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# PALLADIUM CATALYZED SYNTHESIS OF FIVE-MEMBERED NITROGEN-CONTAINING HETEROCYCLES

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**Abstract**
Palladium is the most versatile metal in the transition series. Palladium can initiate a wide variety of organic reactions such as arylation, alkylation, hydrogenation, cyclization, oxidation, cross-coupling, isomerization, radical reactions, cascade, etc. Most of these reactions occur in mild conditions. It can be used in both laboratory and industrial scale. Despite many uses of palladium, new novel and efficient methods are still exploring. Now the focus is more towards sustainability of the process. This article focuses on the synthesis of five-membered nitrogen-containing heterocycles using palladium as a catalyst. Heterocycles plays an important role in pharmaceuticals, agrochemicals and as veterinary products. Some of the natural products e.g. antibiotics and alkaloids have heterocyclic moiety. In this study, we have included palladium catalyzed synthesis of pyrroles, pyrrolidines, imidazolidines, pyrazoles, triazoles and tetrazoles of last one decay.

**Keywords:** Pyrroles; Pyrrolidines; Imidazolidines; Pyrazoles; Triazoles

## Introduction

Heterocycles are the most attractive area for research due to its wide industrial and biological applications.[1] The five-membered nitrogen-containing heterocycles such as pyrroles.[2] pyrazoles,[3] pyrrolidines,[4] isoxazoles,[5] imidazole,[6] imidazolidines,[7] triazoles,[8] and tetrazoles[9], are the part of various natural and pharmaceutically active compounds. These *heterocyclic* ring systems offers a wide variety of biological activities varying from antioxidant,[10] antibacterial,[11] antimicrobial,[12] antihypertensive,[13] anticancer,[14] antifungal,[15] lipoxygenase inhibition,[16] anti-inflammatory[17], and antidiabetic[18].

Among a variety of new synthetic transformations of heterocyclic compounds, transition-metal-catalyzed reactions are one of the most intriguing and appealing methodologies for the synthesis of heterocyclic compounds,[19] as these reactions can be carried out under mild conditions from readily available starting materials. There are two main categories for the development of heterocyclic rings; C-Y bond formation and C-C bond formation (Fig. 1), where Y is a heteroatom.

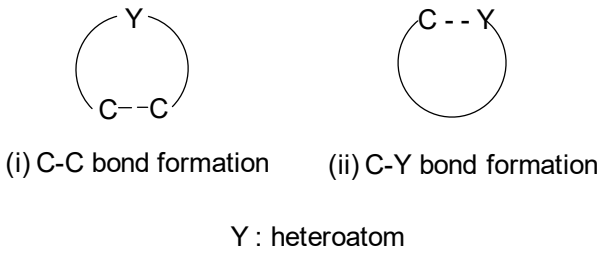
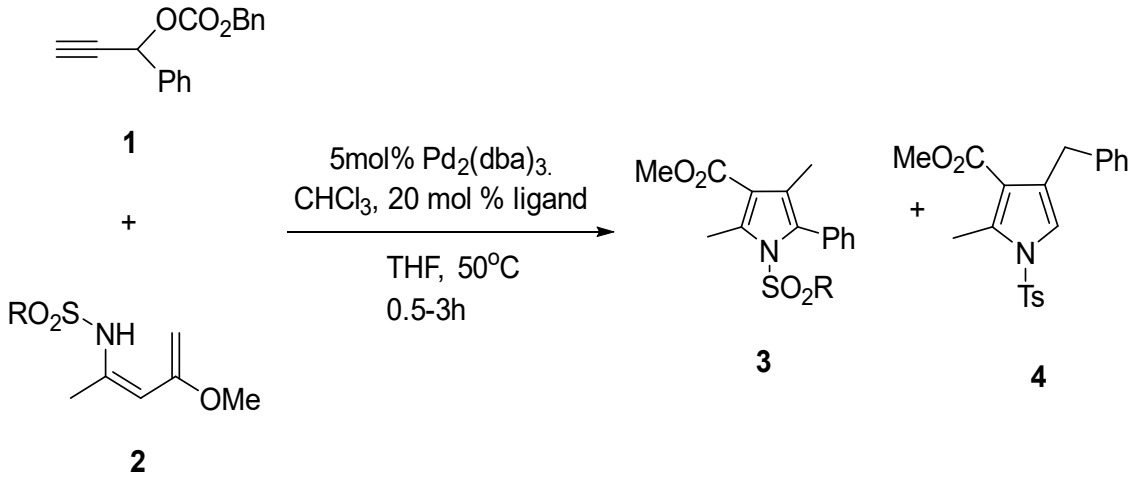



**Fig. 1:** The carbon-carbon and carbon-heteroatom bond formation

Palladium is the most attractive transition metal for the construction of C-N bond.[20] It catalyzed a variety of reaction including amination, hydroamination, N-arylation, C-H arylation, and the Buchwald-Hartwig reaction, etc.[21-22] This study is a survey of literature of last one decade, describing the methods on the palladium catalyzed reactions due to its interesting chemistry as palladium has wide range of functional group tolerance, so it avoids protecting group chemistry. Also, palladium catalyzed reactions are highly regioselective and stereoselective in nature.[23]

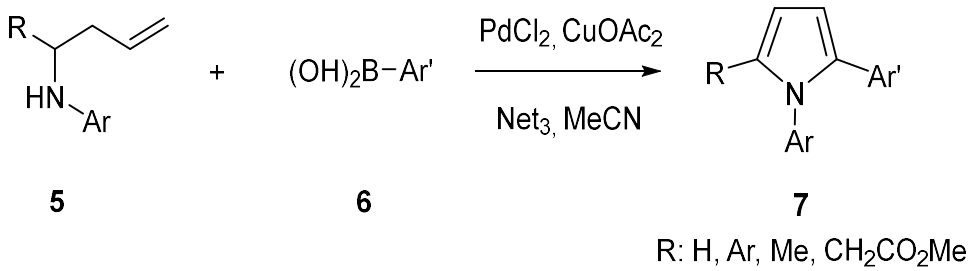
**Synthesis of Pyrroles**

Yoshida *et al*.[24] from the substrate having two nucleophilic moieties **1** and **2** reacted with the complex pi-propargyl palladium through nucleophilic cyclization, the preferred cyclic product **3** and **4** is obtained (Scheme 1).



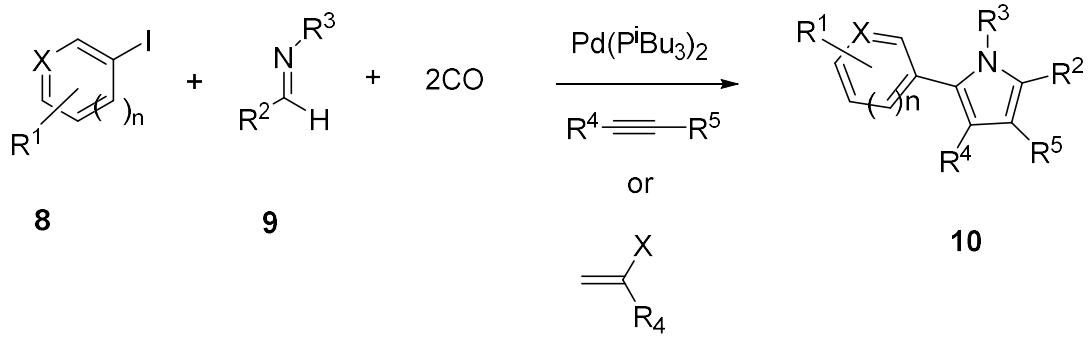

**Scheme 1:** The palladium nucleophilic cyclization of pyrroles

Zheng *et al*.[25] developed a method for the construction of substituted pyrroles 7 from *N*-homoallylic amines **5** and arylboronic acids **6**. This Pd (II)-catalyzed oxidative arylative cyclization of N-homoallylic amines proceeds *via* oxidative arylation of inactive alkenes, followed by intramolecular aza-Wacker cyclization (Scheme 2).



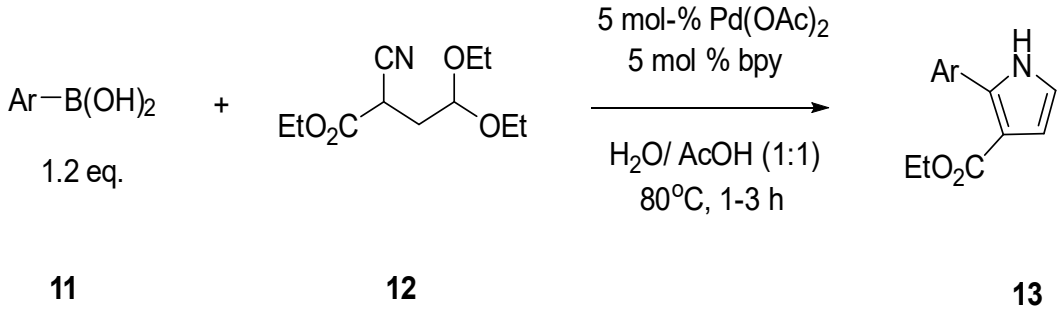

**Scheme 2:** Synthesis of substituted pyrroles 7 from *N*-homoallylic amines and arylboronic acids**.**

Torres *et al.*[26] described a method for the synthesis of polysubstituted pyrroles **10** *via* a multicomponent reaction using aryl iodides **8**, imines **9**, carbon monoxide, and alkynes. The acid chloride and N-acyl iminium salts is formed in *situ* through this Munchnones synthesis (Scheme 3).




**Scheme 3: S**ynthesis of polysubstituted pyrroles *via* a multicomponent reaction

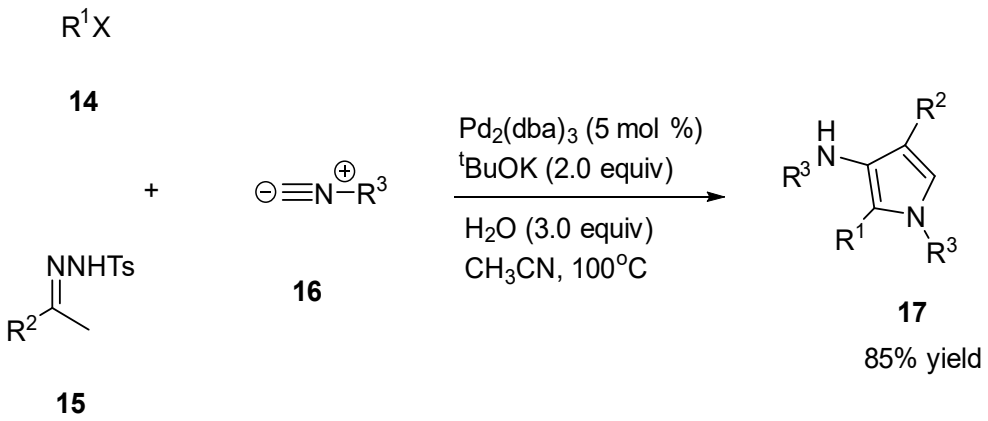
A wide variety of 3-substituted 2-aryl-1H-pyrroles **13** have been synthesized in aqueous acetic acid in presence of Pd (II) catalyst from **11** and **12**.[27] These pyrroles were synthesized by one-pot method in higher yield and have good functional group tolerance (Scheme 4).




**11** **12** **13**

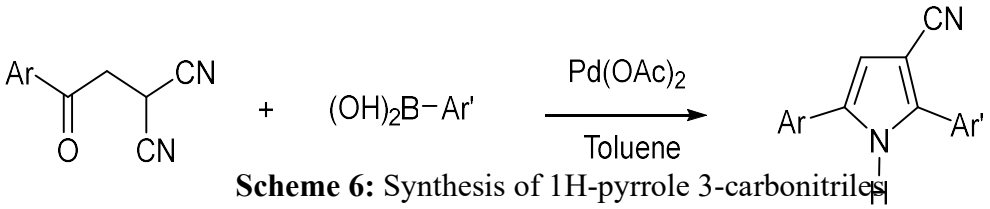
**Scheme 4:** The Pd (II) catalyzed synthesis of 3-substituted 2-aryl-1H-pyrroles

Peng *et al.*[28] synthesized 3-amino pyrroles **17** *via* palladium-catalyzed three-component coupling reaction of aryl halides **14**, N-tosylhydrazones **15**, and isocyanides **16,** in moderate to excellent yield (Scheme 5).




**Scheme 5:** Synthesis of 3-amino pyrroles

The substituted 1H-pyrrole 3-carbonitriles **20** were produced by the reaction of 2-(2-oxo-2-aryl ethyl) malononitriles **18** with boronic acids **19** and palladium(II)-catalyzed provide substituted 1H-pyrrole-3-carbonitriles via C(sp) – C(sp2) coupling followed by intramolecular C-N bond formation (Scheme 6).[29]

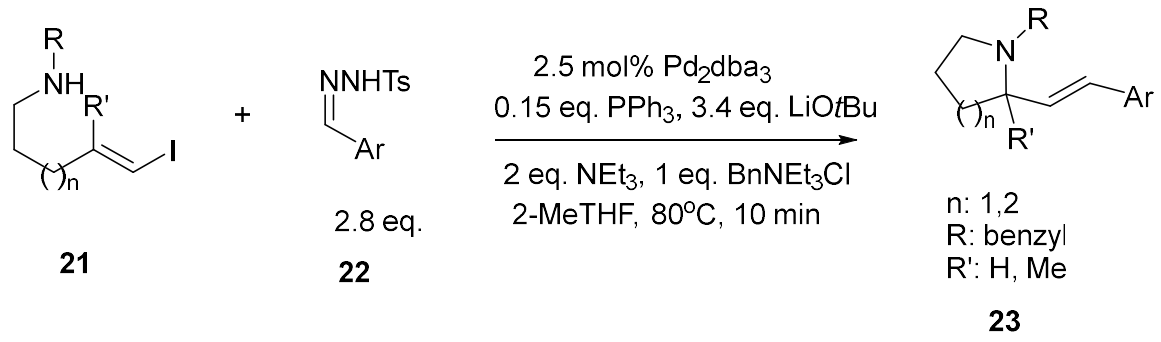



**18** **19** **20**

**Scheme 6:** Synthesis of 1H-pyrrole 3-carbonitriles

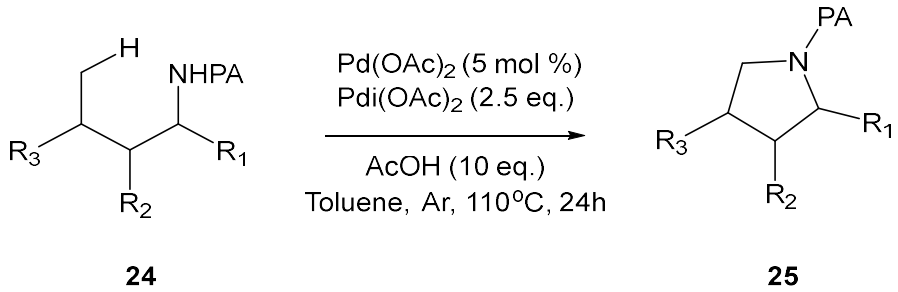
**Synthesis of Pyrrolidines**

A Pd-catalyzed reaction of vinyl iodides **21** and *N*-tosylhydrazones **22** generates pentadienyl amines **23** in good yield (Scheme 7).[30]



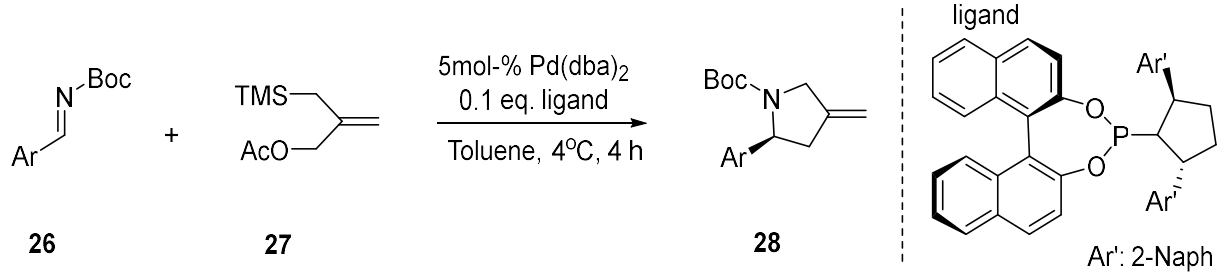

**Scheme 7:** Pd-catalyzed reaction of vinyl iodides and *N*-tosylhydrazones.

He *et al*.[31] developed methods for the synthesis of pyrrolidine derivatives **25** by palladium-catalyzed intramolecular amination of C−H bonds at the γ and δ positions of picolinamide (PA) protected amine substrates (Scheme 8).




**Scheme 8:** Synthesis of pyrrolidine derivatives

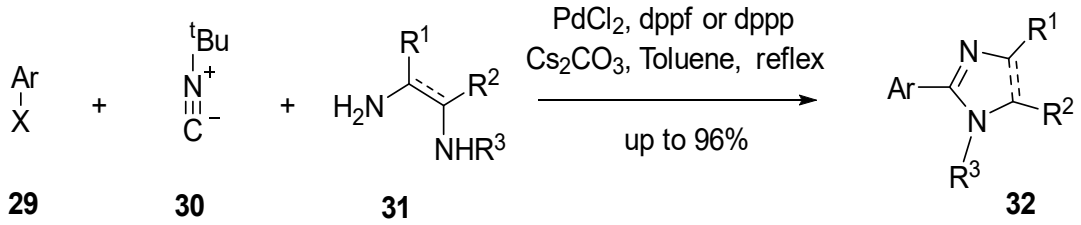
A protocol for the conversion of enantioselective [3 + 2] cycloaddition of 2-trimethylsilylmethyl allyl acetate and imines to Pyrrolidines **28** via Palladium-Catalysis was developed by Trost *et al*.[32] The reaction is given in Scheme 9.




**Scheme 9:** Synthesis of Pyrrolidine

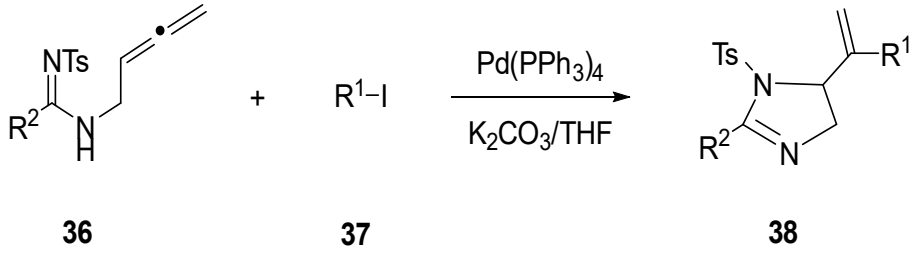
**Synthesis of Imidazolidines**

In 2013, Geden and co-workers[33] developed the synthesis of 2-aryl-2-imidazolines **32**, by three-component reaction, mediated by palladium catalyst. The reaction combines aryl halides **29**, isocyanides **30**, and diamines **31** (Scheme 10).




**Scheme 10:** Synthesis of 2-aryl-2-imidazolines

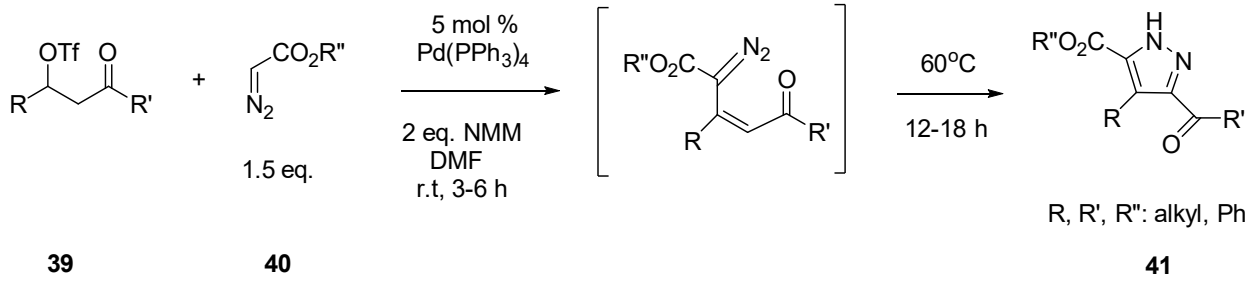
Liu *et al*.[34] developed the synthesis of polysubstituted imidazole **38** *via* a palladium catalyzed reaction. Cyclization of 2,3-allenyl amines **36** with aryl iodides **37** gives the desired product in good yield. The reaction was carried out in presence of $K_2CO_3$, THF at 85 °C (Scheme 11).




**Scheme 11:** Sytnhesis of polysubstituted imidazole

**Synthesis of Pyrazoles**

Babinski *et al*.[35] used electrocyclization reaction for the formation of 3,4,5-trisubstituted pyrazoles **41**. In this reaction, the cross coupling between enol triflates **39** and diazoacetates **40** is catalyzed by using palladium to get desired product (Scheme 5).




**Scheme 12:** Formation of 3,4,5-trisubstituted pyrazole derivatives

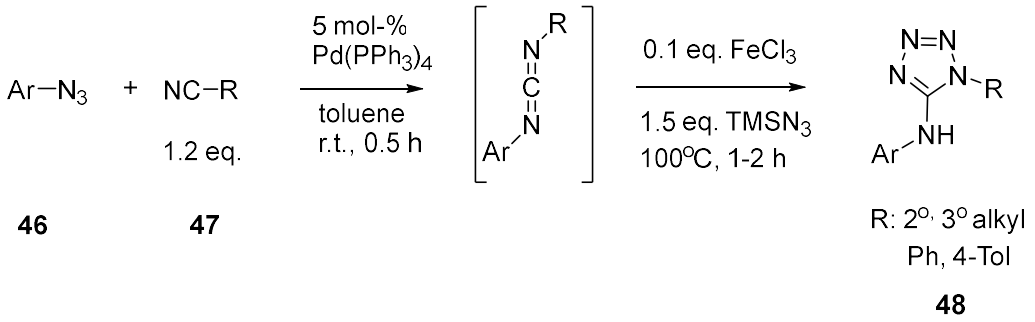
**Synthesis of Triazoles**

Wei *et al.*[36] reported a novel method for the synthesis of substituted triazoles using Cu/Pd trans metalation relay catalysis. The main advantage of this reaction is that triazoles can be formed in one step from three different components i.e. azide **43**, alkyne **42**, and aryl halide **44**. This reaction is incredibly useful for drug development process (Scheme 13).


**Scheme 13:** Synthesis of triazoles

**Synthesis of Tetrazoles**

Aminotetrazoles **48** synthesized by using aryl azides, **46** isocyanides, **47** and $TMSN_3$, through one pot synthesis.[37] The reaction was catalyzed by using Pd(0)/Fe(III). The unsymmetric carbodiimide was an intermediate obtained in this reaction. The product obtained in good yield (Scheme 14).




**Scheme 14:** Synthesis of tetrazoles

**Conclusion**

We discussed various synthetic strategies for the heterocyclic ring formation based on the palladium-catalyzed carbon-hydrogen functionalization/intramolecular carbon-heteroatom bond formation process. The study is focused on the palladium-catalyzed synthesis of five-membered nitrogen-containing heterocycles, including pyrroles, pyrrolidines, imidazolidines, pyrazoles, triazoles, and tetrazoles. The reactions included here have shown a high degree of stereoselectivity and regioselectivity. The efficient, novel and atom economical based methods were studied for the synthesis of palladium-catalyzed five-membered nitrogen-containing heterocycle formation.

The conclusion is that numerous effective reactions, including the cascade reaction, Huisgen rearrangement, enamination-alkenyl hydroamination, cross coupling, alkene carboamination, and

propargylic carbonate with bis-nucleophile reactions, have been established so far. It has been revealed that the synthesis of medium-sized heterocyclic compounds by transition-metal-catalyzed intramolecular C-C and C-Y (Y is heteroatom) bond formation represents an active area of research. Here, we solely took into account five-membered rings because these heterocycles are frequently present in natural products and have a wide variety of biological potential, making them a popular choice for medicinal chemist. Accordingly, it can be concluded that the aforementioned procedures offer an original, broadly applicable synthetic pathway to the above heterocyclic compounds with good functional-group tolerance and high yields.

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