

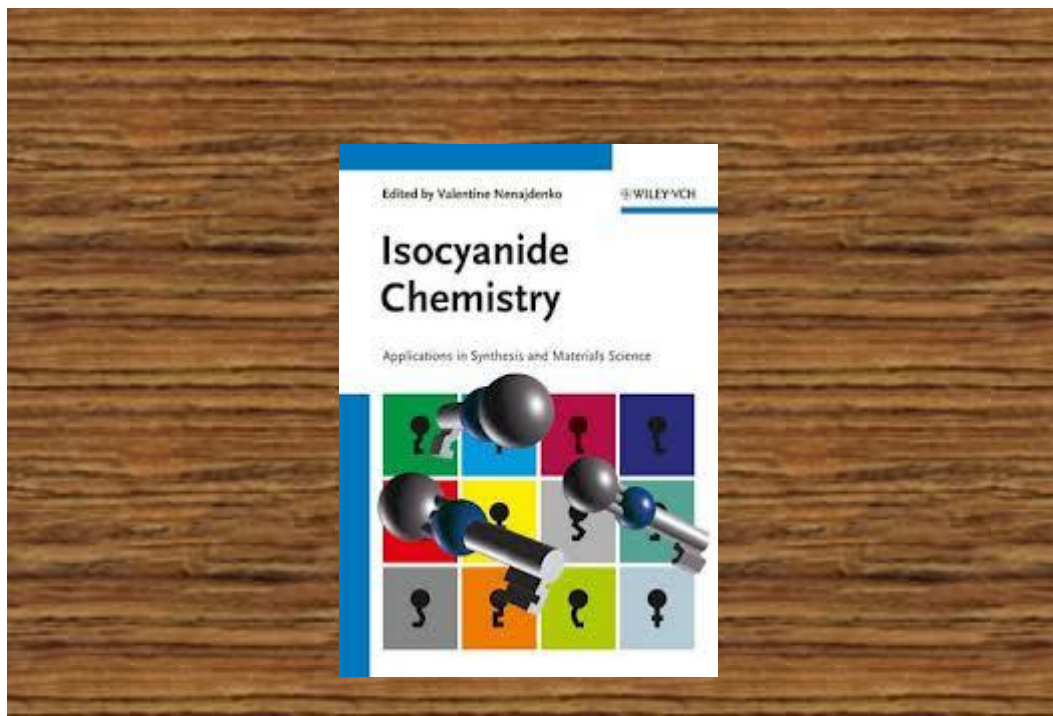
Isocyanide Chemistry

Zhi Ren

2013/9/19

Reference

- Book: Isocyanide Chemistry, edited by Valentine G. Nenajdenko (Moscow state universtiy), published by Wiley in 2012



Outline

- 1. General Reactivity of Isocyanide
- 2. Heterocycle synthesis involving isocyanide
- 3. Isocyanide in organometallics

1. General Reactivity of Isocyanide

- 1.1 Introduction
- 1.2 Preparation
- 1.3 Properties

1.1 Introduction

- The first isocyanide (isonitrile) compound was obtained by Lieke in 1859.
- Ivar Ugi (1930-2005) discover many important chemistry of isocyanides, e.g., the Ugi reaction.
- Isocyanide is a useful synthetic building block. Being stable carbenes, isonitriles are highly reactive compounds that can react with almost any type of reagents (electrophiles, nucleophiles and even radicals).
- Today isocyanide chemistry is a broad and important part of organic chemistry, inorganic, coordination, polymeric, combinatorial and medicinal chemistry.

1.2 Preparation

- Two-Step synthesis from primary amine



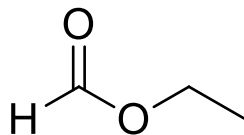
- There are four general methods of formylation and several reagents are available for dehydration.
- Some isocyanides are prepared from alcohol.

1.2 Preparation

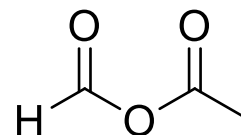
- Four methods for formylation:



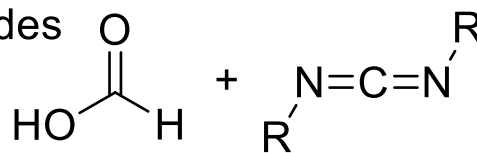
Conditions: 1. react with ethyl formate



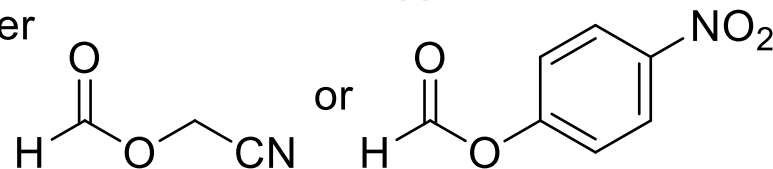
2. react with mixed formic-acetic anhydride



3. react with formic acid and carbodiimides

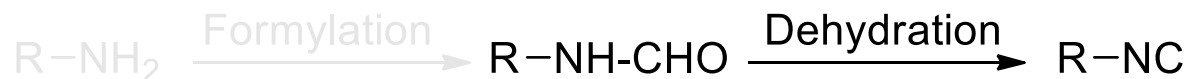


4. react with activated formic ester



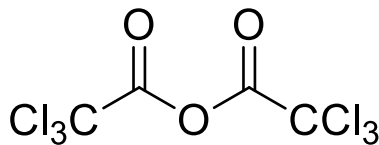
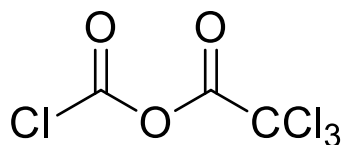
1.2 Preparation

- Four methods for formylation:

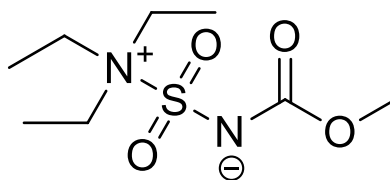


Conditions:

Most common and mild is using $\text{POCl}_3/\text{NEt}_3$ at low temperature
diphosgene and triphosgene are also used.



Less commonly used:
Burgess reagent

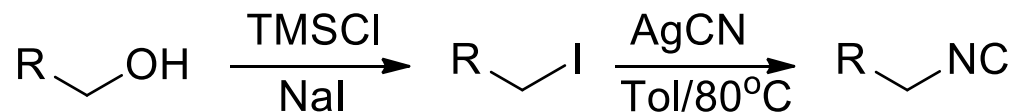


$\text{CCl}_4/\text{PPh}_3/\text{NEt}_3$ system

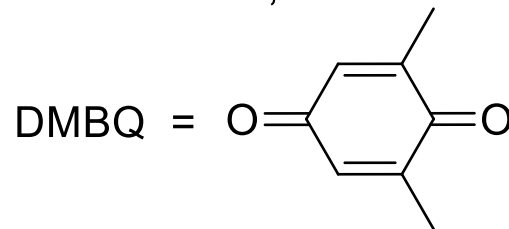
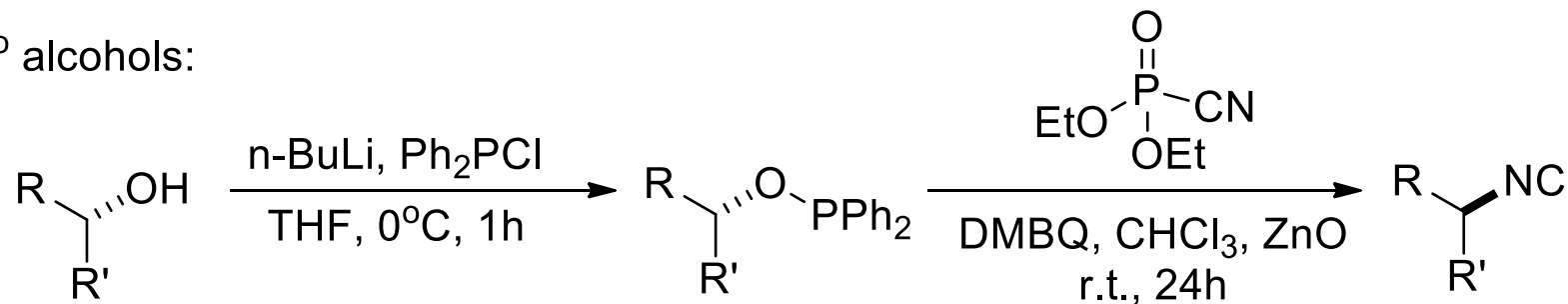
1.2 Preparation

- From Alcohol:

For 1° alcohols only:



For 2° alcohols:

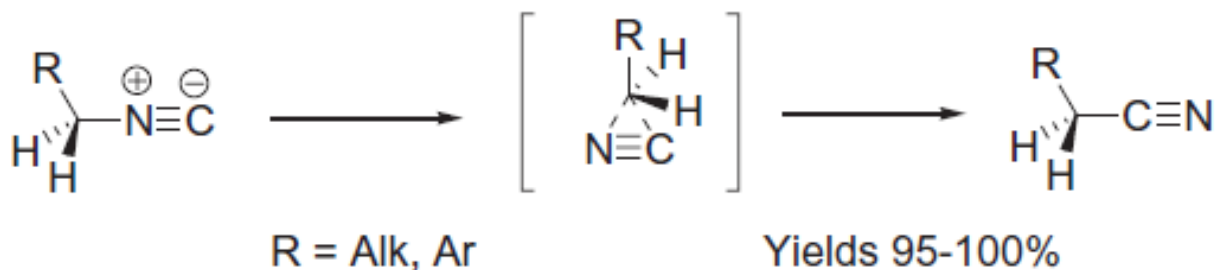


1.3 Properties

- 1.3.1 Isocyanide-Cyanide Rearrangement
- 1.3.2 Oxidation/Reduction of Isocyanide
- 1.3.3 Reactions with Electrophiles
- 1.3.4 Reactions with Nucleophiles

1.3.1 Isocyanide-Cyanide Rearrangement

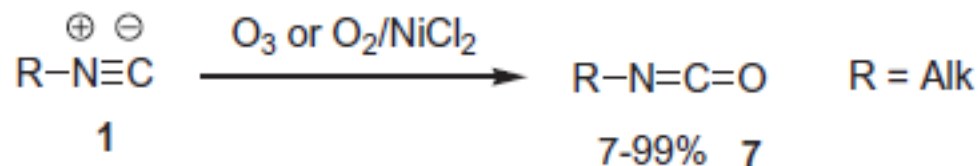
- The thermal rearrangement discovered in 1873 by Weith. The majority of isocyanides isomerize at 200-250°C. The radical inhibitors can suppress the side reaction (Decyano rxn).
- Aromatic isocyanides isomerize about 10 times faster than aliphatic isocyanides.



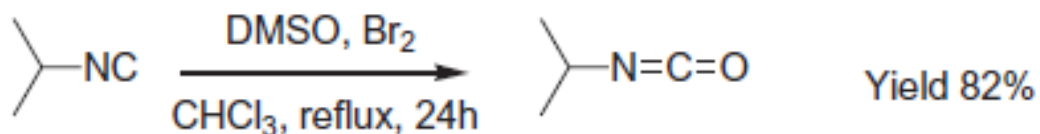
1.3.1 Isocyanide-Cyanide Rearrangement

- The substituent has minimal influence on the rate of this reaction. Because the requirements for bond formation and breakage were in opposition.
- The substituent has influence on the thermal dynamic of this reaction. The isomerization was favored by the σ -accepting or π -donating substituent.

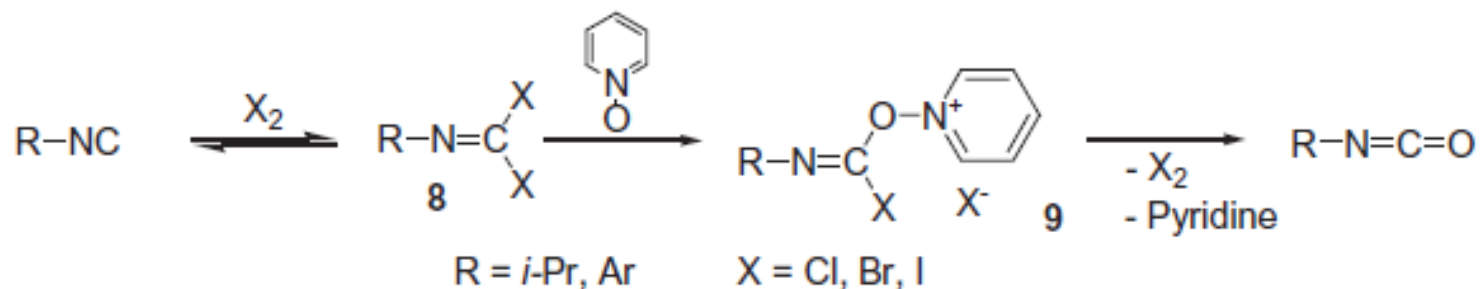
1.3.2 Oxidation/Reduction of Isocyanide



Scheme 2.6

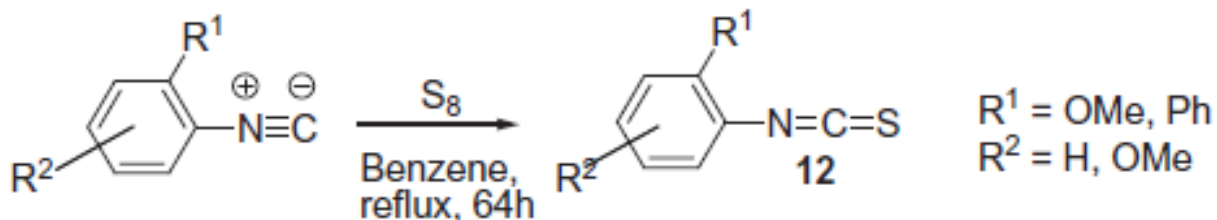


Scheme 2.7

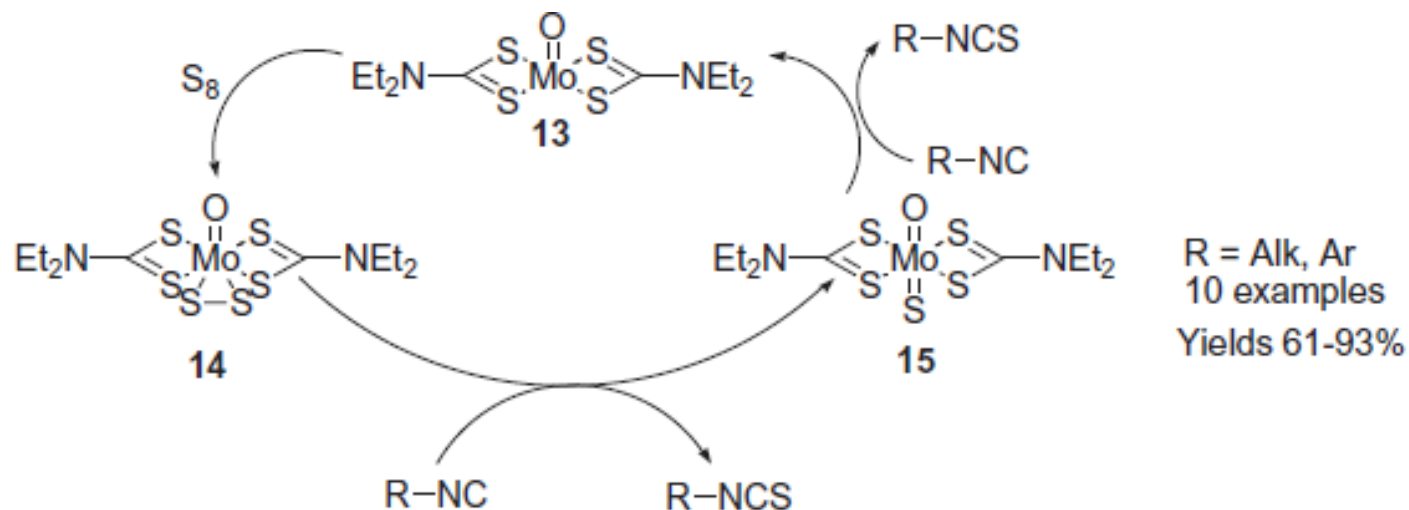


Scheme 2.8

1.3.2 Oxidation/Reduction of Isocyanide

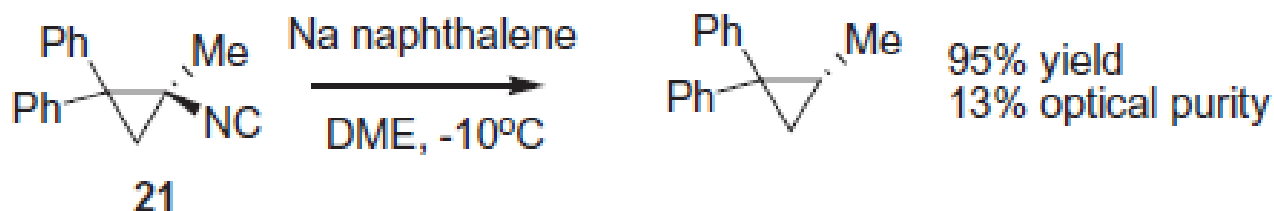


Scheme 2.10

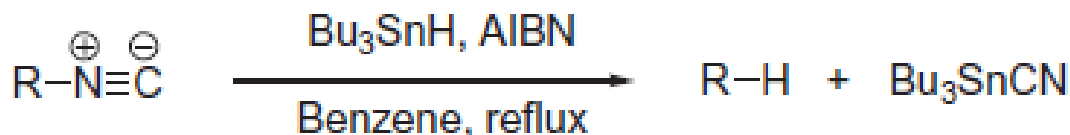


Scheme 2.11

1.3.2 Oxidation/Reduction of Isocyanide

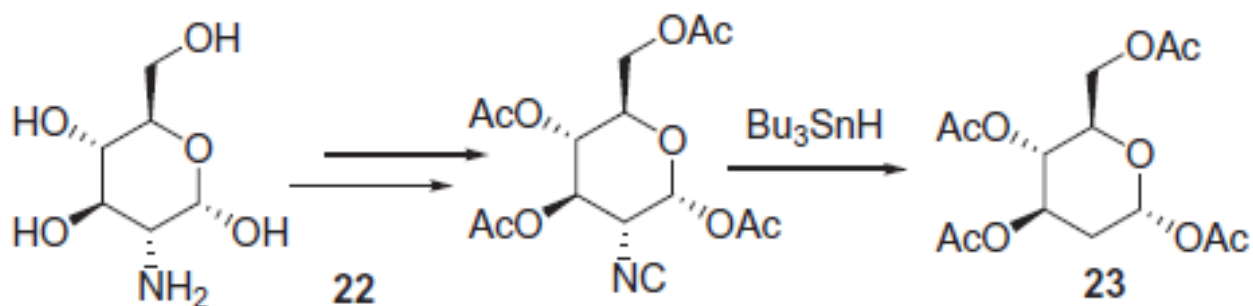


Scheme 2.15



R = Bn (97% yield), *c*-Hexyl (47% yield), *t*-Bu (45% yield)

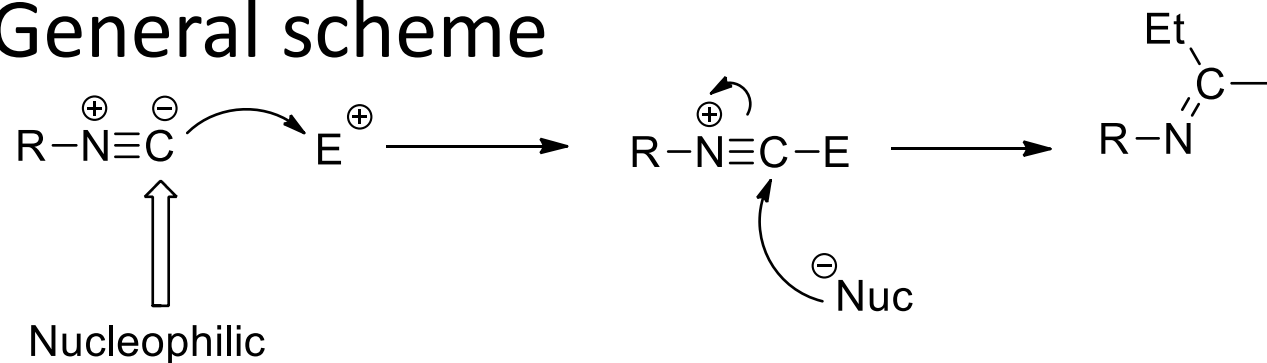
Scheme 2.16



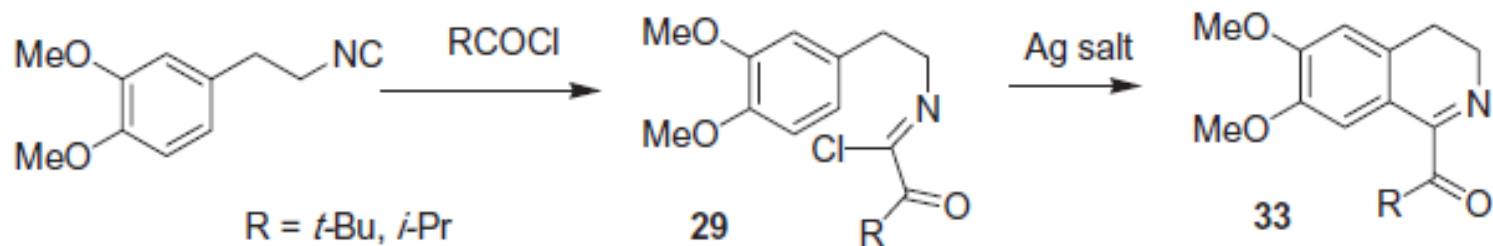
Scheme 2.17

1.3.3 Reactions with Electrophiles

- General scheme



- React with Acyl Halides



Scheme 2.20

1.3.3 Reactions with Electrophiles

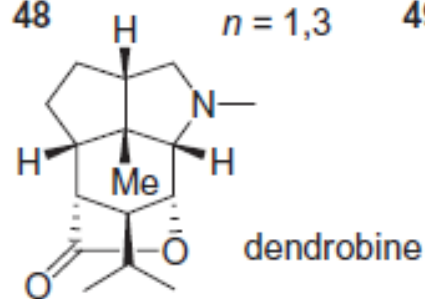
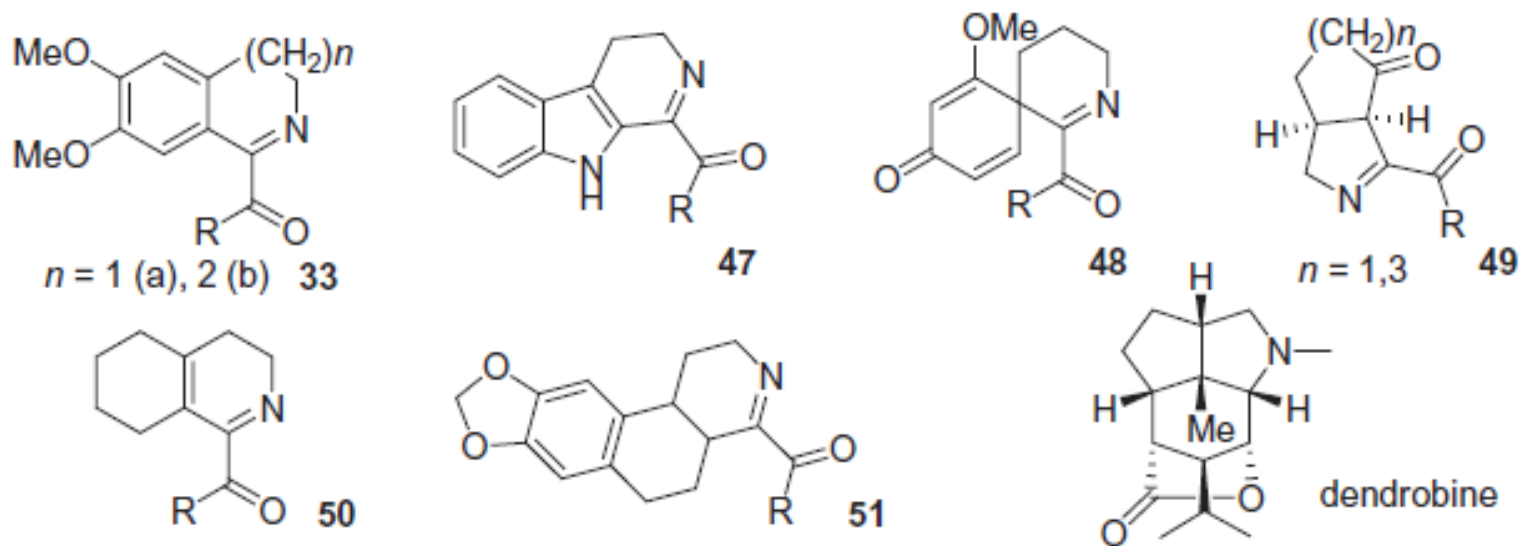
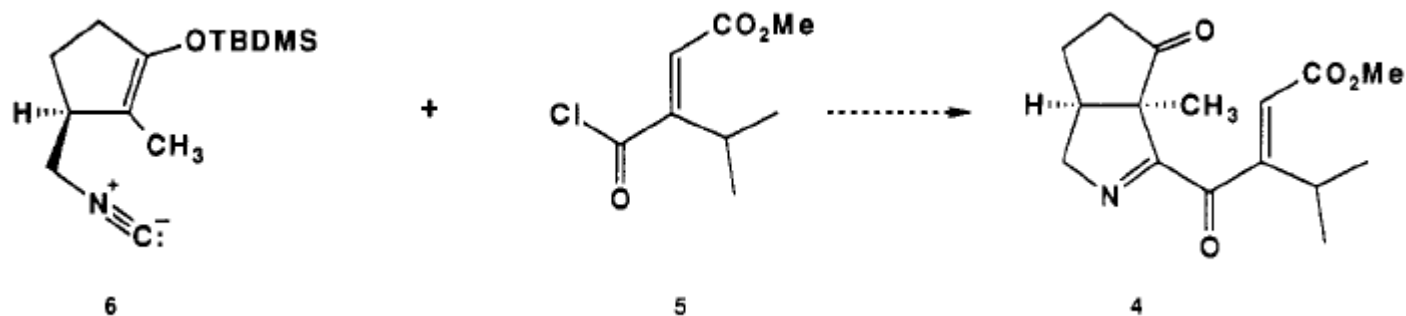


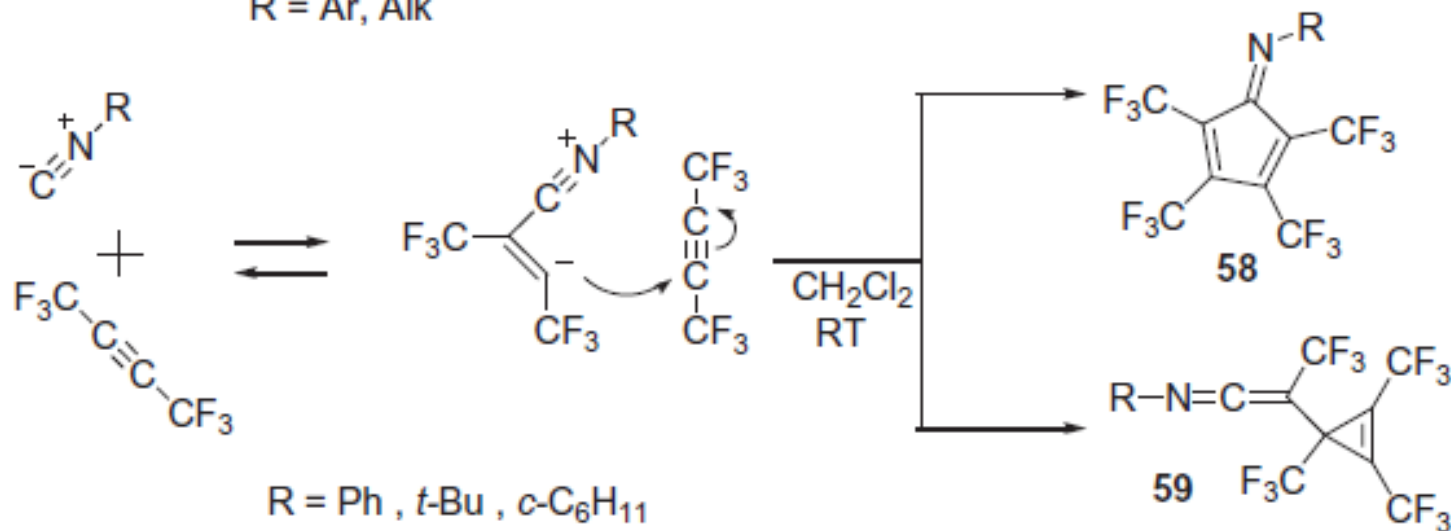
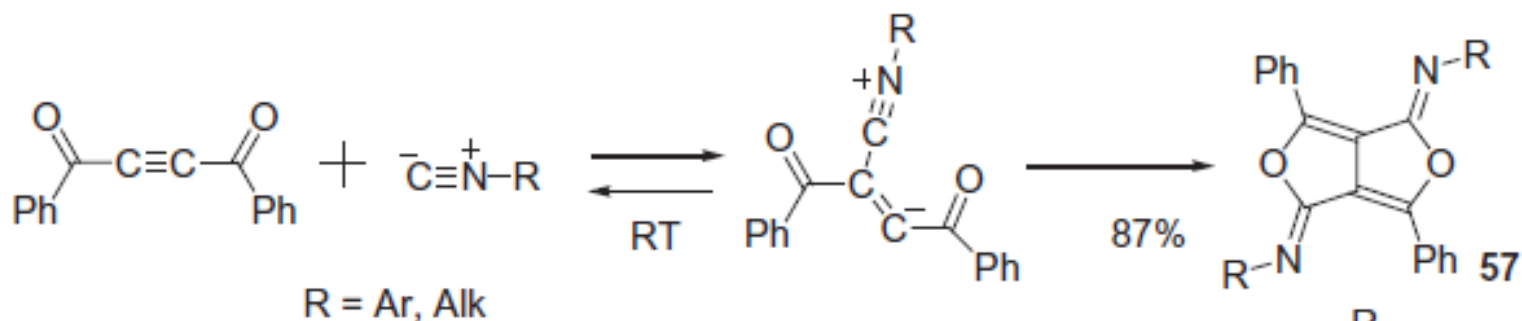
Figure 2.5 Products in reaction of isocyanides with acyl halides.



Tom Livinghouse. J. Am. Chem. Soc., 1987, 109 (2), pp 590–592.

1.3.3 Reactions with Electrophiles

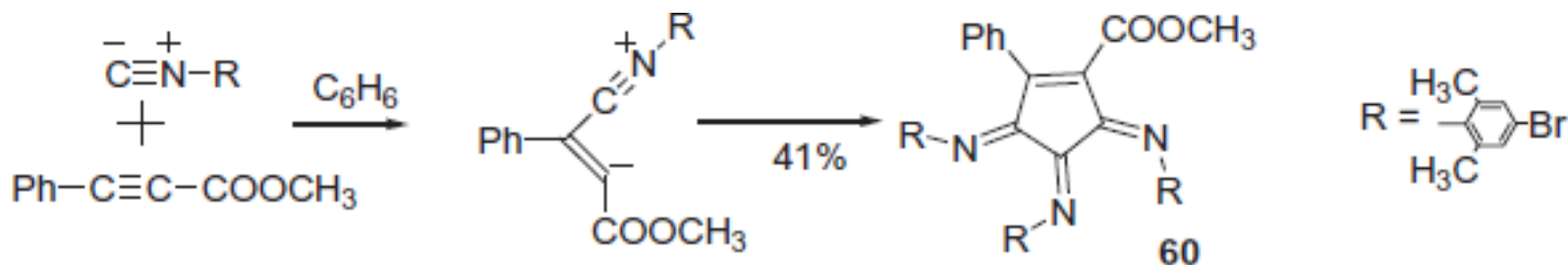
- React with activated alkenes and alkynes



Quast, H. Liebigs Ann. Chem., (4), 635-641.
Nagel, F.J. J. Am. Chem. Soc., 91, 4761.

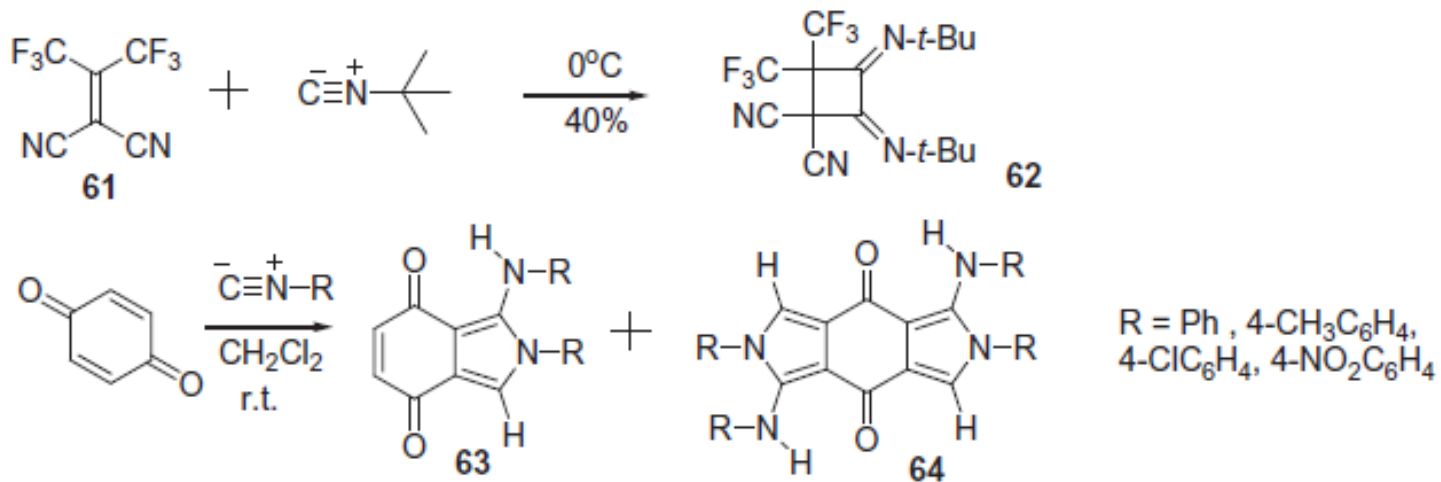
1.3.3 Reactions with Electrophiles

- React with activated alkenes and alkynes



Yanagida, T. *Tetrahedron Lett.*, 10 (39), 3407

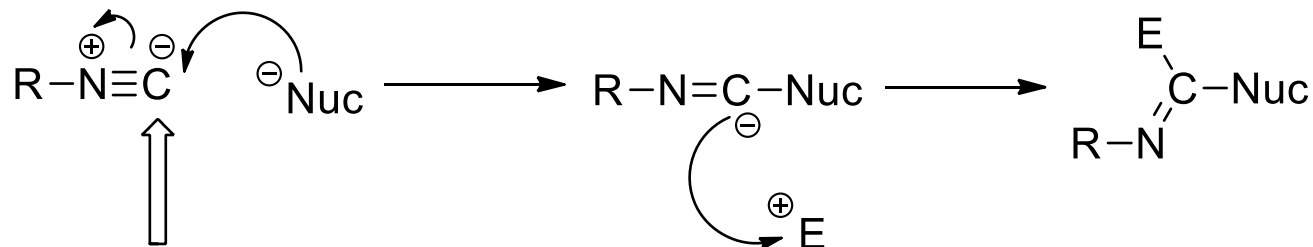
Scheme 2.33



Seidenspinner, H.M. *Liebigs Ann. Chem.*, (5), 1003-1012.

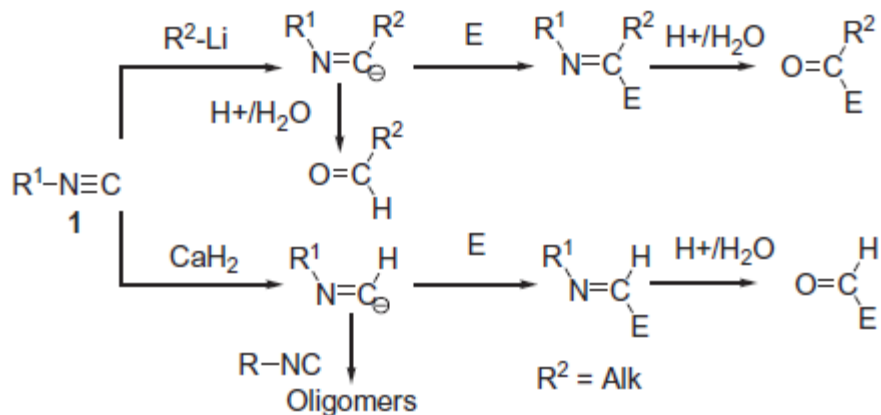
1.3.4 Reactions with Nucleophiles

- General scheme



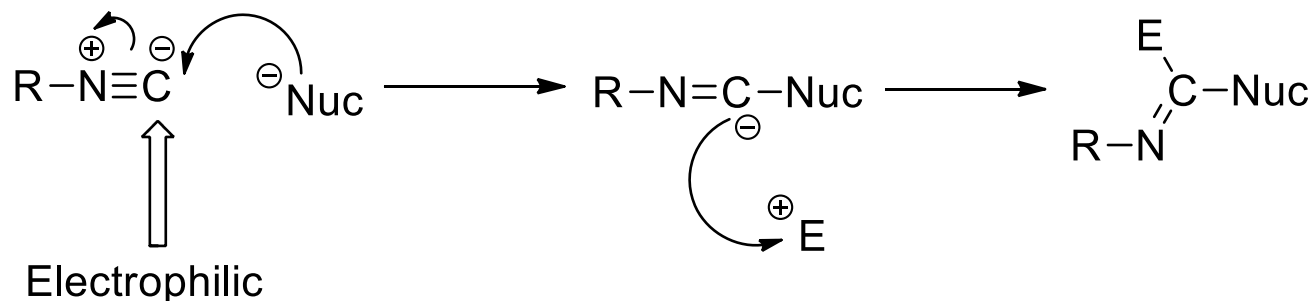
Electrophilic

- React with organometallic compounds



1.3.4 Reactions with Nucleophiles

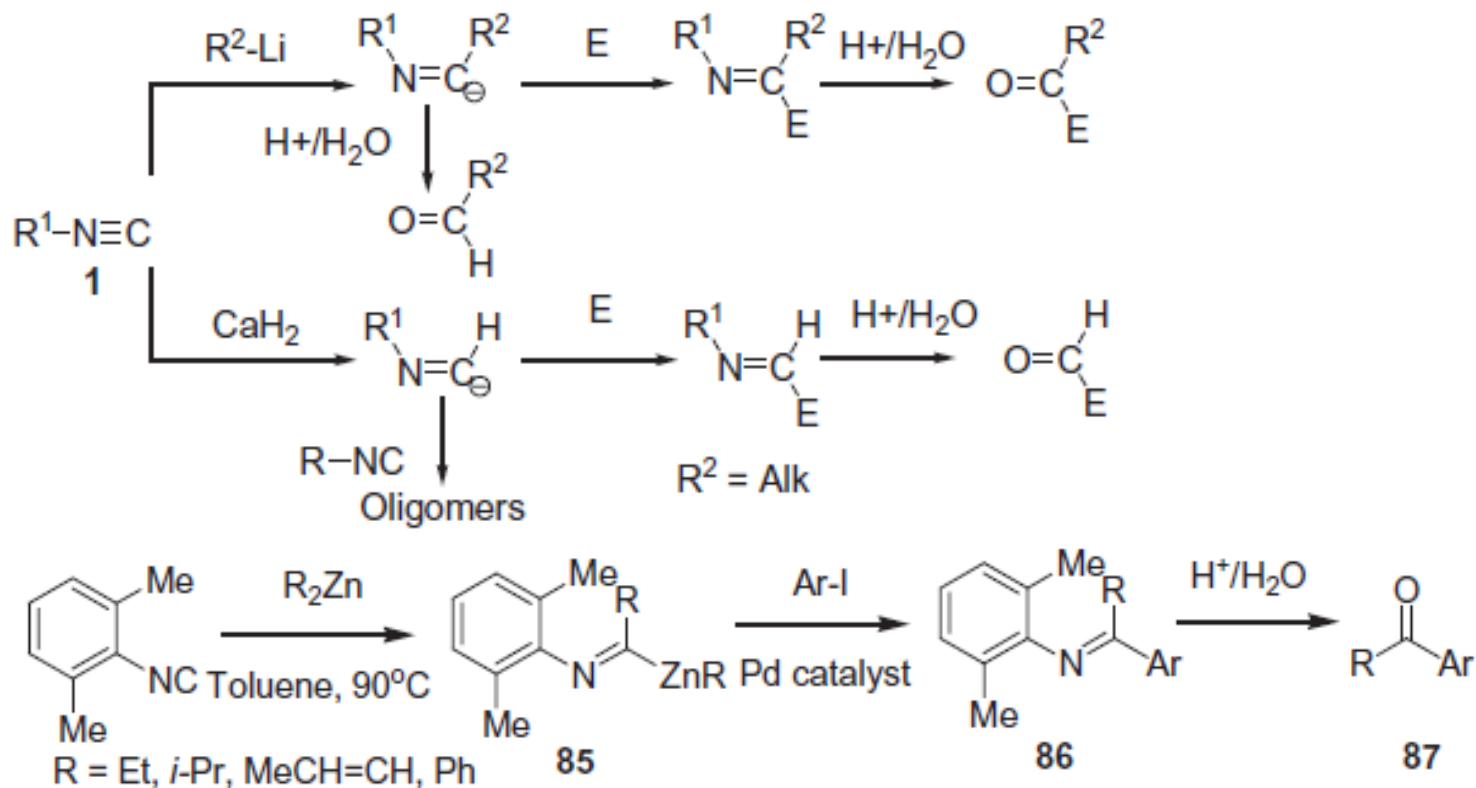
- General scheme



- The isocyanides are very poor electrophiles, that can only react with strong nucleophiles such as organometallic compounds.
- The electron-withdrawing effect of the isocyano group enhances the acidity of the α -C-H bond group in aliphatic isocyanides, as well as the ortho-methyl group in aromatic isocyanides.

1.3.4 Reactions with Nucleophiles

- React with organometallic compounds

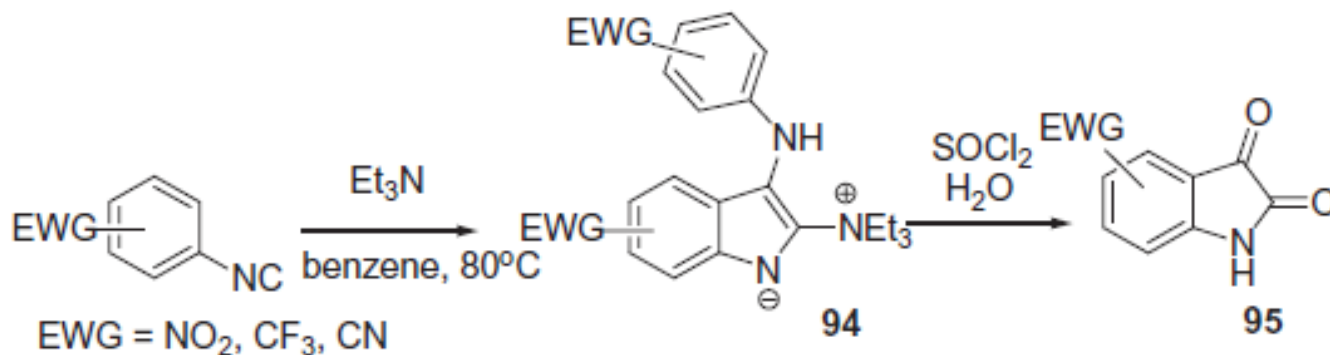


Scheme 2.47

Ito, Y. Chem. Commun., 1990, 403-405.
 Ito, Y. Pure Appl. Chem., 62(4), 583-588.

1.3.4 Reactions with Nucleophiles

- React with hydroxide, alcohols, and amines



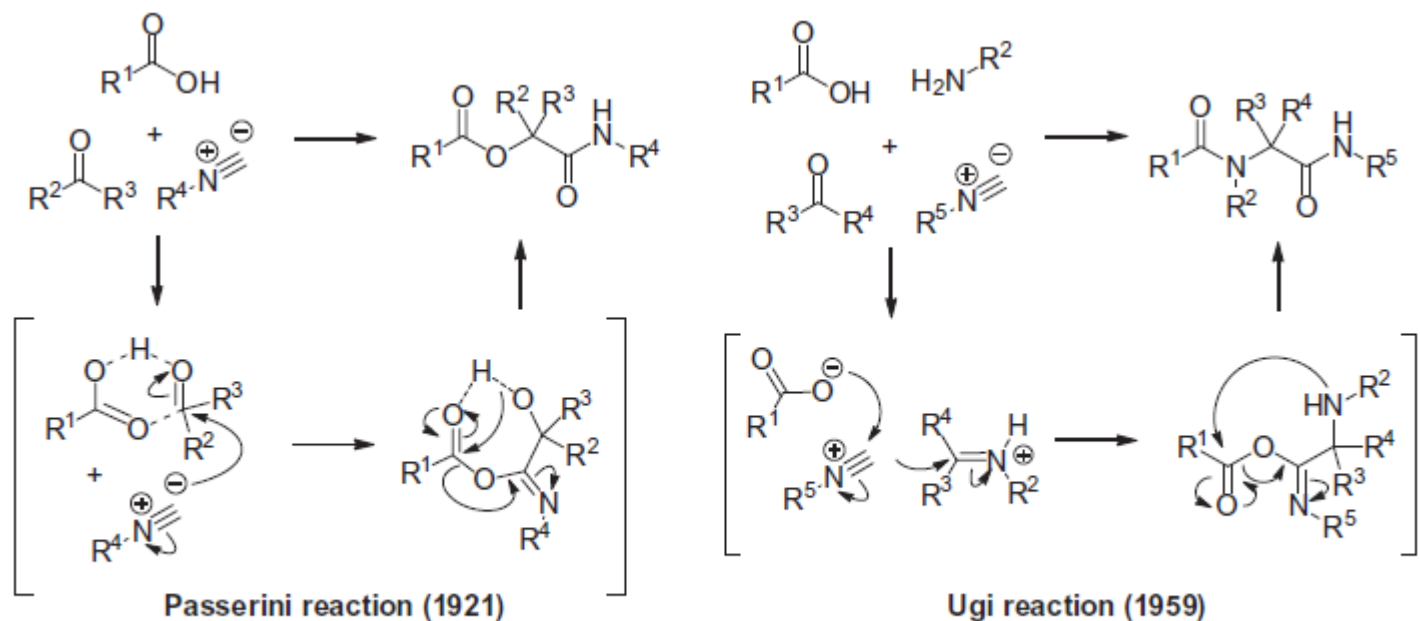
Scheme 2.51

EWG is essential

- Isocyanides are inert towards water, hydroxide, and amines without the addition of catalysts.

2. Heterocycle synthesis involving isocyanide

- MCRs are defined as one-pot processes in which at least three compounds react to form a single product that contains essentially all the atoms of the starting materials.



Scheme 3.2 The Passerini and Ugi reactions—the classical isocyanide-based MCRs.

2. Heterocycle synthesis involving isocyanide

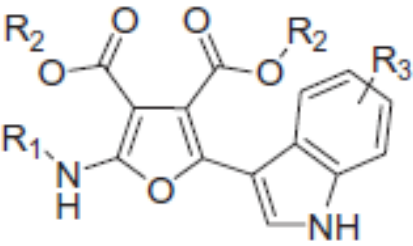
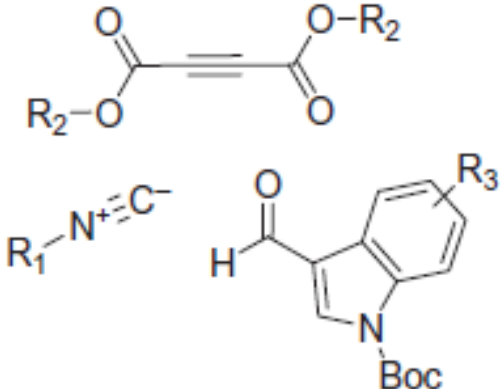
- To save time, I will only use few examples to demonstrate the point, if you are interested, read the book and the recommended reviews from the book (available online).
- The examples are come from the Chapter 13 of the book.

2. Heterocycle synthesis involving isocyanide

- 2.1 Furans
- 2.2 Pyrroles
- 2.3 Oxazoles
- 2.4 Imidazoles
- 2.5 Indoles
- 2.6 Quinolines
- The heterocycles that are not covered in this talk:
Isoxazoles, Pyrazoles, Thioazoles, Benzofurans,
Benzimidazoles, Quinoxaline

2.1 Furans

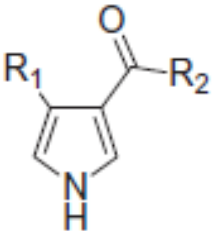
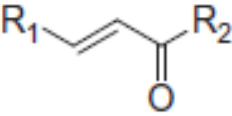
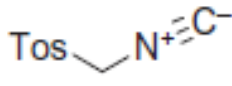
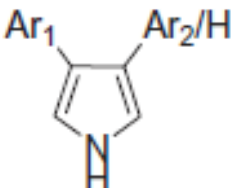
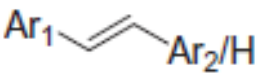
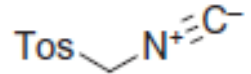
- Tetra-substituted 2-aminofurans is only type that been reported.

Product	Reactants	Conditions (yields %)	Ref.
		Dry benzene, 25 °C, 4–6 h (75–94)	[16]

Sridhar, B. *Synthesis*, 2010, 2571-2576.

2.2 Pyrroles

- 3,4- disubstituted pyrroles (not MCRs)

Product	Reactants	Conditions (yields %)	Ref.
	 	NaH, DMSO/Et ₂ O, r.t., 15 min–3 h (10–88)	[26, 27]
	 	<i>t</i> -BuONa, DMSO, 25–100 °C, 1–18 h (44–91)	[31]

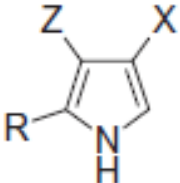
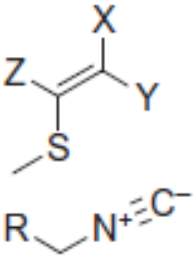
van Leusen, D. *Tetrahedron Lett.*, 1972, 5337-5340.

Perez, O.F.A. *Rev. Soc. Quim. Peru*, 75, 12-16.

Cosford, N.D.P. *Org. Lett.*, 4, 3537-3539.

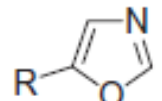
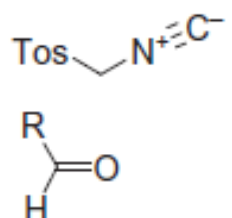
2.2 Pyrroles

- 2,3,4- trisubstituted pyrroles (not MCRs)

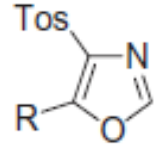
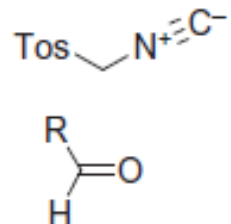
Product	Reactants	Conditions (yields %)	Ref.
 <p>X = NO₂, CN, COPh, COMe, CO₂Et Z = SMe, NR₁R₂ R = CO₂Et, Ts, Ph 4-Cl-Ph</p>	 <p>X = NO₂, CN, COPh, COMe, CO₂Et Y = H, CO₂Et, COPh, COMe Z = SMe, NR₁R₂ R = CO₂Et, Ts, Ph, 4-Cl-Ph</p>	DBU, DMF, 120 °C, 5–8 h or <i>t</i> -BuOK, THF, –78 °C to r.t., 2 h (65–86)	[57]

2.3 Oxazoles

- 5-substituted oxazoles

Product	Reactants	Conditions (yields %)	Ref.
		K_2CO_3 , MeOH, reflux, 2 h (57–71)	[70, 71]

- 4,5-disubstituted oxazoles

		K_2CO_3 , MeOH, 20 °C, 10 min–2.5 h (53–80)	[70]
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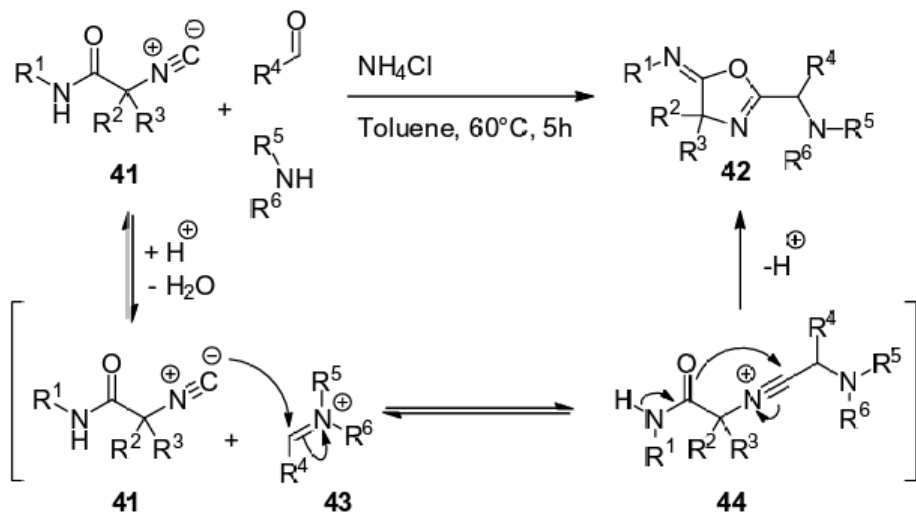
Siderius, H. Tetrahedron Lett., 1972, 2369-2372.

Van Leusen, A.M. Chem. Pharm. Bull., 27, 793-796

2.3 Oxazoles

- 2,5-disubstituted oxazoles

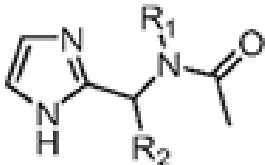
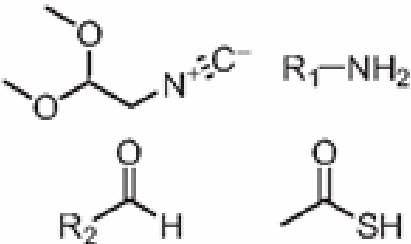
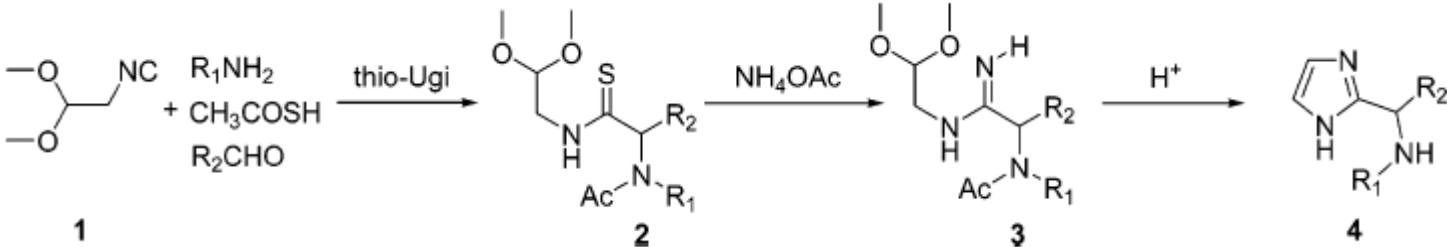
Product	Reactants	Conditions (yields, %)	Ref.
		Et ₃ N·HCl, MeOH, r.t., 12 h (73–92)	[86]



Ganem, B. Tetrahedron Lett., 44, 6825-6827.

2.4 Imidazoles

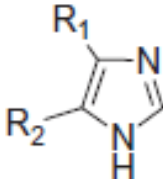
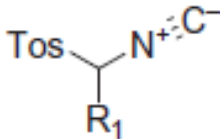
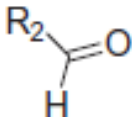
- 2-substituted imidazoles (5-substituted can be synthesis using isocyanide)

Product	Reactants	Conditions (yields, %)	Ref.
		1. MeOH, r.t. (45–83) 2. NH ₄ OAc/EtOH, reflux, then HCl, reflux (59–72)	[129]
			

Nenajdenko, V.G. J. Org. Chem., 72, 7878-7885

2.4 Imidazoles

- 1,4- and 4,5-disubstituted imidazoles

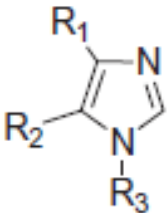
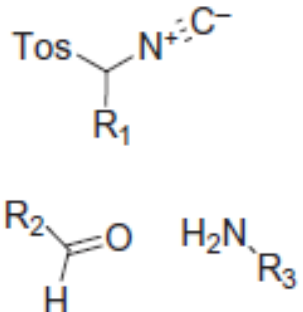
Product	Reactants	Conditions (yields, %)	Ref.
	  NH ₄ OH	Piperazine, THF, r.t. 18 h (23–81)	[73, 134]

Zhu, J. Chem. Eur. J., 17, 880-889.

Mellinger, M. Pure Appl. Chem., 74, 1349–1357

2.4 Imidazoles

- 1,4,5-trisubstituted imidazoles

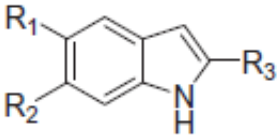
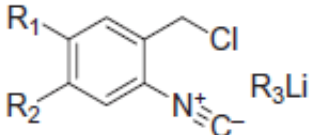
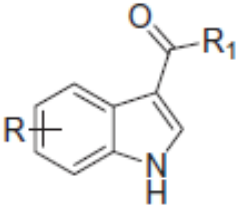
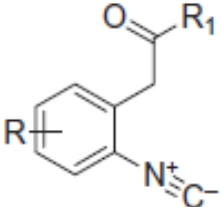
Product	Reactants	Conditions (yields, %)	Ref.
		K_2CO_3 , DMF, r.t., 3–5 h (62–87)	[73, 134]

Zhu, J. Chem. Eur. J., 17, 880–889.

Mellinger, M. Pure Appl. Chem., 74, 1349–1357.

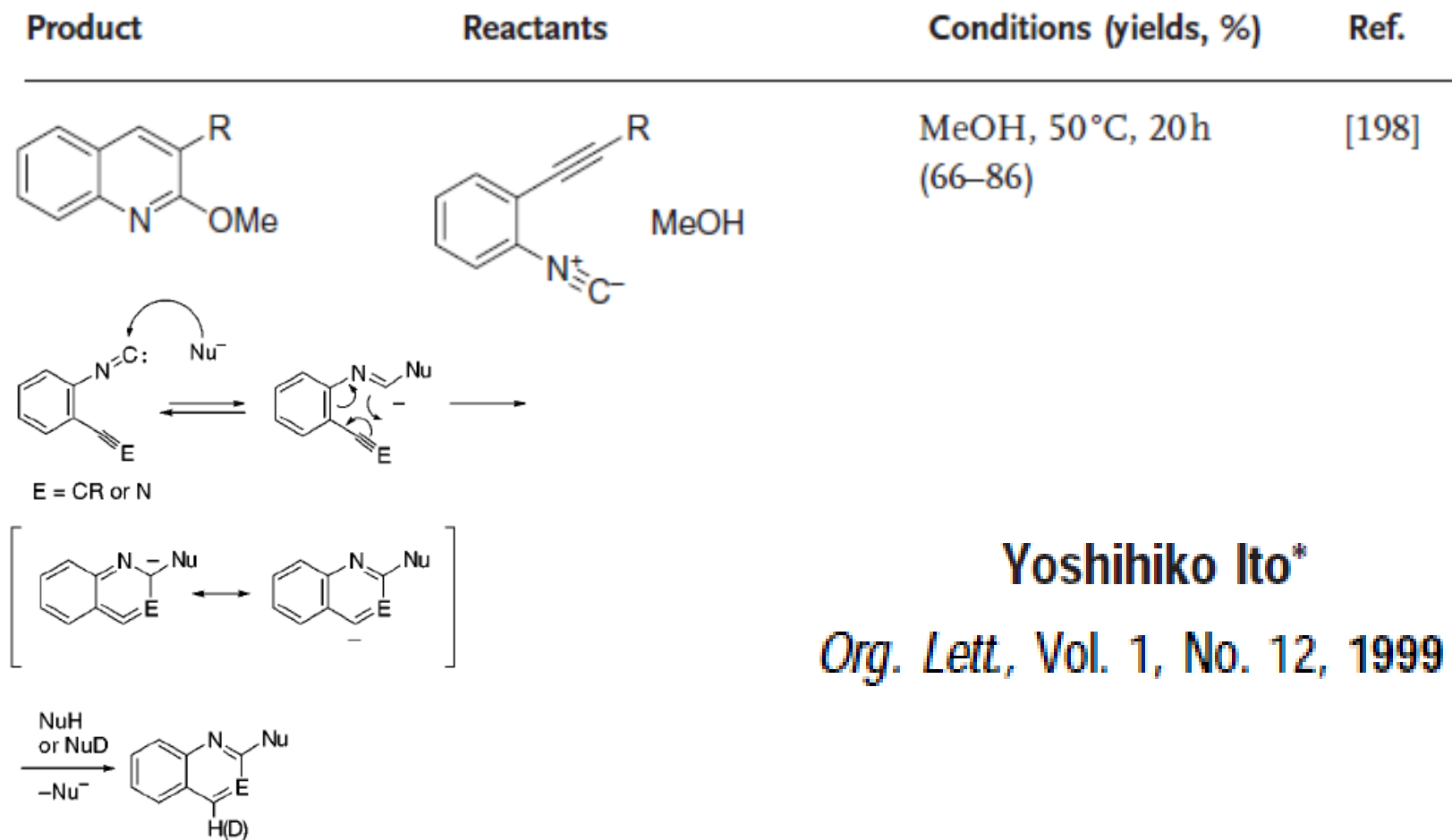
2.5 Indoles

- There are more examples using TM to synthesize indoles.

Product	Reactants	Conditions (yields, %)	Ref.
		THF, -78 °C, 2 h (49–74)	[175]
		2 equiv. LDA or LTMP, -78 °C, diglyme (55–68) or Cu ₂ O, benzene, reflux, 2 h (60–85)	[178, 179]
Hisatoshi Konishi	Tetrahedron 65 (2009) 7523–7526		
Takeo Saegusa	Tetrahedron Lett. No.12, pp 1039		
Takeo Saegusa	J. Org. Chem., 1979, 44 (12), pp 2030–2032		

2.6 Quinolines

- Mainly undergo 6-endo-dig



Yoshihiko Ito*

Org. Lett., Vol. 1, No. 12, 1999

2.7 Summary

- 1. Isocyanides have been used as a powerful tool in the preparation of numerous diverse structures, especially in heterocycles and peptides.
- 2. The MCRs shown in this presentation are very simple. The MCRs can quickly prepare a large number of drug-like scaffolds under mild conditions.

3. Isocyanide in organometallics

- 3.1 Introduction
- 3.2 Low valent complex
- 3.3 Carbene complexes derived from metal bound isocyanides
- 3.4 Application and summary

3.1 Introduction

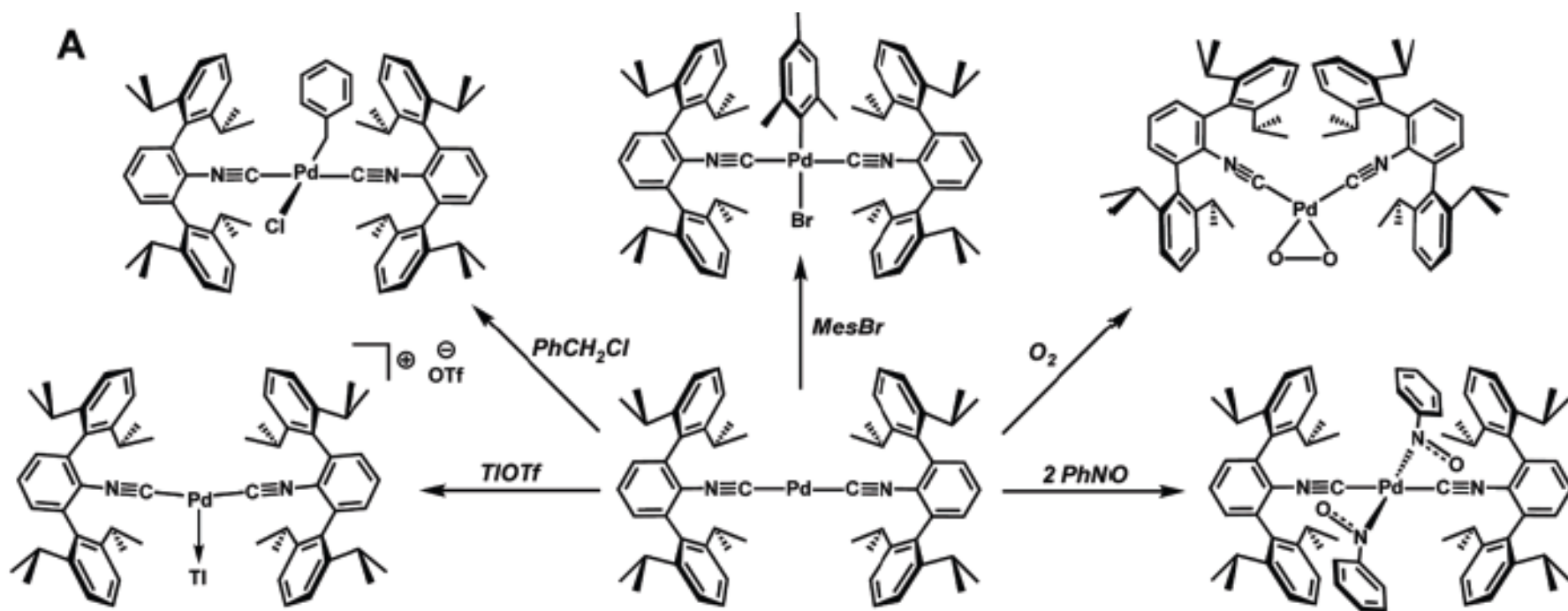
- The first isocyanide complex $\text{Ag}(\text{CNR})(\text{CN})$ was obtained by Gautierin 1869.
- But until 1977, the first zero-valent isocyanide complexes $\text{Co}_2(\text{CNR})_8$ were obtained.
- Now, a large number of isocyanide complexes involving metals from Group 5 to Group 11 and Ti.

3.1 Introduction

- Unlike CO ligand (0.12 Debye), the isocyanide ligands are more polar (NCPh is 3.44 Debye).
- In general, the isocyanide ligands are considered stronger σ -donor and weaker π -acceptor compared to CO.
- Aryl isocyanide are better π -acceptor because the aromatic ring can delocalize the back-donating electron.
- The fluorinated aryl isocyanide are very strong π -acceptors.

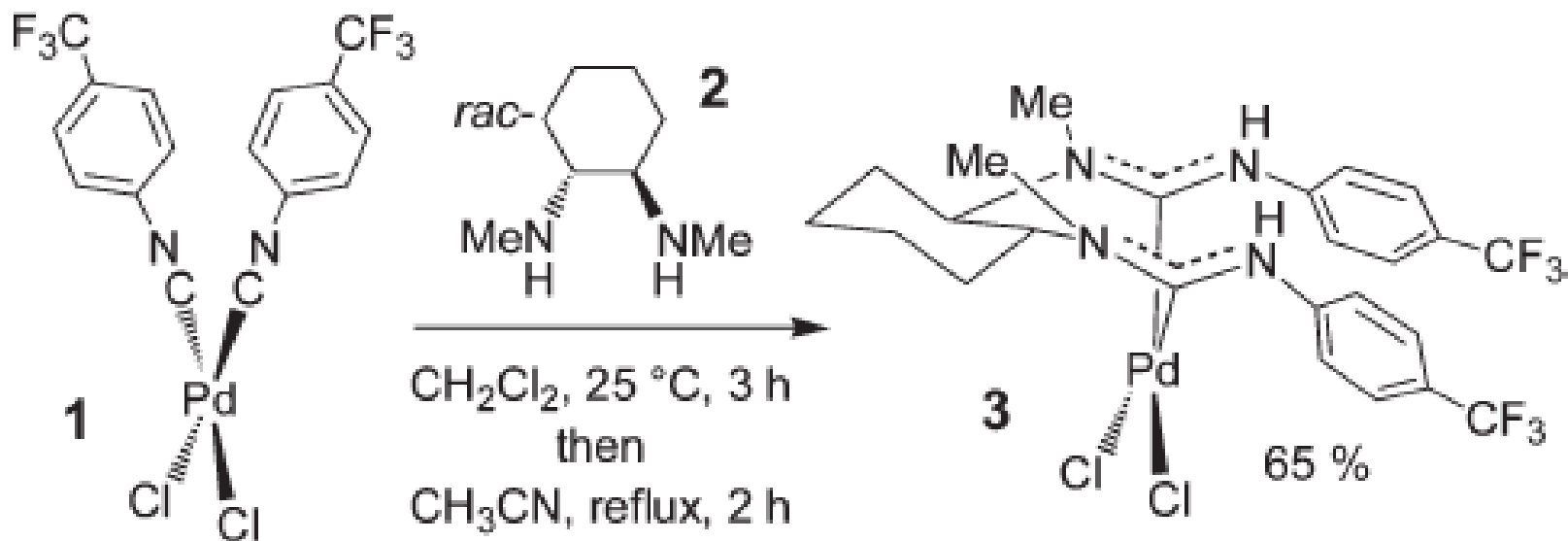
3.2 Low valent complex

- Pd(0) complex as example



3.3 Carbene complexes derived from metal bound isocyanides

- Pd(II) complex as example of coupling of amine or alcohol

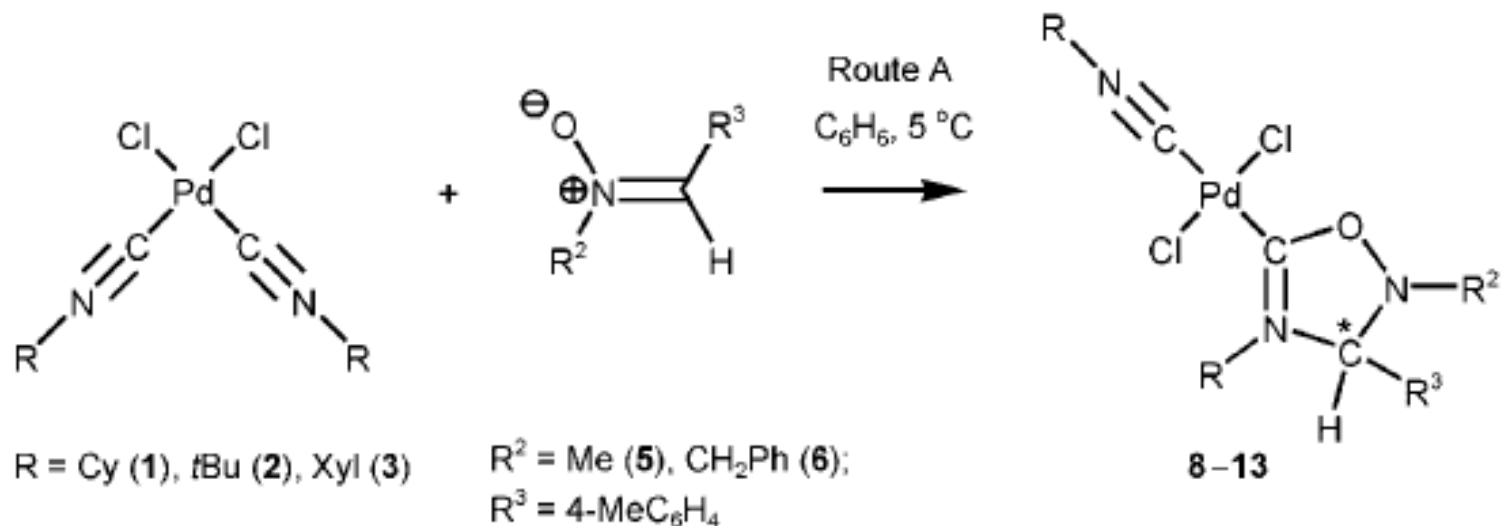


LeGrande M. Slaughter*

Chem. Commun., 2007, 3294–3296

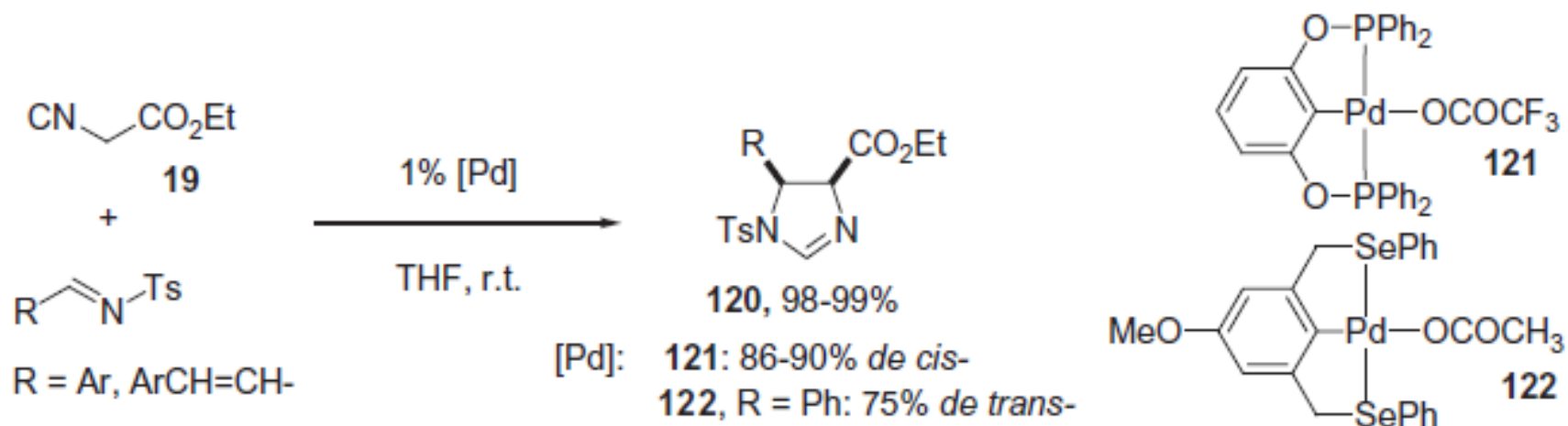
3.3 Carbene complexes derived from metal bound isocyanides

- Pd(II) complex as example of coupling with dipoles



3.4 Application and summary

- Pd-catalyzed imidazoline formation

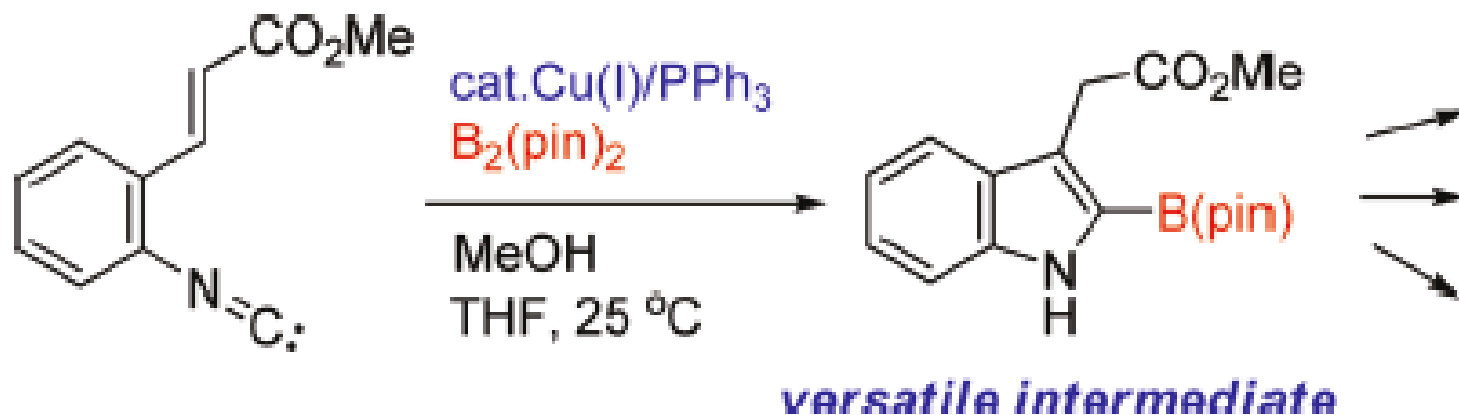


Scheme 4.29

Kálmán J. Szabó^{a,*} *Adv. Synth. Catal.* 2007, 349, 2585–2594

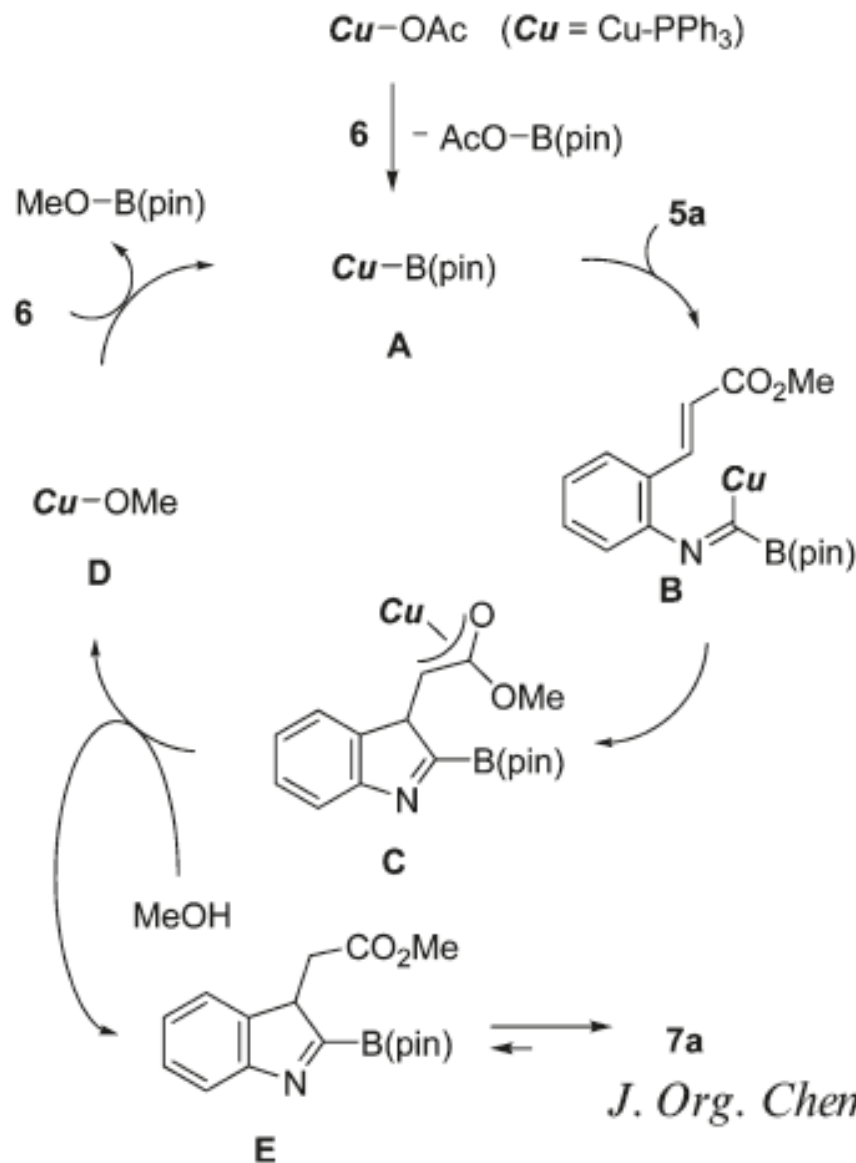
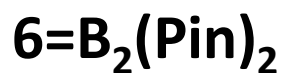
3.4 Application and summary

- Cu(I) catalyzed 2-borylindole synthesis



Naoto Chatani *J. Org. Chem.* Vol. 75, No. 14, 2010

3.4 Application and summary



3.4 Application and summary

- 1. Isocyanide is good ligand, so it is not surprise it can form so many metal complex.
- 2. The catalytic reaction is not very well developed, and similar transformation can be done without using TM. That is why these paper do not have a high impact.
- 3. To design the unique catalytic cycle for the isocyanide-metal complex could have great impact.

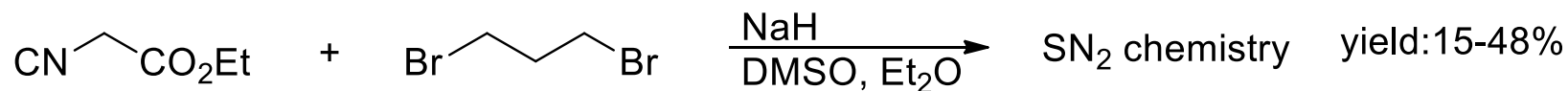
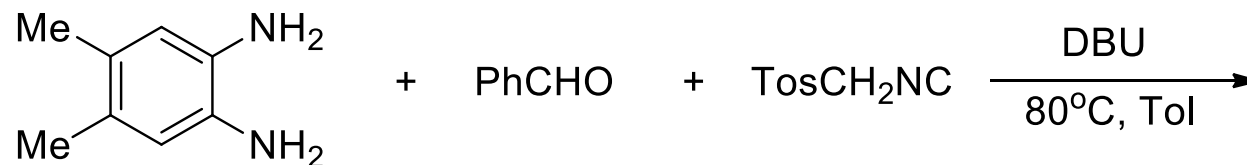
Thanks!

- Happy mid-Autumn festival.

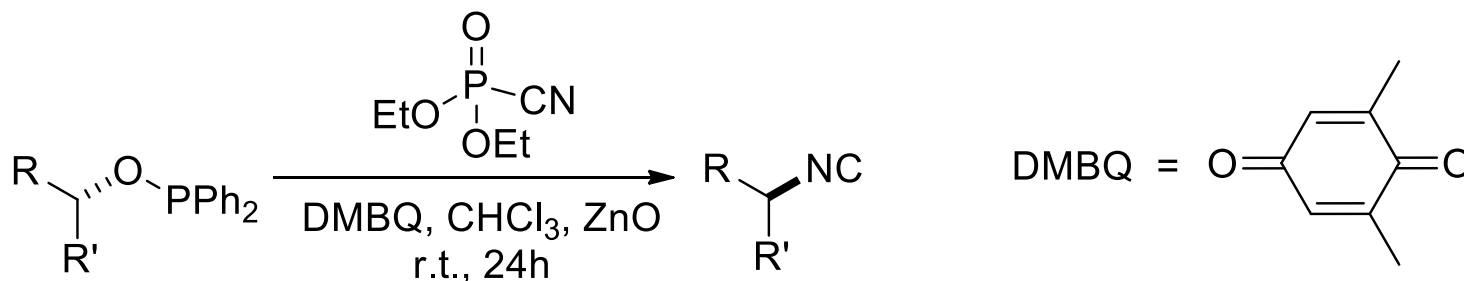


Questions!

1. Predict the products

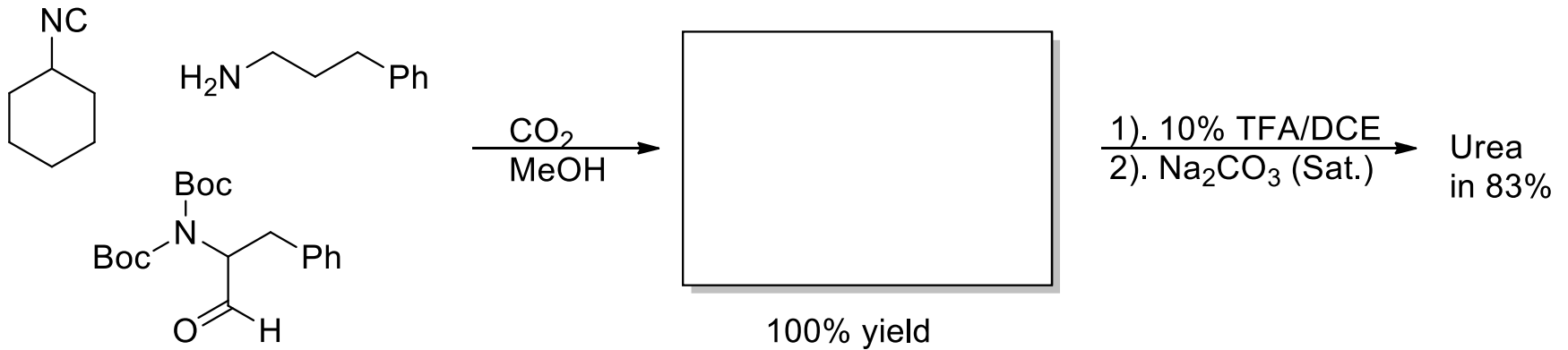


2. Draw the mechanism



Questions!

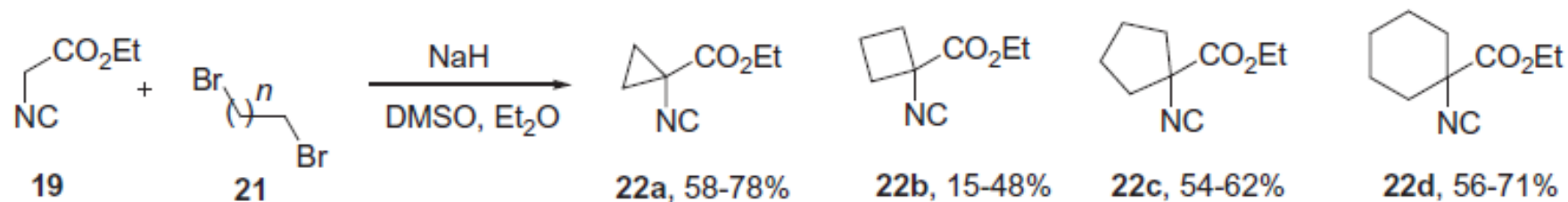
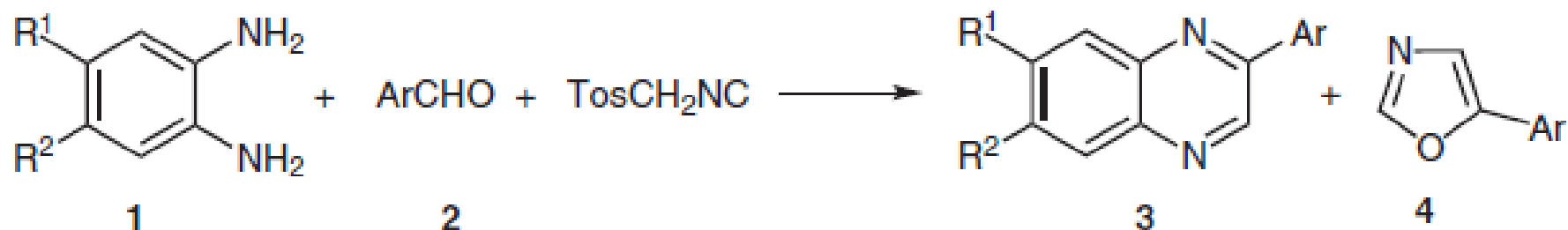
3. Predict the intermediates and draw the mechanism for the first step:



CO_2 and MeOH are involved in the first step

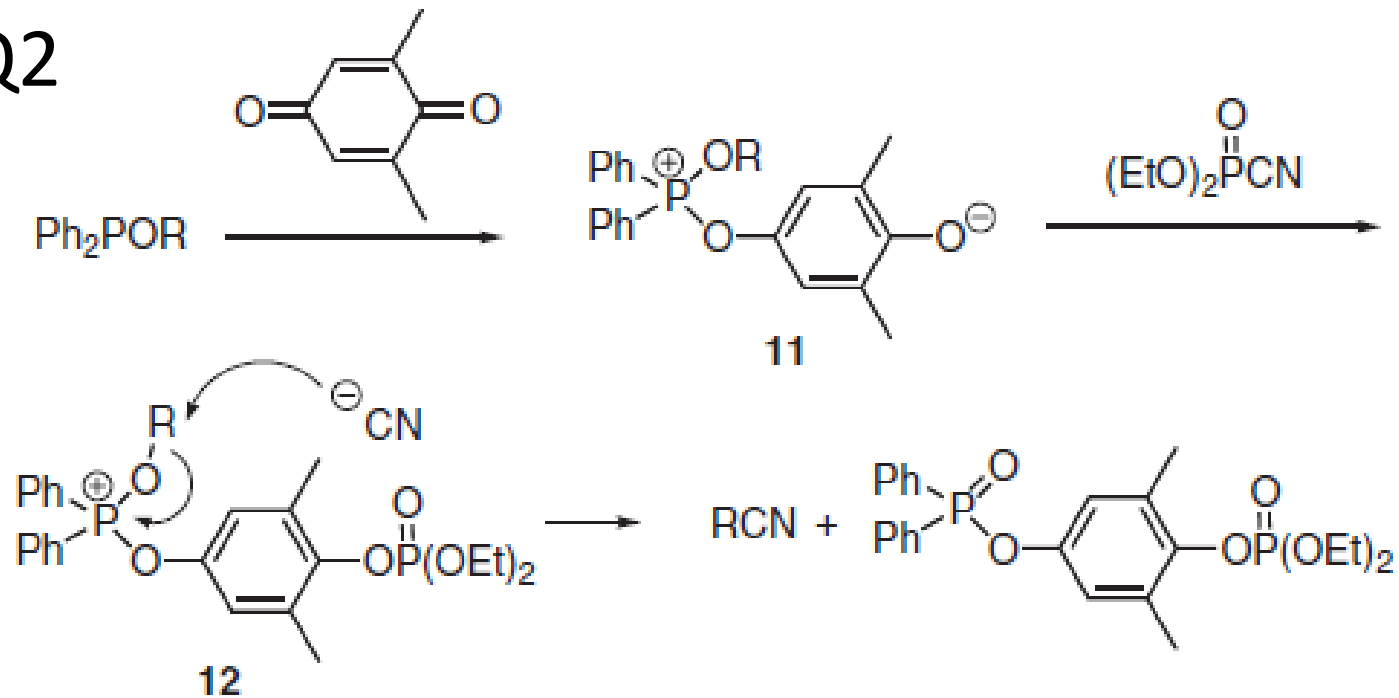
Questions!

- Q1



Questions!

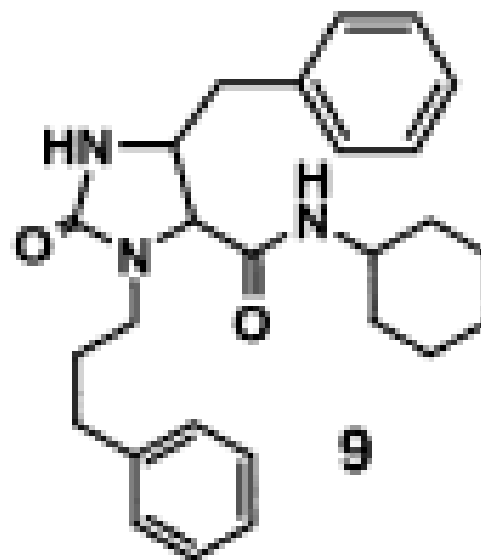
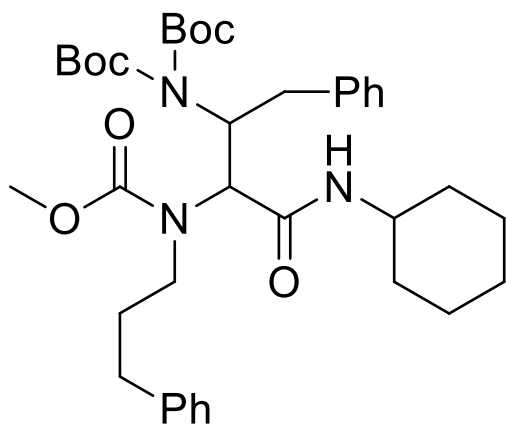
• Q2



Scheme 1.

Questions!

- Q3



Urea