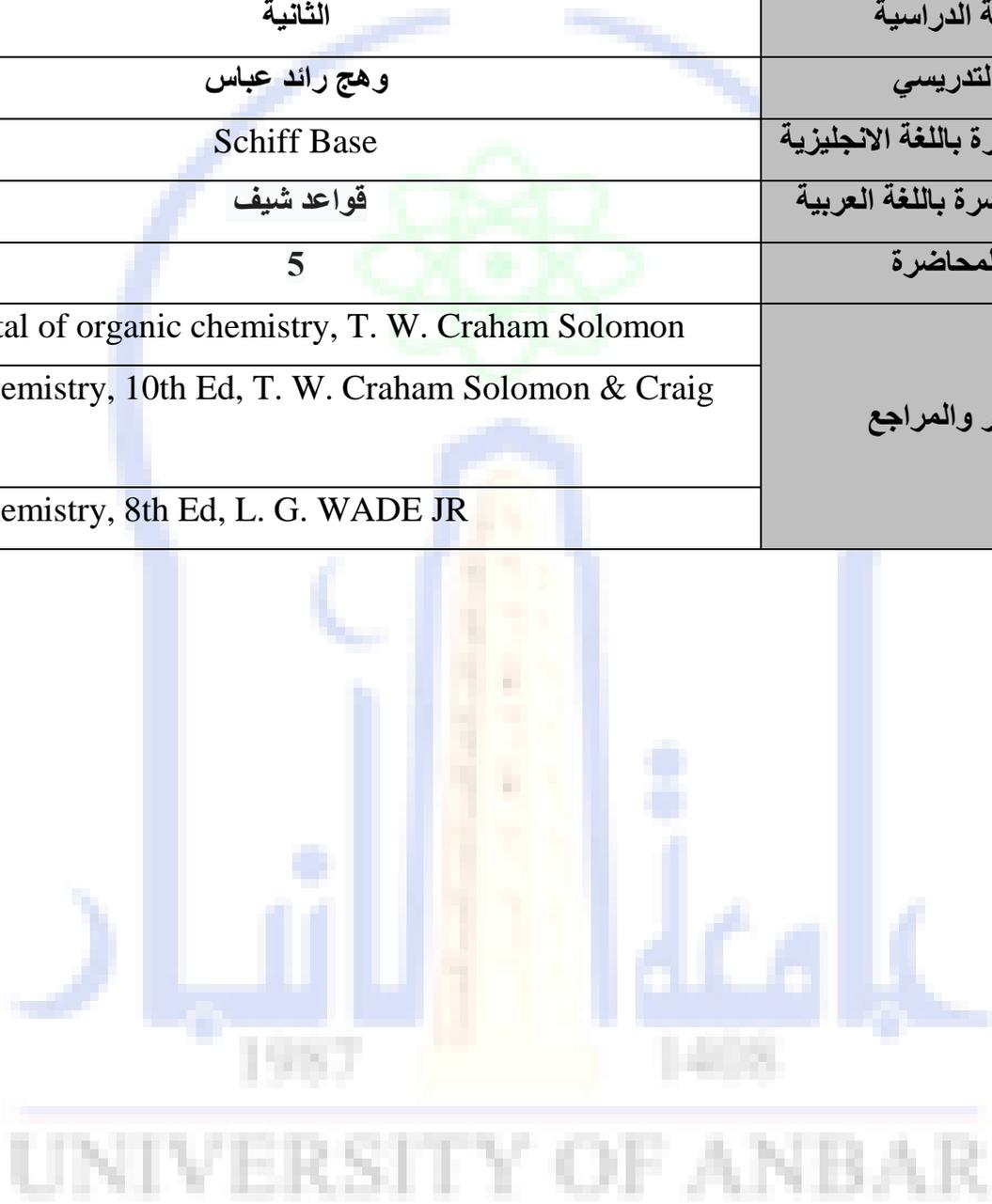


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Schiff Base	عنوان المحاضرة باللغة الانجليزية
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Fundamental of organic chemistry, T. W. Craham Solomon	المصادر والمراجع
Organic chemistry, 10th Ed, T. W. Craham Solomon & Craig B. fryhle	
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# Schiff Base

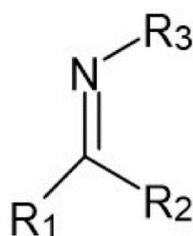
By Wahaj Raed Abbas

## Introduction

The term Schiff's base derives from the name of the German chemist Hugo Schiff, who, in 1864, was the first to describe the products resulting from the reaction of primary amines with carbonyl compounds. Schiff bases are a vast group of compounds characterized by the presence of a double bond linking carbon and nitrogen atoms, the versatility of which is generated in the many ways to combine a variety of alkyl or aryl substituents. Compounds of this type are both found in nature and synthesized in the laboratory. For years, Schiff bases have been greatly inspiring to many chemists and biochemists. In this article, we attempt to present a new take on this group of compounds, underlining of the importance of various types of Schiff bases. Among the different types of compounds that can be classified as Schiff bases, we chose hydrazides, dihydrazides, hydrazones and mixed derivatives such as hydrazide-hydrazones. For these compounds, we presented the elements of their structure that allow them to be classified as Schiff bases. While hydrazones are typical examples of Schiff bases, including hydrazides among them may be surprising for some. In their case, this is possible due to the amide-iminol tautomerism. The carbon-nitrogen double bond present in the iminol tautomer is a typical element found in Schiff bases. Schiff bases are characterized with azomethine (imine) groups. Also, it regarded subclass of

imines, the imine or azomethine group ( $>C=N-$ ) as being essential for the Schiff base

active and functional. Because the N atom of an imine is surrounded by three groups (two atoms and a lone pair), it is  $sp^2$  hybridized, making the C – N – R" bond angle  $\sim 120^\circ$  (not  $180^\circ$ ).



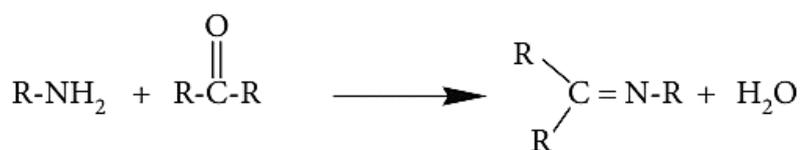
## Synthesis

Schiff bases are versatile compounds synthesized from the condensation reaction of a primary aliphatic or aromatic amine group and a carbonyl (alkanal (aldehyde) or alkanone (ketone) group under certain conditions. The

aromatic alkanals with efficient conjugated systems were more stable than aliphatic alkanals because aliphatic alkanals are unstable and polymerize freely. further compared both alkanals and alkanones in condensation reaction and stated that alkanals' reactivities are usually faster than those of alkanones.

1- General preparation of imine: (reaction of aldehyde and ketone with 1° amine)

Treatment of an aldehyde or ketone with a 1° amine affords an imine. Nucleophilic attack of the 1° amine on the carbonyl group forms an unstable carbinolamine, which loses water to form an imine. The overall reaction results in replacement of (C = O) by (C = NR). Imine formation is fastest when the reaction medium is weakly acidic.

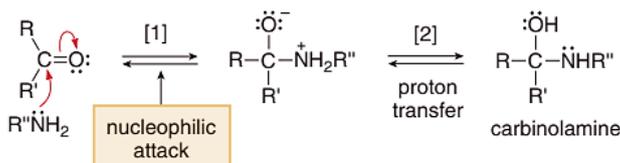


Primary amine      Alkanal or alkanone      Schiff base      Water

R = H (Alkanal)

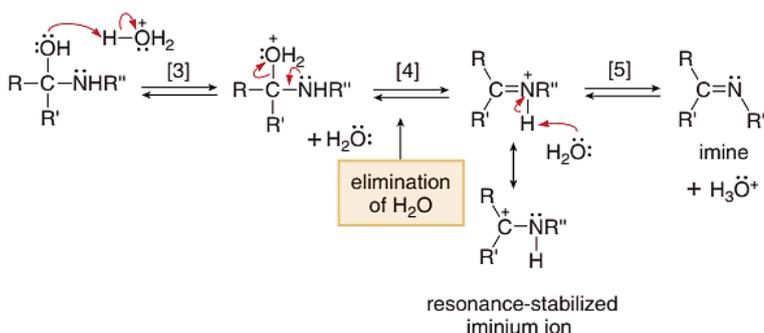
The mechanism of imine formation can be divided into two distinct parts: nucleophilic addition of the 1° amine, followed by elimination of H<sub>2</sub>O. Each step involves a reversible equilibrium, so that the reaction is driven to completion by removing H<sub>2</sub>O.

**Part [1]** Nucleophilic addition forms a carbinolamine.



- **Nucleophilic attack** of the amine followed by proton transfer forms the unstable carbinolamine (Steps [1]–[2]). These steps result in the addition of H and NHR'' to the carbonyl group.

**Part [2]** Elimination of H<sub>2</sub>O forms an imine.

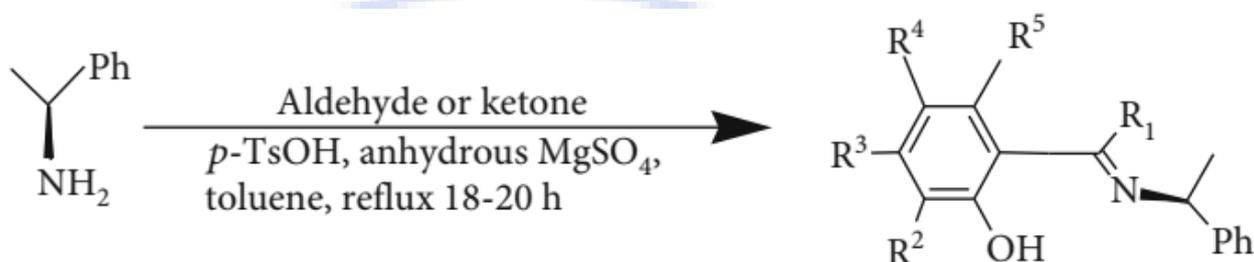


- Elimination of H<sub>2</sub>O forms the imine in three steps. Protonation of the OH group in Step [3] forms a good leaving group, leading to **loss of water** in Step [4], giving a resonance-stabilized **iminium ion**. Loss of a proton forms the imine in Step [5].
- Except for Steps [1] (nucleophilic addition) and [4] (H<sub>2</sub>O elimination), all other steps in the mechanism are acid–base reactions—that is, moving a proton from one atom to another.

## 2- Chiral Schiff base

Jaworska et al.'s Reaction, they synthesized nine bidentate Schiff bases

from pure enantiomerically (S)- $\alpha$ -methylbenzylamine as chiral ligands in the electronically controlled asymmetric addition of diethylzinc to aldehyde. They achieved an enantiomer excess (e.e) of 8 to 94% based on the substrate, and the finest was observed for (S, e)-2-(1-(1-phenylethylimino)-ethyl) phenol. Additionally, chiral Schiff bases with substituent were reported to have strong influence on a catalyst's effectiveness, enantioselectivities, and reactivities.



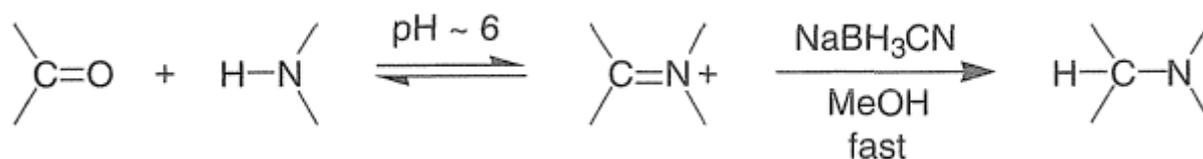
## Reaction of Schiff bases

### Reduction

The majority of reductions of carbonyl, imines and nitriles compounds with nucleophilic reducing agents, such as  $\text{M}[\text{AlH}_2]$  and  $\text{M}[\text{BH}_4]$ , proceed via nucleophilic transfer of a hydrogen atom with two electrons called a "hydride" from the reducing agent to the compounds.

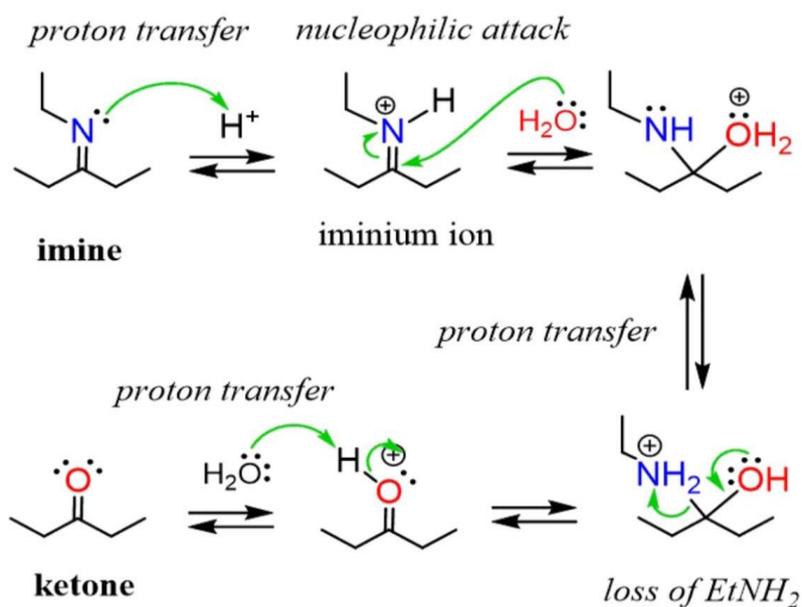
Lithium aluminum hydride (LAH) is a powerful reducing agent but is not very chemoselective. It must be used in nonprotic solvents such as THF. While, Sodium Cyanoborohydride ( $\text{NaBH}_3\text{CN}$ ) Because of the presence of the electron withdrawing cyano group,  $\text{NaBH}_3\text{CN}$  is less nucleophilic and hence is more selective than  $\text{NaBH}_4$ .

Since the reduction of an iminium salt by  $\text{NaBH}_3\text{CN}$  occurs more readily than the reduction of a carbonyl group,  $\text{NaBH}_3\text{CN}$  is the reagent of choice for the reductive amination of aldehydes and ketones. The reaction entails condensation of the carbonyl compound with  $\text{NH}_3$ ,  $\text{RNH}_2$ , or  $\text{R}_2\text{NH}$  at pH 5 to 8 to give the corresponding iminium salts.



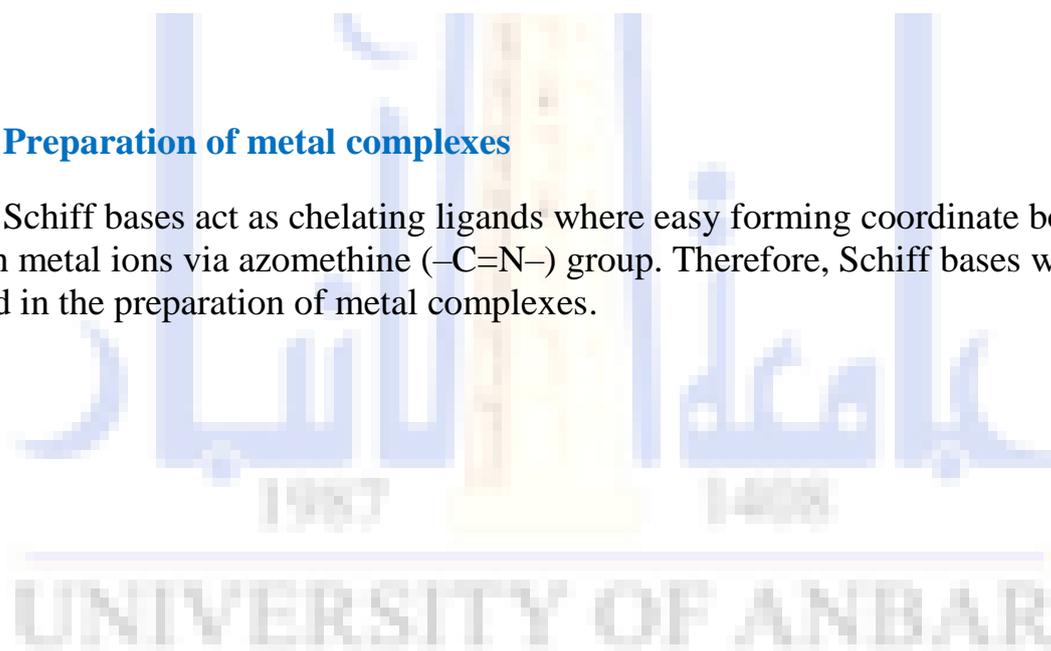
### Hydrolysis

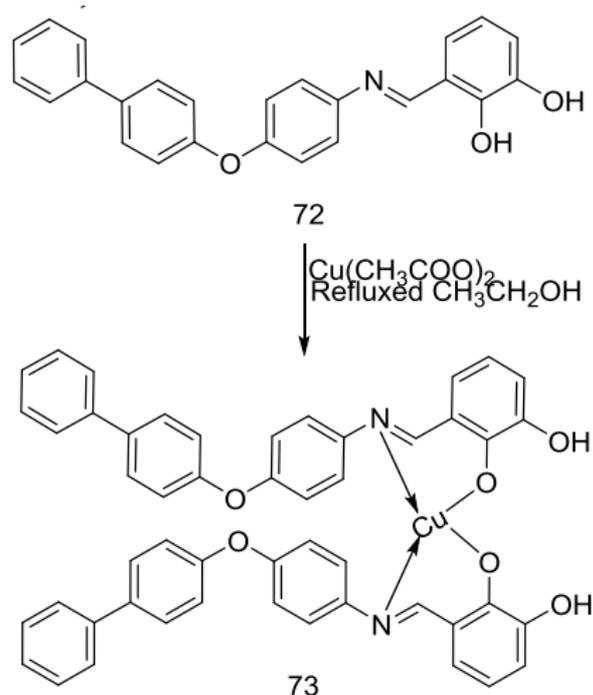
The reaction involves the same intermediates as the formation of imines and only the steps are reversed. It starts by protonation of the nitrogen converting the imine into iminium ion which is very electrophilic and is attacked by water in the next step.



### Preparation of metal complexes

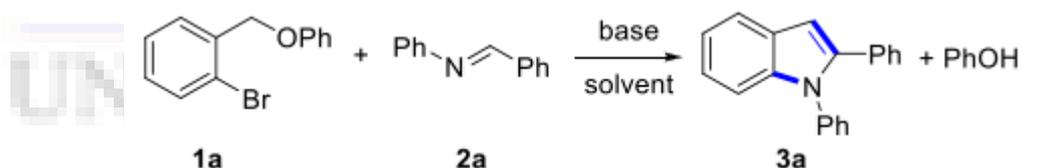
Schiff bases act as chelating ligands where easy forming coordinate bonds with metal ions via azomethine ( $-C=N-$ ) group. Therefore, Schiff bases were used in the preparation of metal complexes.





### Imine cyclization

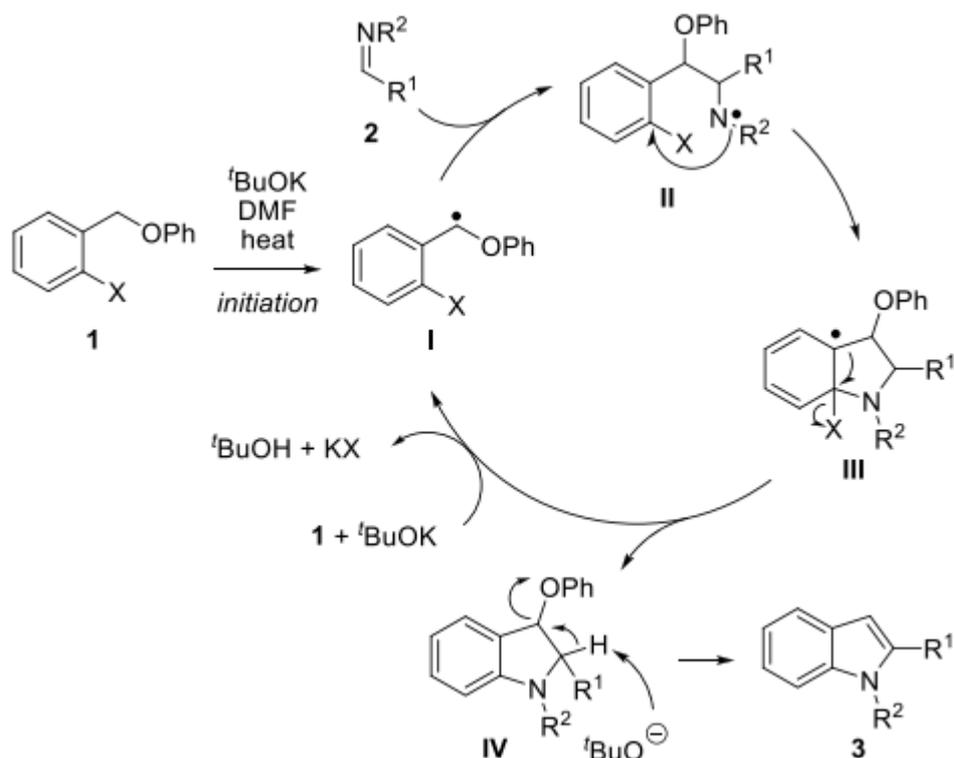
1- indole synthesis via the 3 + 2 cyclization: indole synthesis via the formal 3 + 2 cyclization of aryl halides and imines, this method involves the radical coupling of 2-halotoluenes with imines, in which only a base is used to promote the reaction. Reaction conditions were first explored. 1-Bromo-2- (phoxymethyl)-benzene **1a** and imine **2a** were subjected to various bases, the only reagents to promote this reaction. **1a** could be readily prepared from 2-bromotoluene, and the phenoxy group works as a recyclable leaving group. Decreasing the reaction temperatures from 90 to 50 °C increases the yields from 74 to 84% for some cases, while in another further decreasing the temperature to 30 °C results in the loss of yield. Other bases such as NaOt-Bu, LiOt-Bu, Cs<sub>2</sub>CO<sub>3</sub>, and NaH are not effective.



Aryl iodides or bromides are more reactive than chloride and fluoride analogues. In addition to **3a**, from dibromo substrates, all bromo-substituted indoles were obtained in 73–94% yields without loss of bromo groups under such basic conditions. These indoles are useful intermediates because they can be converted to bromo-substituted indoles with a cross-coupling

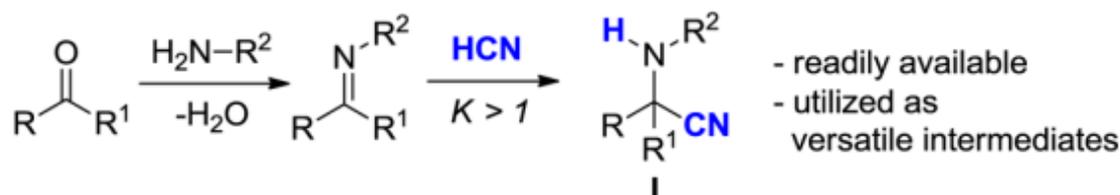
reaction.

Mechanism of reaction :

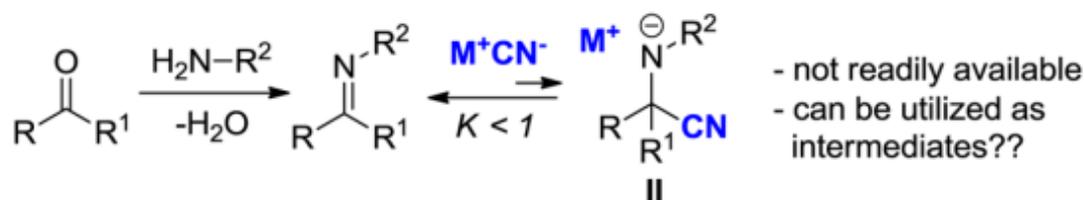


2- The addition of HCN to imines derived from carbonyls and amines leading to  $\alpha$ -aminonitriles has been subject of great interest because the resulting Strecker products I have been widely used as versatile intermediates. similar addition of cyanide anion ( $\text{CN}^-$ ) to imines has been known for a long time, synthetic protocols utilizing the resulting cyanide adducts II as synthetic intermediates have been far less developed than those with HCN adducts I.

(a) addition of HCN to imines

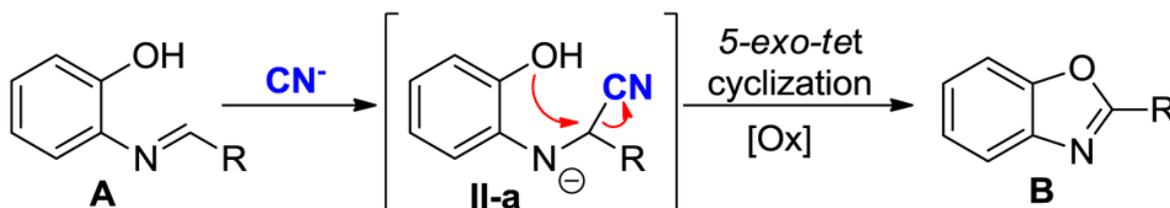


(b) addition of  $\text{CN}^-$  to imines

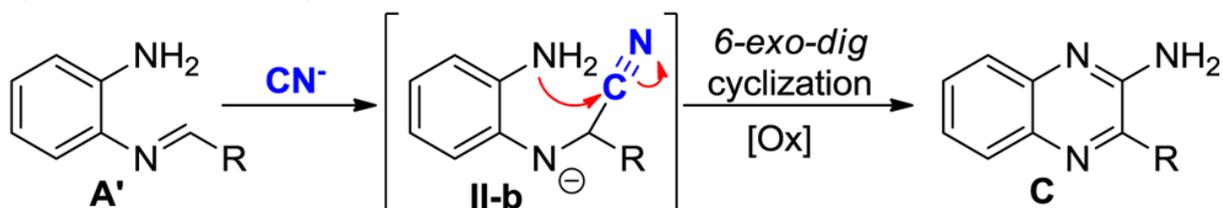


cyanide adduct II-a readily underwent cyclization through favored 5-exo-tet cyclization and subsequent aerobic oxidation of the cyclized product provided benzoxazole B. When we attempted to extend this method to the synthesis of benzimidazoles with ophenylenediamine, intermediate II-b underwent 6-exo-dig cyclization rather than the expected 5-exo-tet cyclization, leading to the formation of 2-aminoquinoxaline C after aerobic oxidation.

(a) previous work: synthesis of benzoxazoles



(b) previous work: synthesis of 2-aminoquinoxalines



(c) this work: conversion of imines to amides

