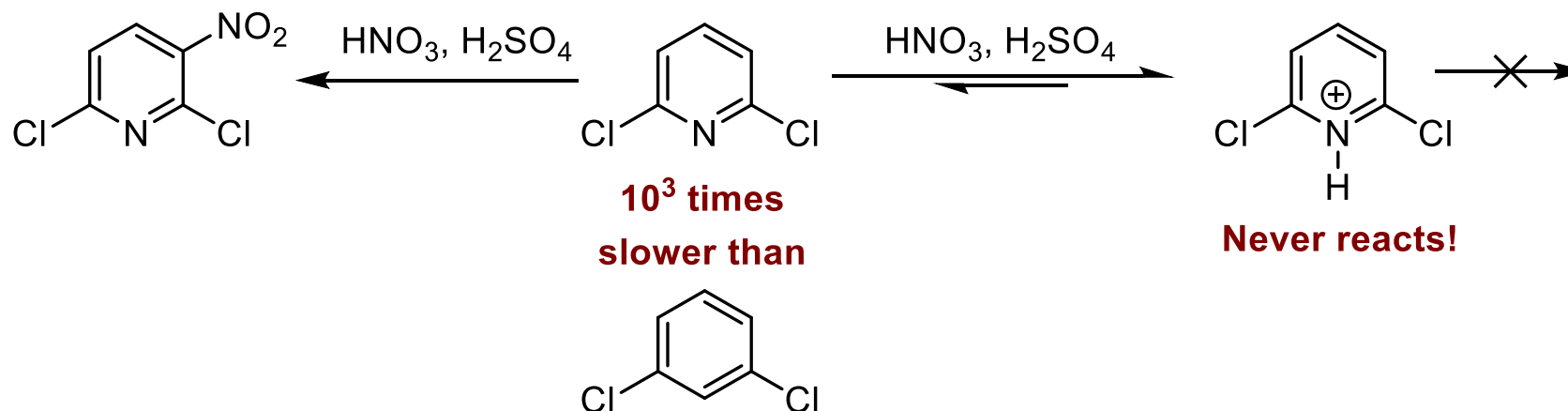


Positions of electrophilic attack on pyridines carrying activating substituents

2) Substitution Reactions – Electrophilic

2.1) Six-membered heterocycles

- Substituents that reduce the basicity of a pyridine nitrogen can lead to the **increased proportion of neutral (more reactive) pyridine** present at equilibrium

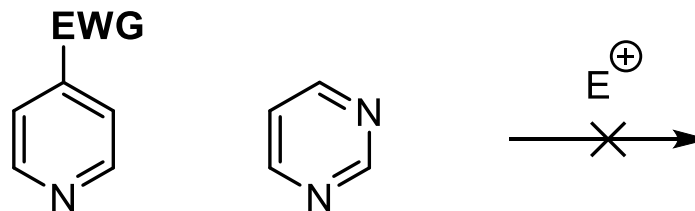


2) Substitution Reactions – Electrophilic

2.1) Six-membered heterocycles

Rule-of-thumb

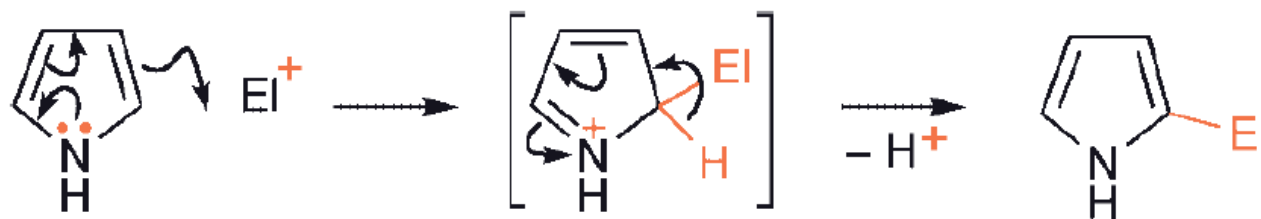
- Pyridines with a $pK_{aH} > 1$ will nitrate **as cations**, slowly unless strongly activated
- Weakly basic pyridines, $pK_{aH} < -2.5$, nitrate **as free bases**
- Pyridines carrying **strongly electron-withdrawing** substituents, or heterocycles with **additional heteroatoms**, diazines for example, are so deactivated that electrophilic substitutions do not take place (except containing strongly activated groups)



2) Substitution Reactions – Electrophilic

2.2) Five-membered heterocycles (*electron-rich heterocycles*)

- Pyrrole, thiophene and furan undergo a range of electrophilic substitutions with **great ease**
- The reaction can occur at either type of ring position, but with a preference for **attack adjacent to the heteroatom** – at their α -positions

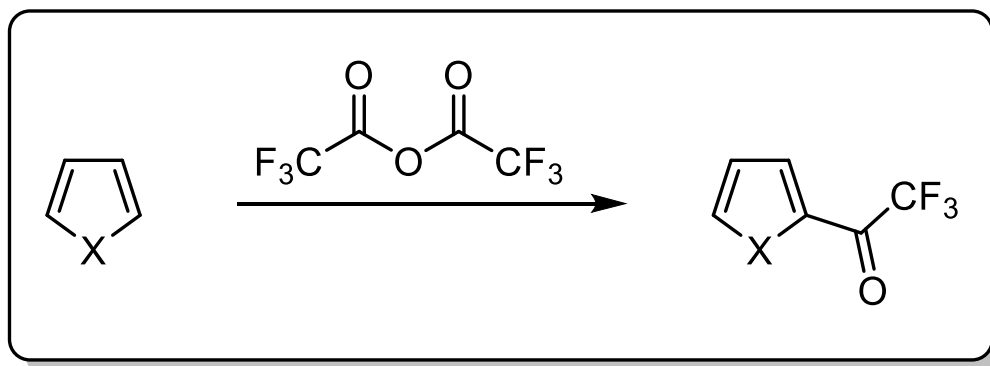


- These substitutions are facilitated by **electron release from the heteroatom**: pyrroles are more reactive than furans, which are in turn more reactive than thiophenes

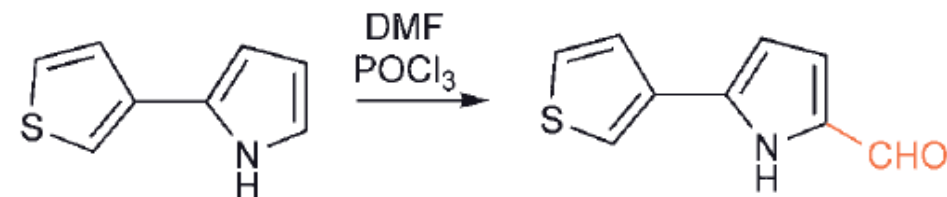
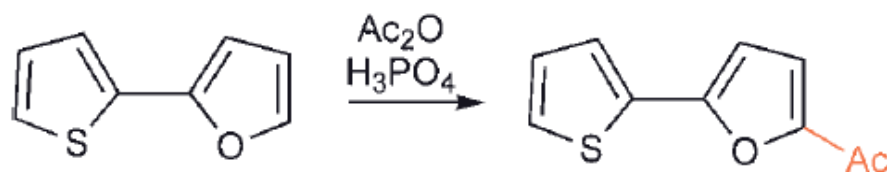
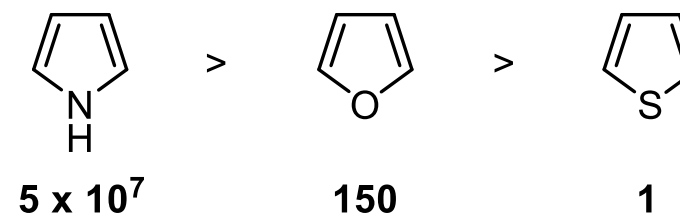
2) Substitution Reactions – Electrophilic

2.2) Five-membered heterocycles (*electron-rich heterocycles*)

Examples : pyrrole vs. furan vs. thiophene



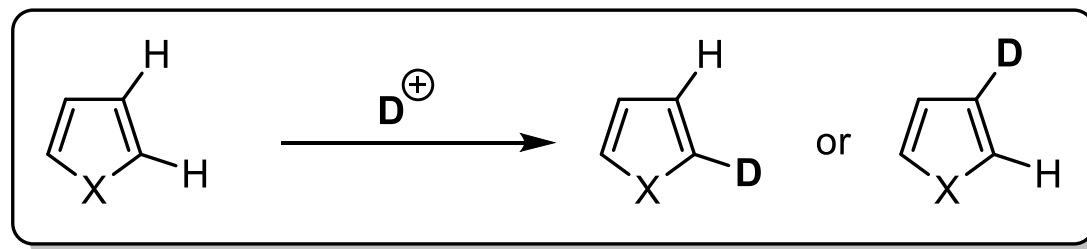
Relative Rate:



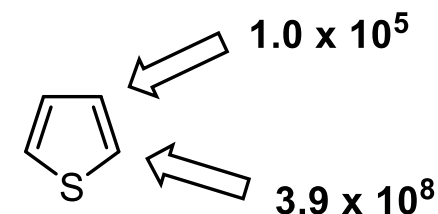
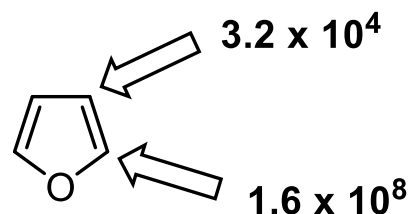
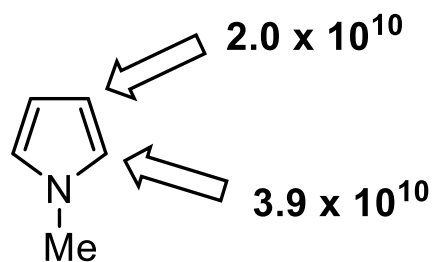
2) Substitution Reactions – Electrophilic

2.2) Five-membered heterocycles (*electron-rich heterocycles*)

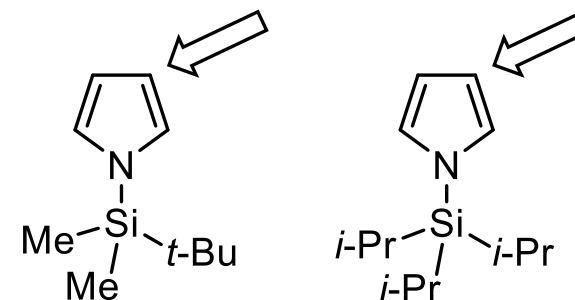
Examples : α vs. β



Partial rate factors:



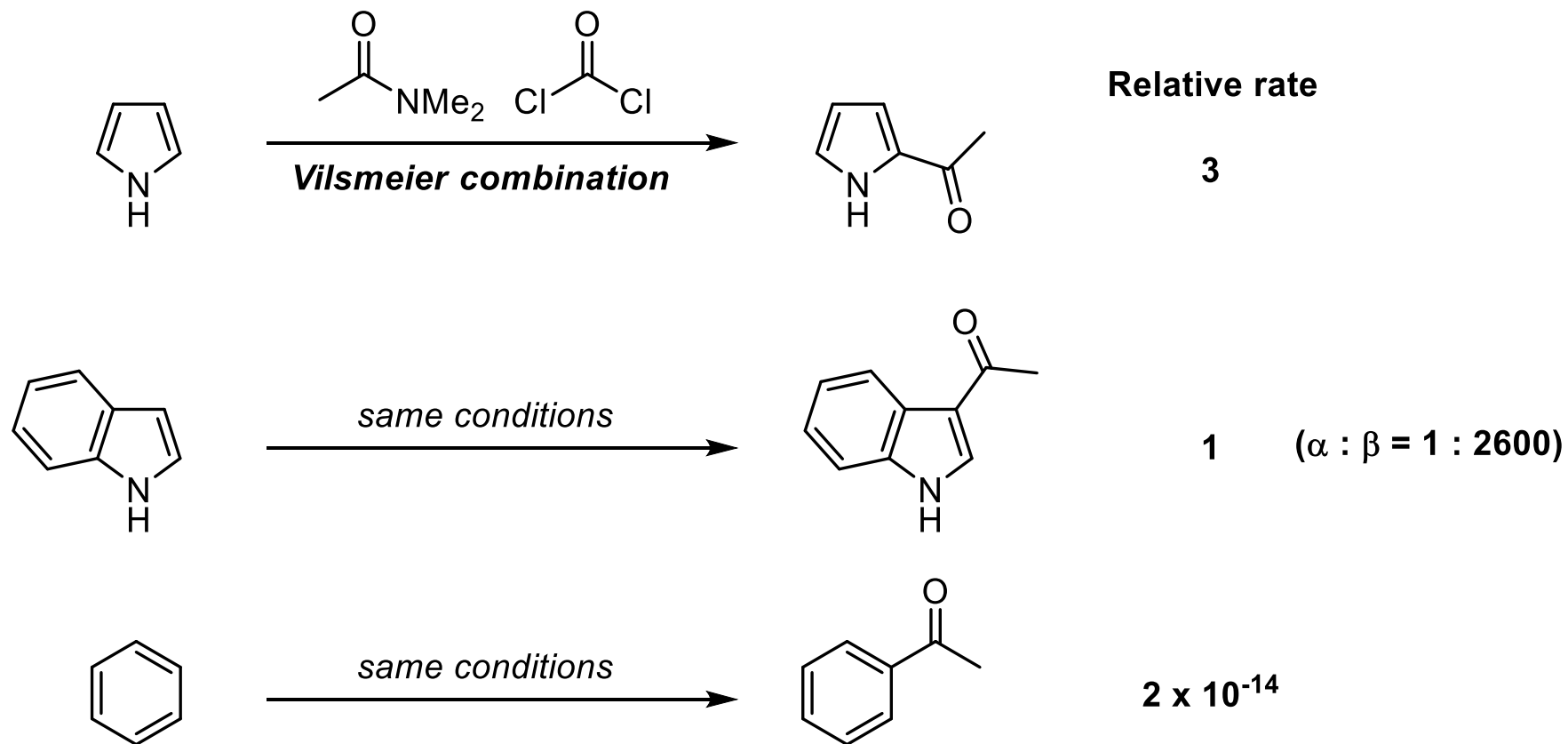
- The positional selectivity of attack on pyrroles can be completely altered by the presence of **bulky groups on nitrogen**



2) Substitution Reactions – Electrophilic

2.2) Five-membered heterocycles (*electron-rich heterocycles*)

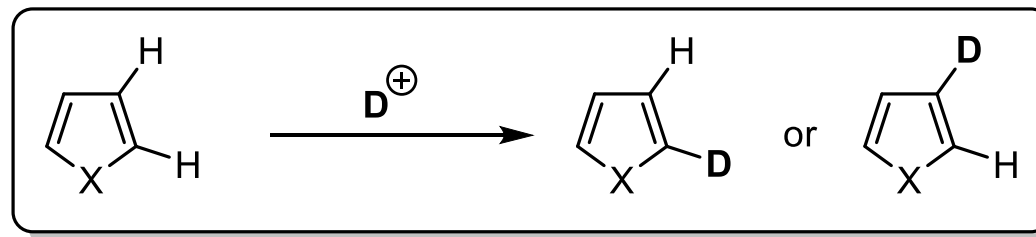
Indoles : Indoles are only slightly less reactive than pyrroles, electrophilic substitution taking place in the heterocyclic ring, at a **β -position**



2) Substitution Reactions – Electrophilic

2.2) Five-membered heterocycles (*electron-rich heterocycles*)

1,2- and 1,3-azoles : the imine basic nitrogen **reduces the reactivity** of the heterocycle towards electrophilic attack at carbon, both by **inductive** and **mesomeric** withdrawal, and importantly by **addition of electrophilic species** to the imine nitrogen



Partial rate factors:

