Career of Paul Frøyen: Wittig Reaction

selected paper: 1960s to 1990s

Sorensen Group Meeting
Ximing Li
March 9, 2018

A Summary

- **Academic Career**

    1966   University of Bergen, Norway

    1976   University of Oslo, Norway

    1991   Agricultural University of Norway, Norway
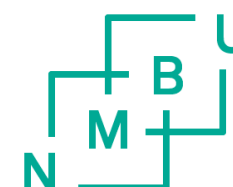   (Now: Norwegian University of Life Sciences)

- **Associate Editor: Acta Chemica Scandinavica**

- **Papers published: ~90**

- **Research focus:**

    '66-'67   Alkaline Hydrolysis Kinetics

    '68-'74   Ylide/Aza Ylide Reaction & Kinetics
               (Ylide with Aldehyde & Isocyanate)

    '74-   Acyclic Oxyarsoranes Chemistry
   & Staudinger Reaction

Prof. Paul Ragnar Frøyen

Norwegian University
of Life Sciences

Study of the Applicability of the Wittig Reaction in Synthesis of Allenes

- *Acta Chem. Scand. 22 (1968) No. 7*

Year	Reaction		Product	Condition required
1949, Wittig & Haag	$Ph_3P=C(CH_3)_2$	$+ \; Ph_2C=C=O$	$Ph_2C=C=C(CH_3)_2$	**150°C *in vacuo***
1922, Luscher	$Ph_3P=CPh_2$	$+ \; Ph_2C=C=O$	$Ph_2C=C=CPh_2$	**140°C**
1967, Birum & Matthews	$Ph_3P=C=C(CF_3)_2$	$+ \; Ph_2C=C=O$	$Ph_2C=C=C=C(CF_3)_2$	**r.t.**
1961, Wadsworth & Emmons	$(EtO)_2POCHCO_2Et$	$+ \; Ph_2C=C=O$	$Ph_2C=C=CHCO_2Et$	**r.t.**

Reaction temp
(R = alkyl, phenyl)

A	B	C
r.t.	**150°C**	**250°C**
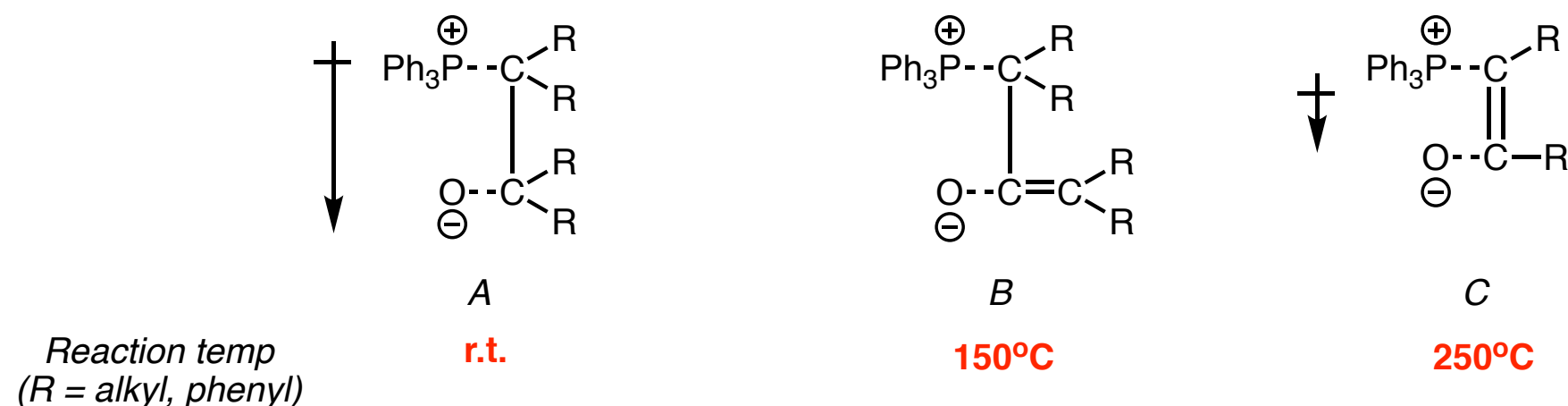
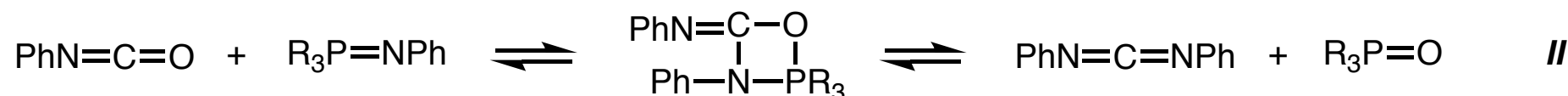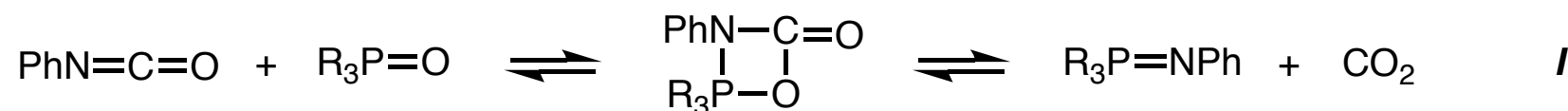The stability of the betaines increases from **A** to **C** because:

1) The charge on oxygen can be successively reduced through conjugation, making oxygen less nucleophilic and phosphorus less electrophilic;
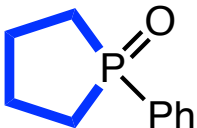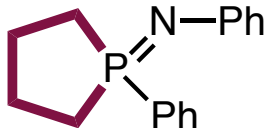
2) The betaine **A** has two sp^3-hybridized carbon atoms, the betaine **B** has one sp^3- and one sp^2- hybridized carbon atom, and betaine **C** has two sp^2-hybridized carbon atoms in the 4-membered ring intermediate. The net result is a success increase of the P-C-C and C-C-O angles, making the closure of the f4-membered ring corresponding difficult.

Study of Reactions between Phenyl Isocyanate and Phosphine Oxides, respectively Phosphine Imines

- *Acta Chem. Scand. 23 (1969) No. 8*

1962, Monagle:

$$PhN{=}C{=}O \;+\; R_3P{=}O \;\rightleftharpoons\; \begin{array}{c} PhN{-}C{=}O \\ R_3P{-}O \end{array} \;\rightleftharpoons\; R_3P{=}NPh \;+\; CO_2 \qquad \textbf{\textit{I}}$$

$$PhN{=}C{=}O \;+\; R_3P{=}NPh \;\rightleftharpoons\; \begin{array}{c} PhN{=}C{-}O \\ Ph{-}N{-}PR_3 \end{array} \;\rightleftharpoons\; PhN{=}C{=}NPh \;+\; R_3P{=}O \qquad \textbf{\textit{II}}$$

| Phosphine oxide	k_{rel} @ 80°C	Activation Energy (kcal/mol)		Imino phosphorane	k_{rel} @ 25°C	Activation Energy (kcal/mol)
$Ph_3P{=}O$	$0.15{*}10^5$	**14.1**		$Ph_3P{=}N{-}Ph$	0.79	**9.8**
$Ph_2EtP{=}O$	$0.56{*}10^5$	**16.1**		$Ph_2EtP{=}N{-}Ph$	2.93	**9.4**
$PhEt_2P{=}O$	$1.97{*}10^5$	**16.6**		$PhEt_2P{=}N{-}Ph$	12.45	**9.7**
$Et_3P{=}O$	$4.63{*}10^5$	**13.6**		$Et_3P{=}N{-}Ph$	58.2	**9.5**
(phospholane oxide, Ph)	$2177{*}10^5$	**11.6**		(phospholane imine, N–Ph, Ph)	127	**9.6**

1) Step **I** is **r.d.s.** (from Activation energy numbers)

2) The activation energy of the phosphine imine-phenyl isocyanate reaction is **independent** of the substituents linked to phosphous. This is in remarkable contrast to the phosphine oxide-phenyl isocyanate reaction where the actication energy is found to **depend** strongly on the substituents. — **Why?**

Study of Reactions between Phenyl Isocyanate and Phosphine Oxides, respectively Phosphine Imines

- *Acta Chem. Scand. 23 (1969) No. 8*

A modification of reaction scheme:
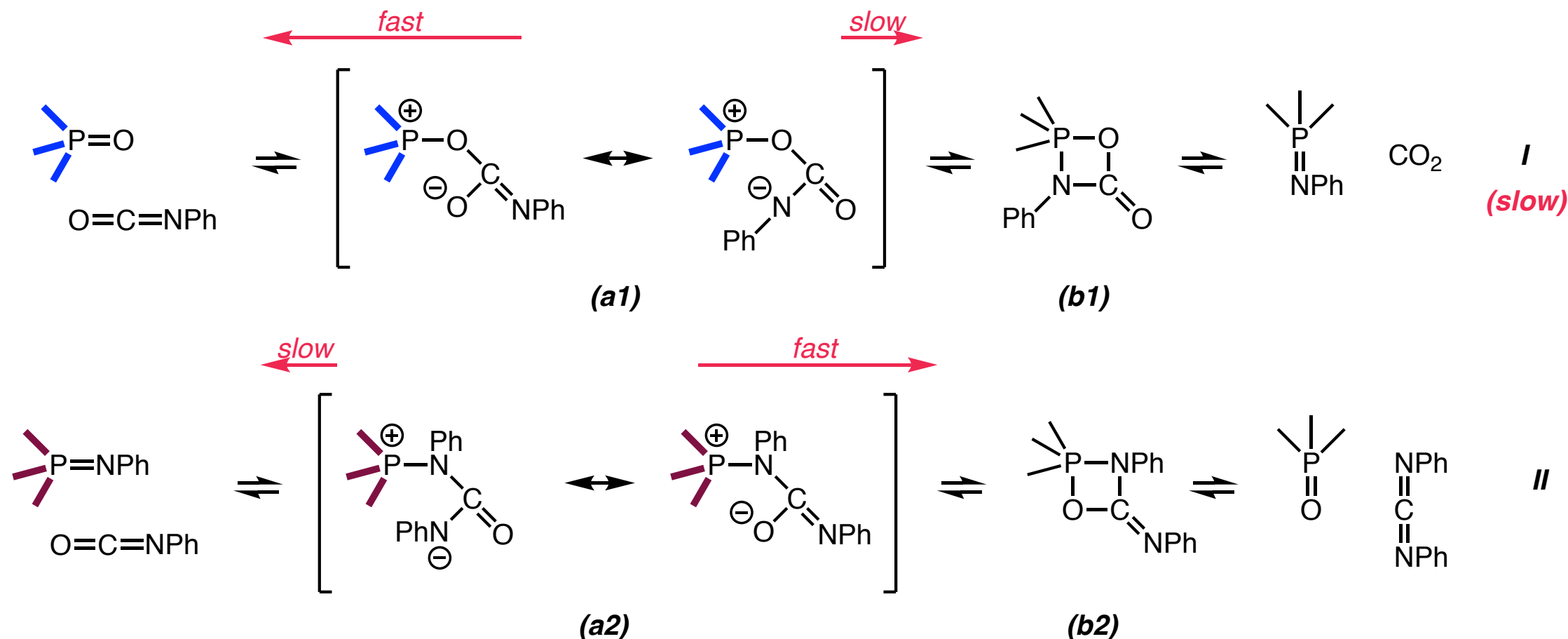
Since oxygen is a harder Nucleophile than nitrogen, oxygen is also the most reactive atom towards the hard phosphorus center in tetravalent phosphorus compounds. It allows therefore that,

1) In step **I**, the rate of decomposition of the intermediate **a1** back to reactants should be much faster than the rate of the formation of the pentacovalent intermediate **b1**.

2) In step **II**, the betaine intermediate **a2** is more easily transformed to the pentacovalent intermediate **b2** than back to the reactants.

Synthesis and Reactions of Arsine Imines

Arsine imines are generated as intermediates in the reaction between arsine oxides and phenyl isocyanate leading to diphenyl carbodiimide:
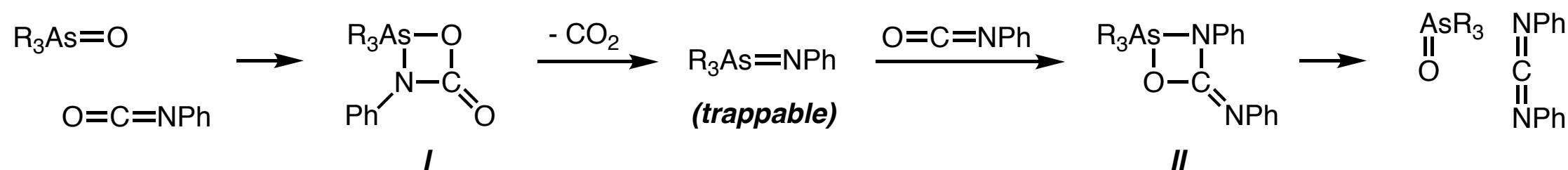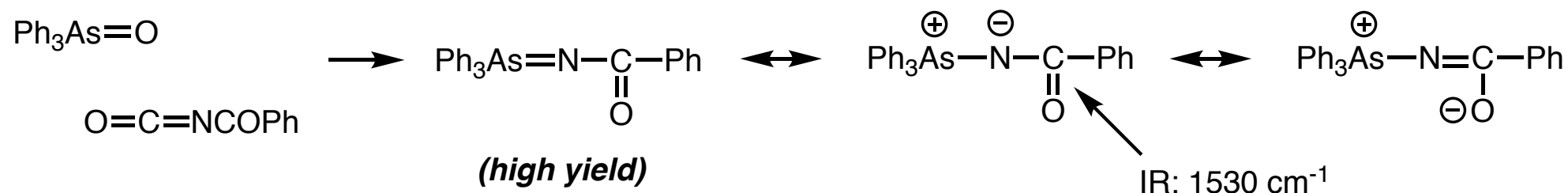

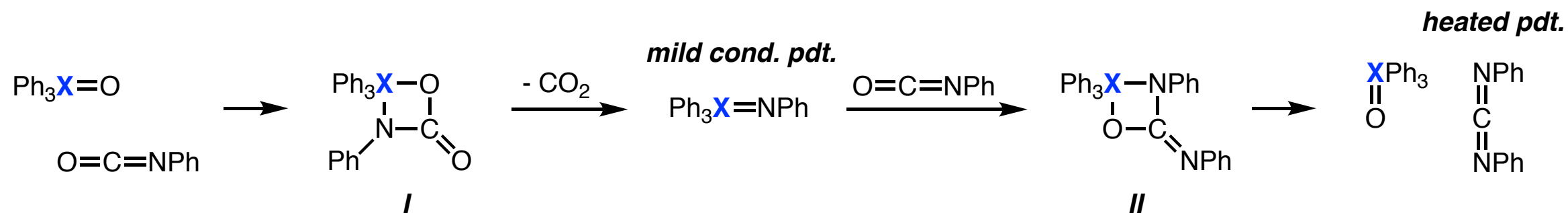| k_{rel} *(for P)* | 1 | $10^5 \sim 10^7$ |
| k_{rel} *(for As)* | ? | probably much slower |

Evidence: (?)

The delocalization of electronic density between nitrogen, arsenic, and oxygen, lowers the nucleophilicity of nitrogen and correspondingly reduces its reactivity towards the carbonyl carbon the isocyanate.

Synthesis of Some Arsine Imine Derivatives

Ph₃**X**=O

O=C=NPh

→

Ph₃**X**—O
   | |
   N—C
  Ph   ‖
        O

I

$-CO_2$ →

mild cond. pdt.

Ph₃**X**=NPh

O=C=NPh →

Ph₃**X**—NPh
        | |
        O—C
            ‖
            NPh

II

→

heated pdt.

XPh₃   NPh
 ‖   ‖
 O   C
            ‖
            NPh

k_{rel} *(for P)*	1 (r.d.s.)	$10^5 \sim 10^7$
k_{rel} *(for As)*	much faster	much slower (r.d.s.)

Reasoning:

↓

Dipole moment: Ph₃**P**=O   4.31 D

                 Ph₃**As**=O   5.50 D

Orbital overlap: Ph₃**P**=O   more effective

                  Ph₃**As**=O   less effective

↓

Ph₃**P**=NPh   less reactive

Ph₃**As**=NPh   more reactive

(for aformentioned reason)

However, BDE: $E(\text{P-O})$ 156 kcal - high driving force

                $E(\text{As-O})$ 93 kcal - low driving force
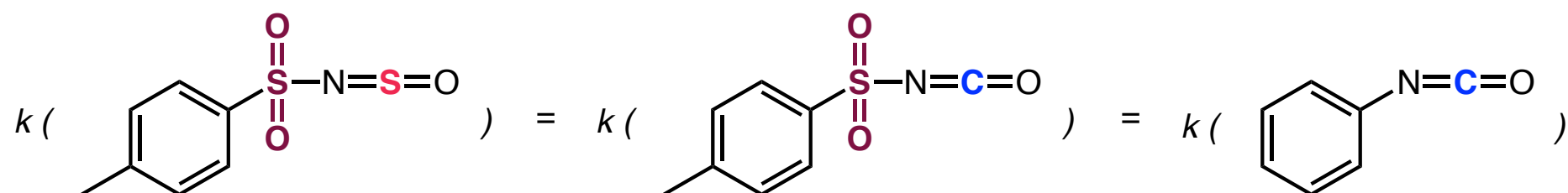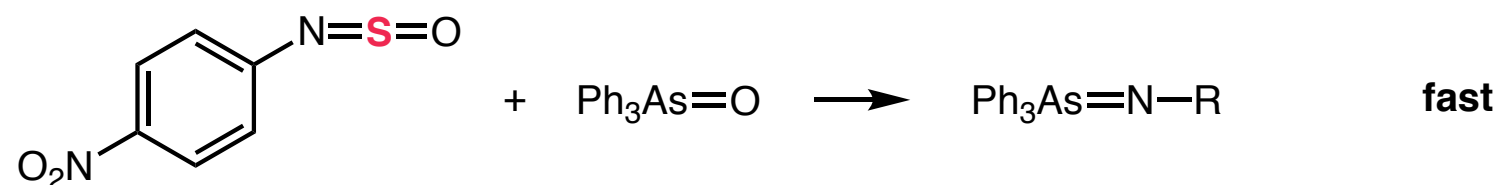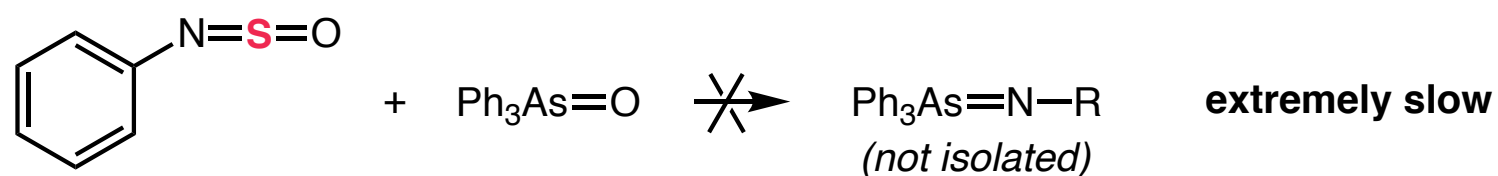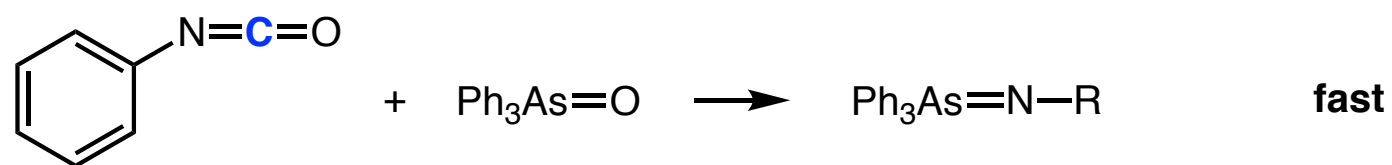
Synthesis of Some Arsine Imine Derivatives

- *Acta Chem. Scand. 25 (1971) No. 3*

N-sulfinyl amides:

$$R-N=S=O \quad + \quad Ph_3As=O \quad \longrightarrow \quad \begin{array}{c} Ph_3As-O \\ | \quad | \\ N-S \\ / \quad \| \\ R \quad O \end{array} \quad \xrightarrow{-SO_2} \quad Ph_3As=N-R \qquad \textbf{fast}$$
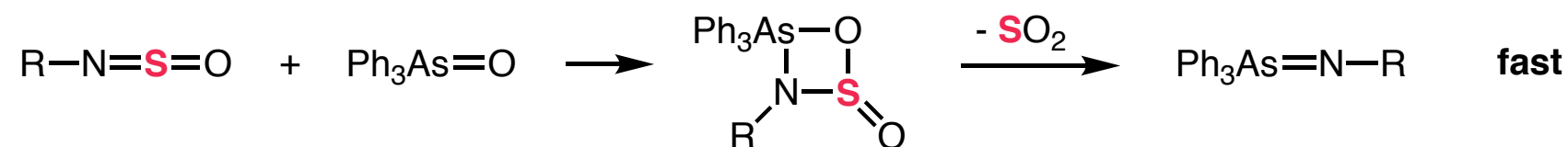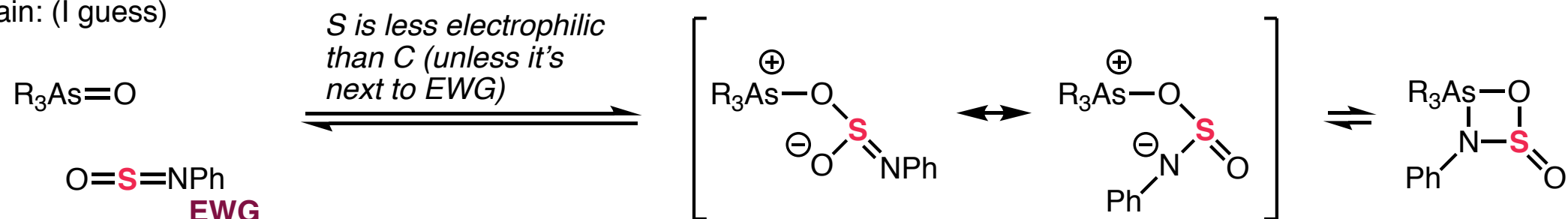
R = PhCO-, (EtO)₂P(O)-, *p*-Me-C₆H₄SO₂-, PhSO₂-, MeSO₂-

N-sulfinylaniline:

$$\text{Ph}-N=C=O \quad + \quad Ph_3As=O \quad \longrightarrow \quad Ph_3As=N-R \qquad \textbf{fast}$$

$$\text{Ph}-N=S=O \quad + \quad Ph_3As=O \quad \xrightarrow{\quad\times\quad} \quad Ph_3As=N-R \qquad \textbf{extremely slow}$$
(not isolated)

$$O_2N-\text{C}_6\text{H}_4-N=S=O \quad + \quad Ph_3As=O \quad \longrightarrow \quad Ph_3As=N-R \qquad \textbf{fast}$$

$$k\left(\text{Tol}-SO_2-N=S=O \right) \;=\; k\left(\text{Tol}-SO_2-N=C=O \right) \;=\; k\left(\text{Ph}-N=C=O \right)$$

Explain: (I guess)

R₃As=O

O=S=NPh
EWG

S is less electrophilic than C (unless it's next to EWG)

$$\left[\begin{array}{c} \overset{\oplus}{R_3As}-O \\ \underset{\ominus O}{}S=NPh \end{array} \quad \longleftrightarrow \quad \begin{array}{c} \overset{\oplus}{R_3As}-O \\ \underset{Ph-N^{\ominus}}{}S=O \end{array} \right] \quad \rightleftharpoons \quad \begin{array}{c} R_3As-O \\ | \quad | \\ N-S \\ / \quad \| \\ Ph \quad O \end{array}$$

Kinetic Studies (of Wittig Reaction)

- *3 papers: Acta Chem. Scand. 25 (1971) No. 7: of rxn between stabilized arsonium ylides and p-Nitrobenzaldehyde*
  26 (1972) No. 5: of rxn between phosphine N-phenylimines and p-Nitrobenzaldehyde
  26 (1972) No. 6: of rxn between fluorenylidene phosphoranes and p-Nitrobenzaldehyde

"R_3X-YR R" + ArCHO →

betaine
(X=P, As; Y=C, N)

?

cyclic intermediate

stabilized arsonium ylides

phosphine N-phenylimines

fluorenylidene phosphoranes
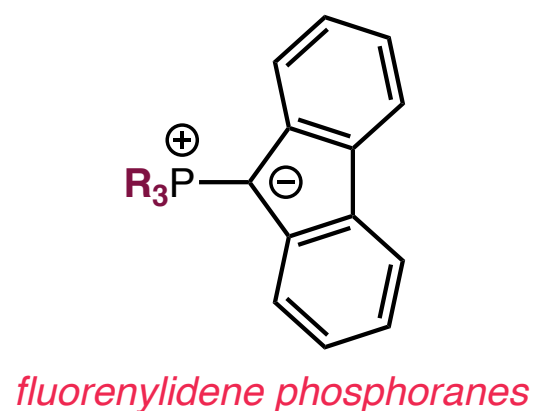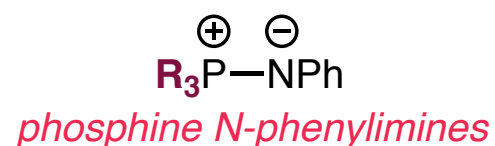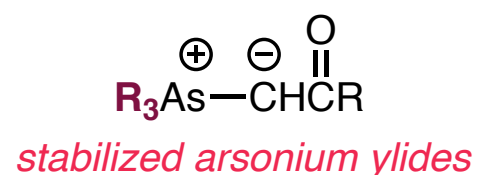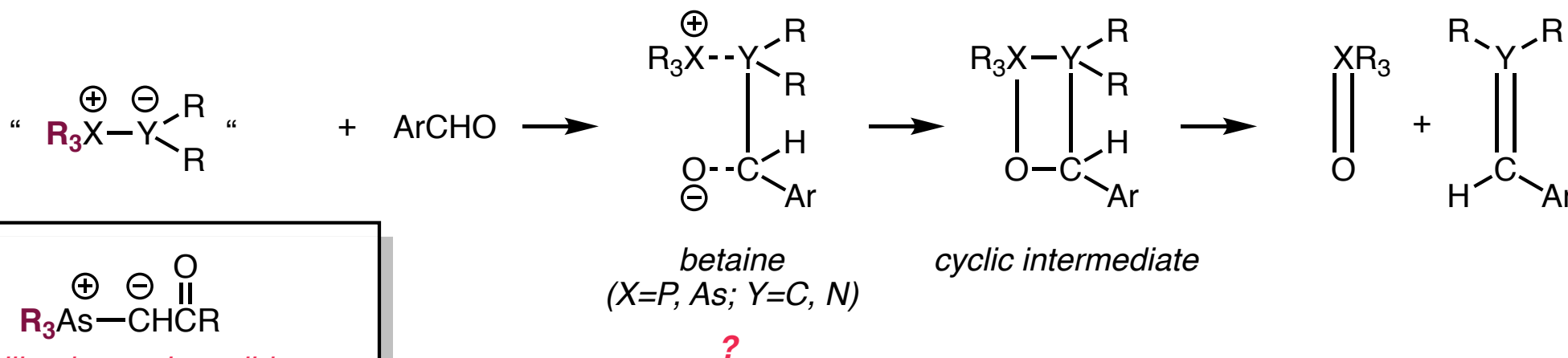
- *Interest: Intermediacy of betaine in these reactions*

- *Kinetic: Generally, **k(benzeze) > k(DMSO) > k(DMF);***

  k(MeOH) > k(benzene).

- ***N**ot **consistent** with: formation of **a betaine as TS**.*

  ***C**onsistent with: A **synchronized** reaction mechanism*

- *Other evidences:*

  Large negative entropy; Very low activation energy;

  Catalysis by hydrogen bonding solvents

- *This is also observed in our optimization*

More Interesting Reactions: AsPh$_3$

- *Acta Chem. Scand. 25 (1971) No. 7*

$$Ph_3As{=}NPh \ + \ ArNO \ \longrightarrow \ Ph_3As{=}O \ + \ PhN{=}NAr$$

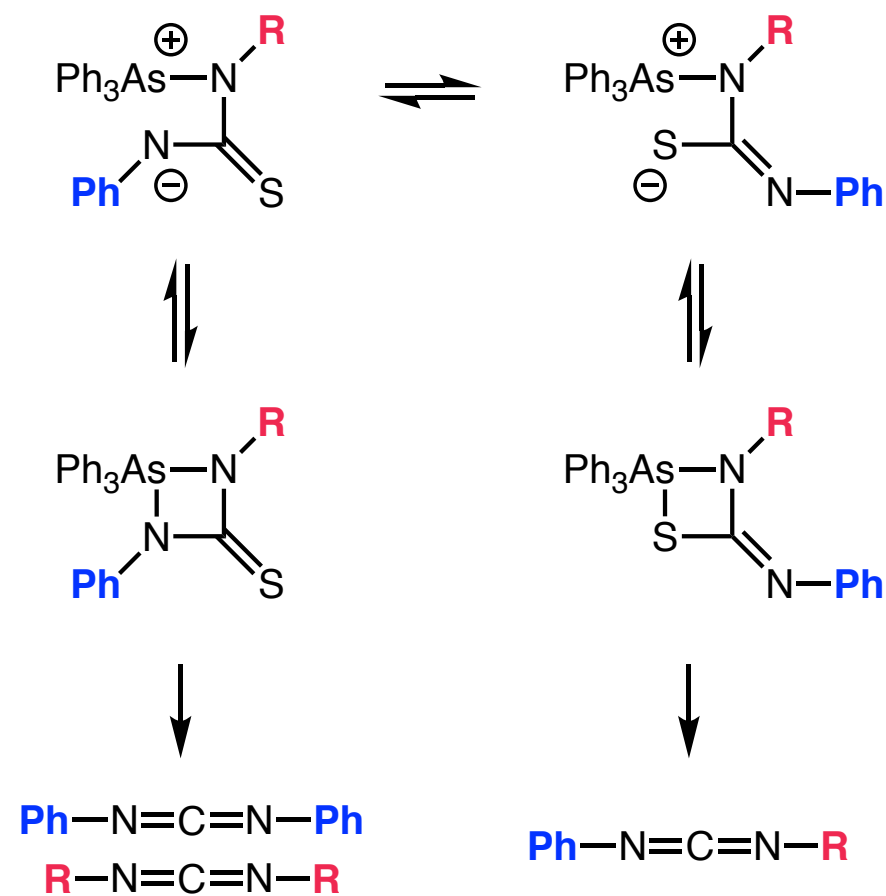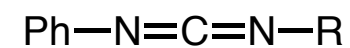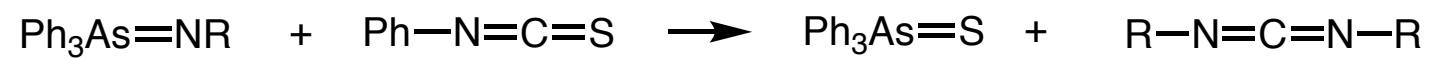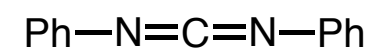- *Phosphorus, Sulfur, and Silicon, 1993, Vol. 81*
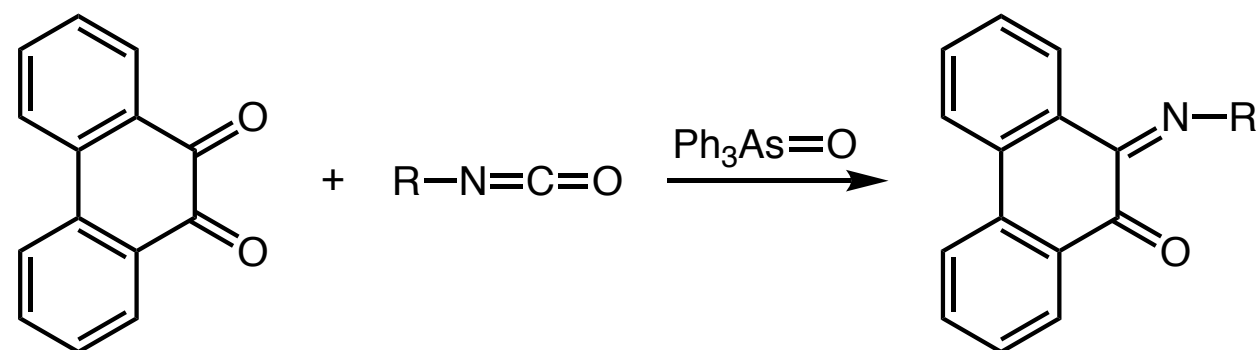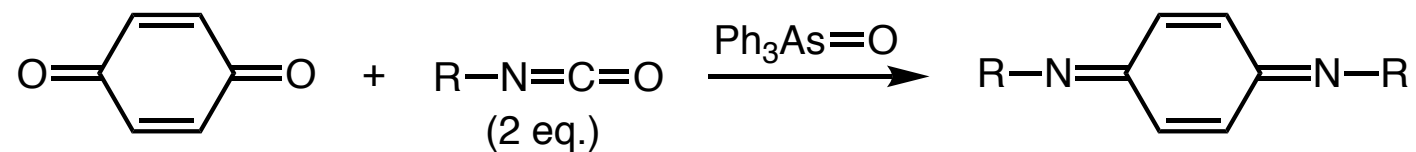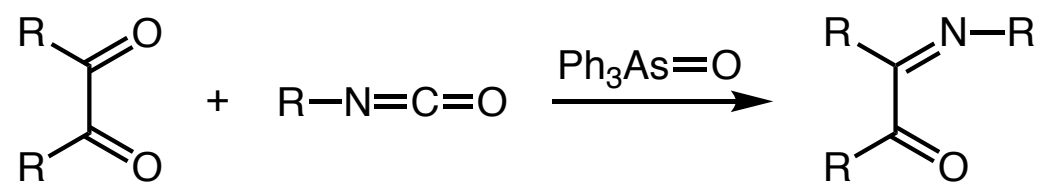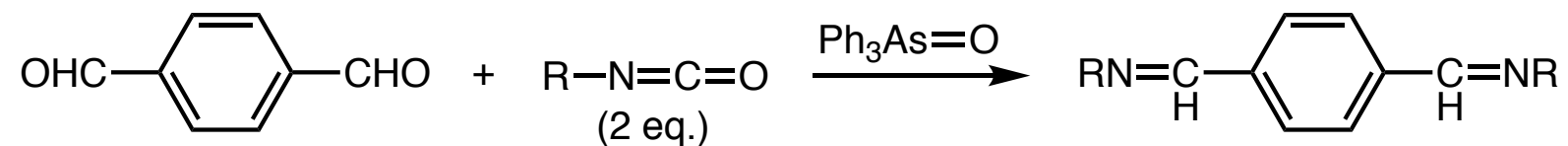
More Interesting Reactions: AsPh₃

■ *Phosphorus, Sulfur, and Silicon, 1993, Vol. 81*

$$Ph-N=C=N-Ph$$

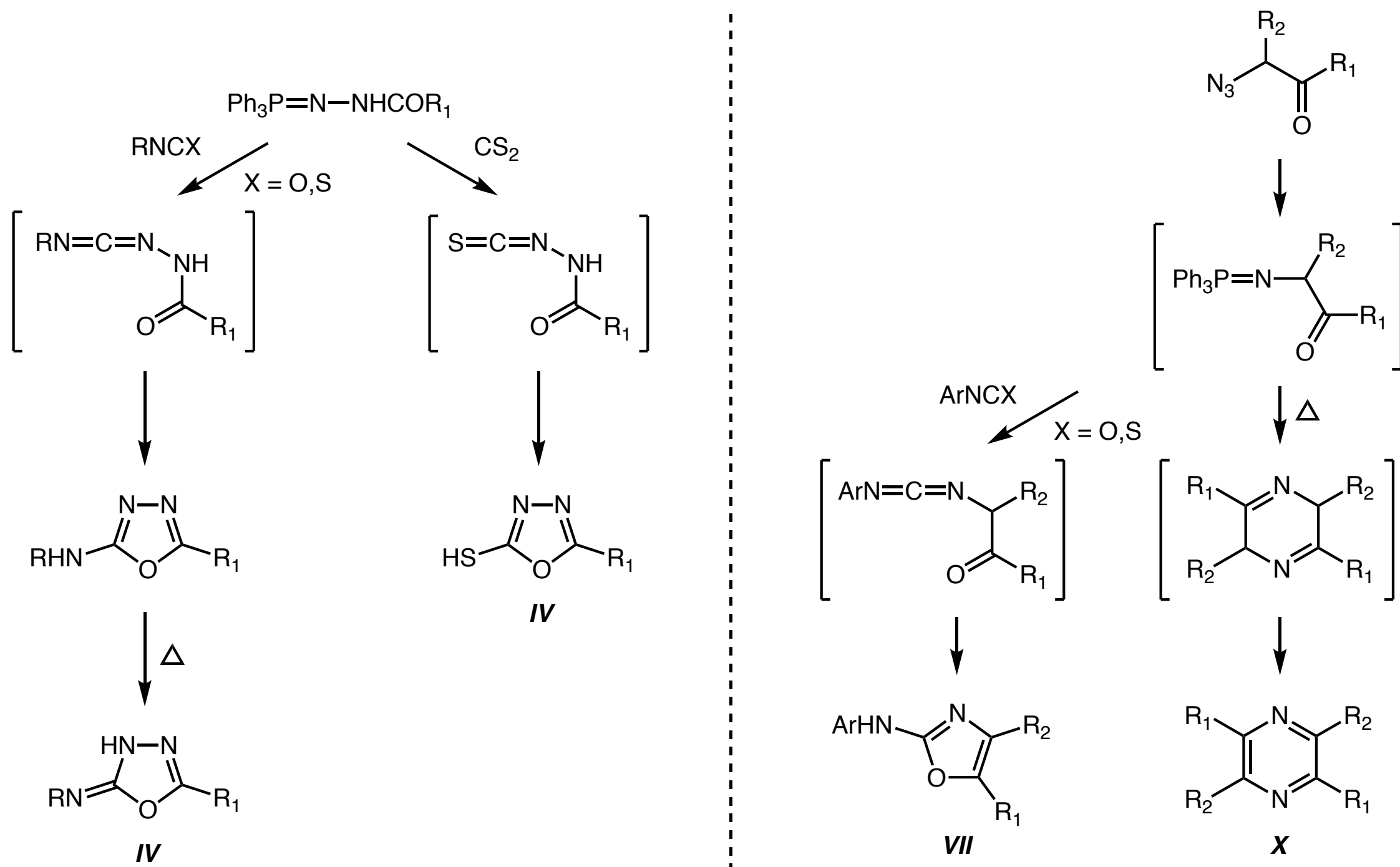$$Ph_3As=NR \quad + \quad Ph-N=C=S \quad \longrightarrow \quad Ph_3As=S \quad + \quad R-N=C=N-R$$

$$Ph-N=C=N-R$$

Even more Interesting Reactions: PPh₃

- *one-pot transformations: Phosphorus, Sulfur, and Silicon, 1994, Vol. 91: Carboxylic Acid Esters (**I**)*
  *Phosphorus, Sulfur, and Silicon, 1996, Vol. 116: Alkyl Iodides (**II**)*
  *Phosphorus, Sulfur, and Silicon, 1995, Vol. 102: Acyl Bromides (**V**)*
  *Phosphorus, Sulfur, and Silicon, 1994, Vol. 89: Acyl Azides (**VIII**)*
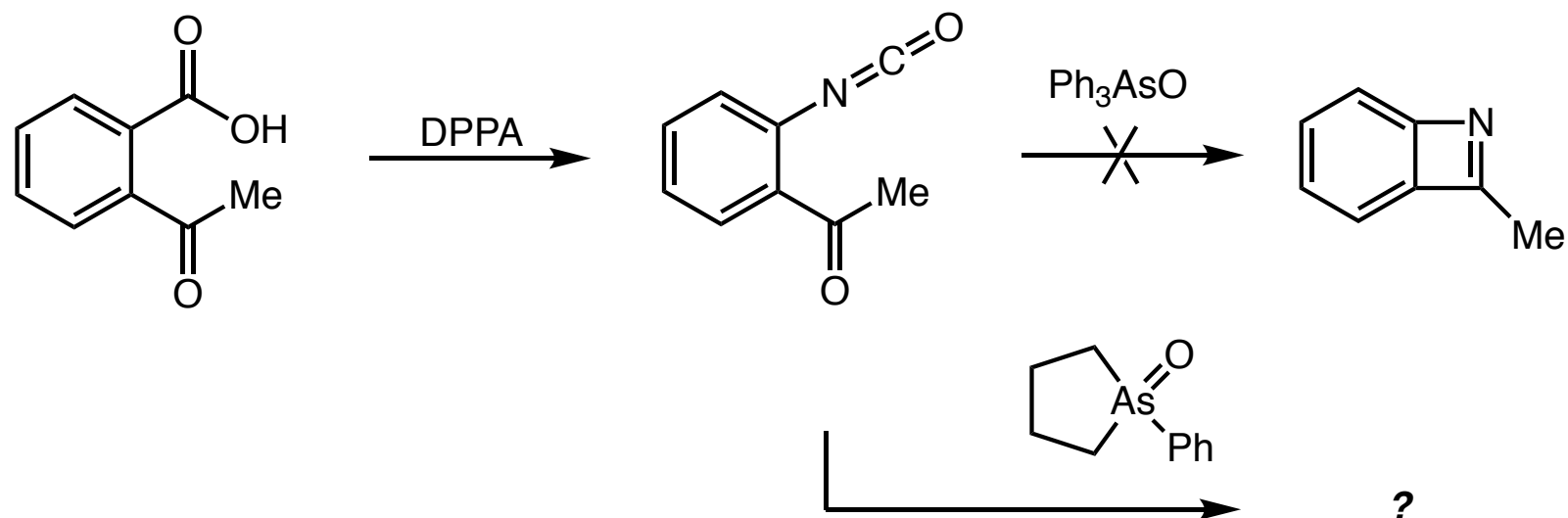 *Syn. Comm, 1995, 25(7), (1995): Amides (**IX**)*
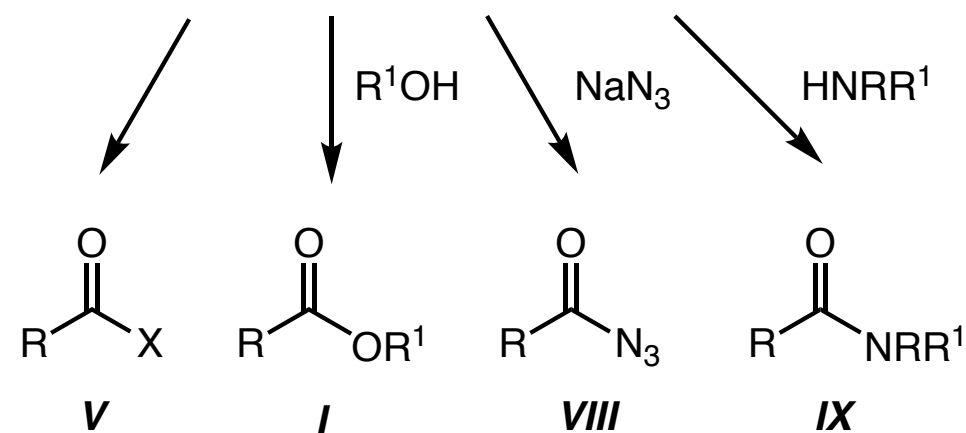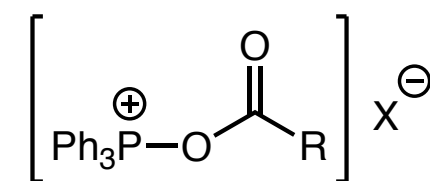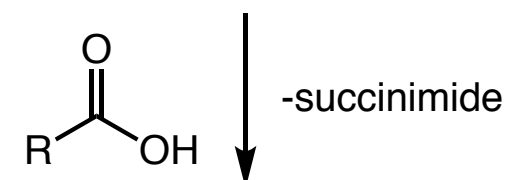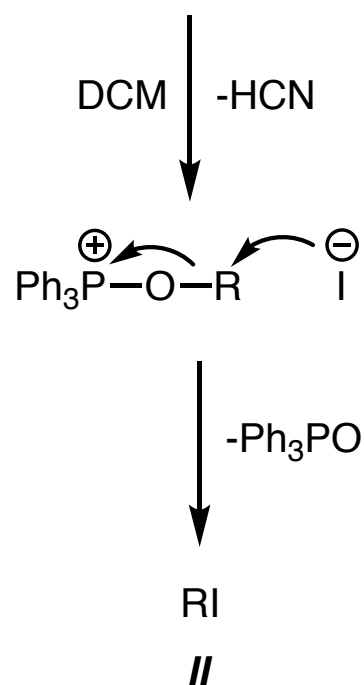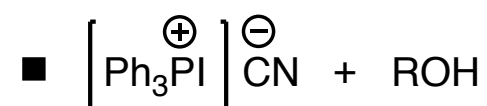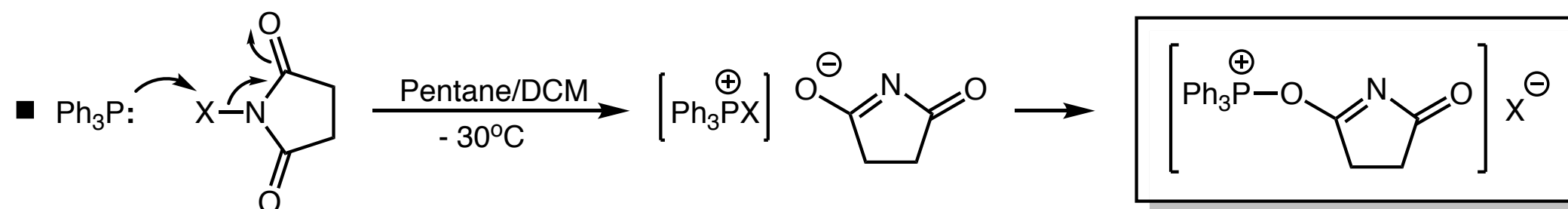
Even more Interesting Reactions: PPh$_3$

- *heterocycles formation: Phosphorus, Sulfur, and Silicon, 1991, Vol. 57: 1,3,4-Oxadiazoles (**IV**)*
  *Phosphorus, Sulfur, and Silicon, 1991, Vol. 60: 2-Amino-1,3-Oxazoles (**VII**)*
  *Phosphorus, Sulfur, and Silicon, 1991, Vol. 63: Pyrazines (**X**)*
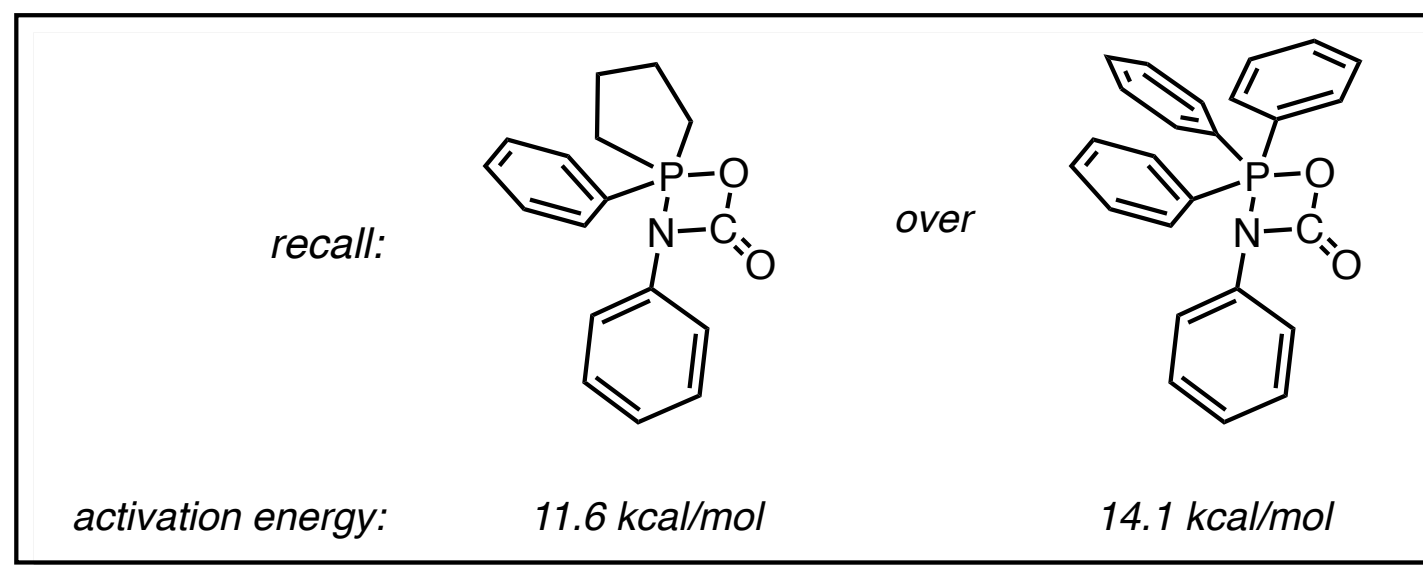
What can we learn?

■ *Currently*

what if

recall: over

activation energy: 11.6 kcal/mol   14.1 kcal/mol

■ *Unique reacticity of As over P*