

# The Sonogashira Coupling

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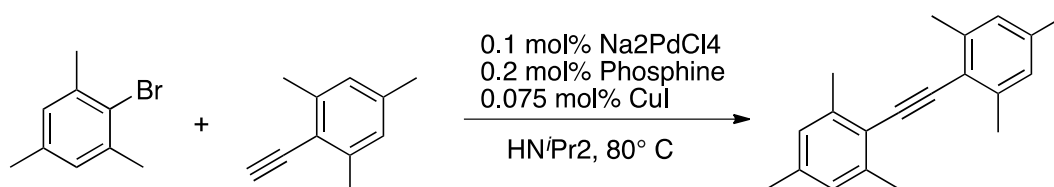
## Abstract:

The Sonogashira coupling reaction is one of the most widely used methods for the coupling of vinyl or aryl halides with terminal alkynes to form conjugated enynes or aryl alkynes. The reaction has become an essential tool in the synthesis of these compounds, which have applications in natural products chemistry, pharmaceuticals, and material science.<sup>2</sup>

## 1. Introduction:

Kenkichi Sonogashira discovered the Sonogashira Coupling reaction in 1975. The mechanism was first published in the Tetrahedron Letters with Sonogashira as the primary author and Yasuo Tohda and Nobue Hagihara as his co-authors. This discovery was made during Sonogashira's time as a professor at Osaka University in Japan.<sup>3</sup>

The traditional reactants in the Sonogashira coupling are vinyl or aryl halides and terminal alkynes. An example of a Sonogashira coupling reaction between an aryl bromide and a terminal alkyne is shown below:<sup>4</sup>

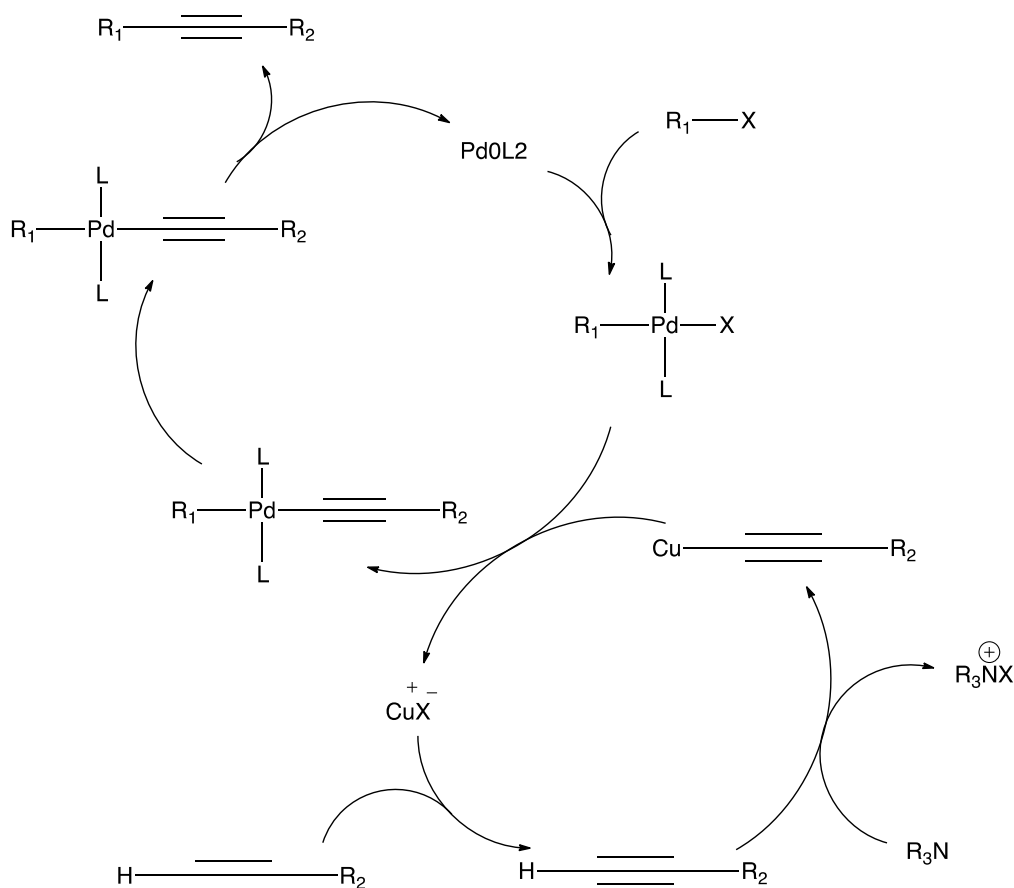


When an aryl or vinyl Halide is coupled with a terminal alkyne, thousands of different products can be produced, as shown in the extensive amounts of literature that details specific Sonogashira reactions. In the past, the reaction has been commonly performed in a system involving a Palladium catalyst, a Copper Iodide co-catalyst, and supplemental amines.<sup>5</sup> The reaction's system and conditions have been continuously modified since the reaction was discovered in 1975. Specifically, the past 10 years have brought a rush of researchers who are working to solve issues commonly associated with the Sonogashira reaction by modifying the reaction conditions.

## 2. Description and Discussion:

### 2.1 Mechanism

The complete mechanism for the Sonogashira reaction is not completely understood because of the difficulty of isolating and analyzing the organometallic compounds that are present only as intermediates in the reaction. However, the mechanism is predicted to proceed along the following path:<sup>1</sup>

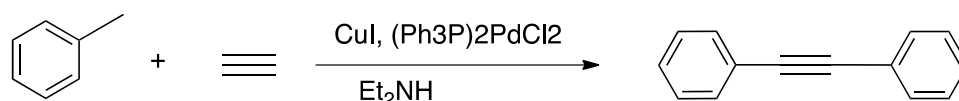


### 2.2 Reaction Conditions

The Sonogashira reaction was responded to very positively when it was first published because it presented solutions to several issues that researchers had been struggling with when trying to synthesize specific alkyne compounds. The reaction introduced the concept of utilizing copper Iodide as a co-catalyst. This new reagent, when paired with a Palladium catalyst, allowed conjugated enynes and aryl alkynes to be produced at room temperature. Older reactions and procedures required the reaction to be performed at temperatures as high as  $100^\circ\text{C}$ .<sup>3</sup> The

reaction soon became the most commonly used reaction in the synthesis of these specific alkynes.

The original reaction mechanism utilized Phenyl Iodide and Acetylene as the reactants. It involved reacting these two compounds in a system of Copper Iodide,  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ , and  $\text{Et}_2\text{NH}$  under an atmosphere of Nitrogen. The reaction was completed at room temperature and yielded the diphenylacetylene ( $\text{C}_{14}\text{H}_{10}$ ). The mechanism is shown below:<sup>3</sup>



After Sonogashira published his findings, the reaction was adopted as one of the most widely used procedures for synthesizing aryl alkynes and conjugated enynes. Many experimenters tested other reagents and reactants to form new compounds. Researchers have since studied the efficiency of procedures utilizing other reagents compared to the efficiency of Sonogashira's original design. The original Palladium catalyst,  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ , has been occasionally substituted with  $\text{NaPdCl}_4$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ ,  $\text{PdCl}_2$ , and  $\text{PdI}_2$  catalysts.<sup>2,4</sup> The catalyst can also be paired with Phosphines to increase the efficiency of the reaction. Phosphines, such as  $\text{PtBu}_3$ ,  $t\text{Bu}_3\text{PCy}$ ,  $t\text{Bu}_3\text{PCy}_2$ , and  $\text{PCy}_3$  have been used as additional reagents to improve the reaction design.<sup>4</sup>

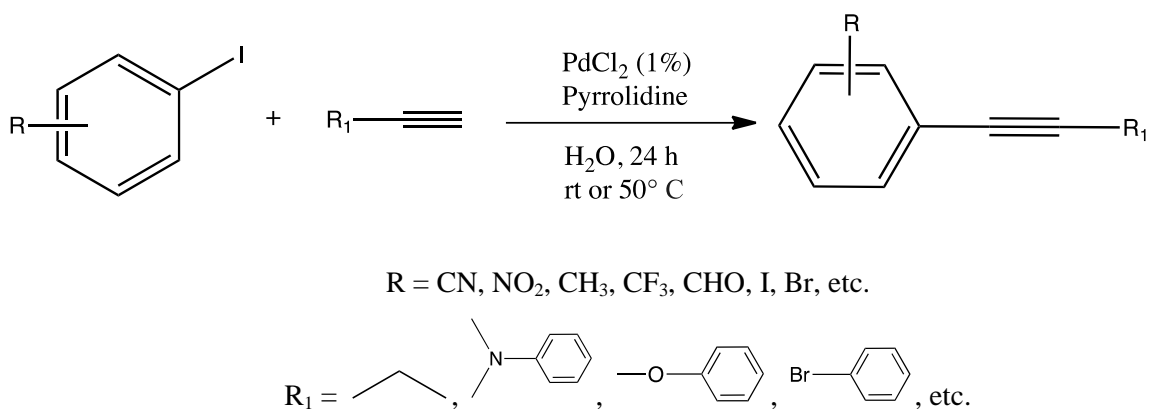
The copper co-catalyst has also been replaced with other reagents in modified versions of the reaction. This catalyst has been replaced with other zinc, tin, boron, aluminum, and  $\text{Ag}_2\text{O}$  catalysts in the past, however, this co-catalyst and the Nitrogen atmosphere in which the reaction is normally performed have been the topics of a major effort by the scientific community to revise the reaction conditions.<sup>2</sup> This effort has been spurred by an increasing awareness of issues with the current Sonogashira reaction's efficiency and convenience.

### ***2.3 Efforts to Modify Reaction Conditions***

Although the Sonogashira Reaction is a major foundation for the synthesis of alkynes, there are some drawbacks and issues with the reaction that are still prevalent today. For example, when the copper co-catalyst is exposed to air, the copper acetylide undergoes homocoupling with itself instead of undergoing the desired cross-coupling with the vinyl or aryl halide compound.<sup>6</sup>

This causes decreased efficiency due to unwanted side-products and wasted terminal alkynes, which are expensive to purchase and require a multi-step synthesis mechanism to form.

In the past few decades, mechanistic studies and various trials have been performed to achieve new designs for the Sonogashira reaction that do not involve the use of a copper co-catalyst. Researchers are working to develop new designs to allow the reaction to be performed in aerobic conditions, which cause homocoupling when used with the current reaction procedure. These new procedures are called Copper-free Sonogashira reactions and are being produced through the use of many different modifications to the original procedure. One example of a modification for these Copper-free reactions is the use of Pyrrolidine as a base with a Platinum catalyst ( $\text{PdCl}_2$  was used). This procedure was performed in water in an aerobic environment at  $50^\circ\text{C}$  and produced only trace amounts of the undesired homocoupling product; therefore, it did not react as drastically to the aerobic conditions. The reaction can be seen below:<sup>2</sup>



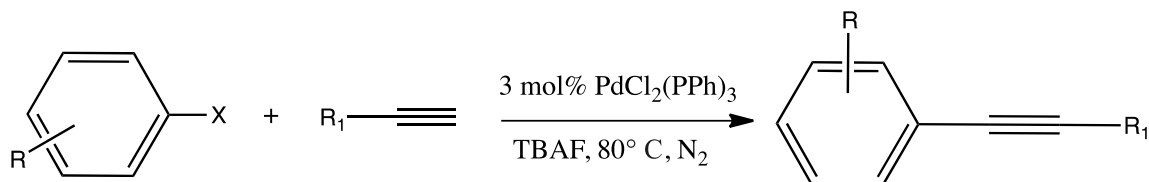
#### Copper-Free Sonogashira Coupling with Pyrrolidine

The presence of aerobic conditions is one of the two largest focus points of the scientific modification of the Sonogashira reaction. Scientists are studying how to use aerobic conditions during a modified procedure with the final goal being increased efficiency of the reaction. However, they are also studying changes that will directly reduce the production of the homocoupling product without performing the reaction in aerobic conditions.

Other researchers have studied the effects of changing the atmospheric conditions for the reaction to determine the efficiency of the reaction. For example, Hydrogen has been used to degass the reaction and then a mixture of Hydrogen and Nitrogen has been applied to the reactants to show an increase in the production of the cross-coupling product and a decrease in the production of the homocoupling product.<sup>6</sup>

Although atmospheric conditions are crucial to the current problems with the Copper co-catalyst in the Sonogashira reaction, the scientific community is more positively receiving studies with a focus on the modification of reagents instead of ones with manipulated atmospheric conditions. Another reported reagent change to create a Copper-free Sonogashira reaction involves the addition of tetra-*n*-butylammonium fluoride (TBAF) as a base.

The use of tetra-*n*-butylammonium fluoride (TBAF) has been shown to be successful in the formation of the cross-coupling product when added to the system with  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  under a Nitrogen Atmosphere. This reaction design is copper-free and does not use amines, which can be environmentally unfriendly if disposed of in large quantities. This modified reaction is shown below:<sup>5</sup>



$\text{X} = \text{Br, I, Cl}$

$\text{R} = \text{CH}_3\text{O}, \text{NO}_2, \text{CHOCH}_3, \text{CH}_3, \text{etc.}$

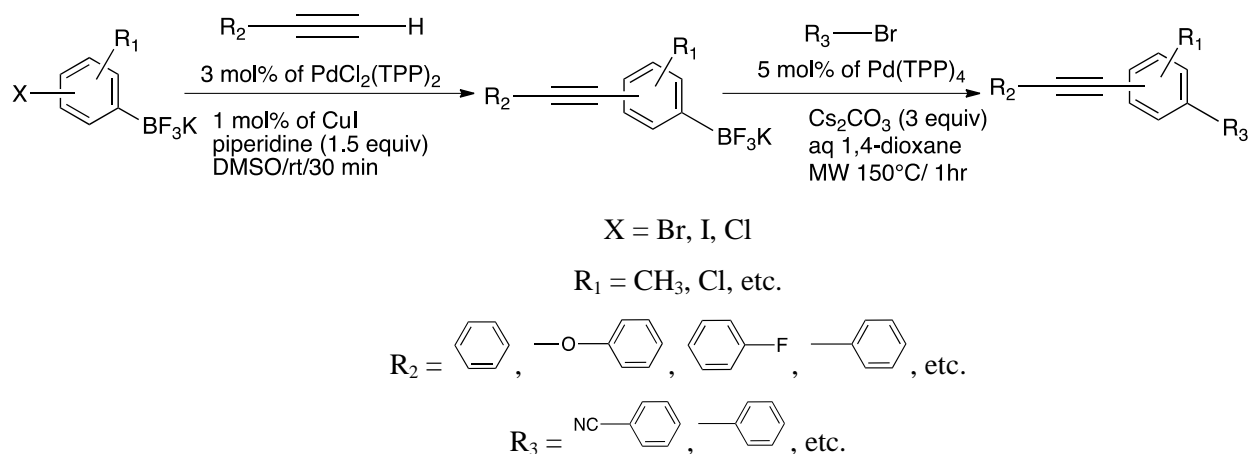
$\text{R}_1 = \text{C}_8\text{H}_{17}, \text{CH}_2\text{OH}, \text{C}_6\text{H}_5, \text{C}_6\text{H}_4\text{F}, \text{etc.}$

#### Copper-Free Sonogashira Coupling with tetra-*n*-butylammonium

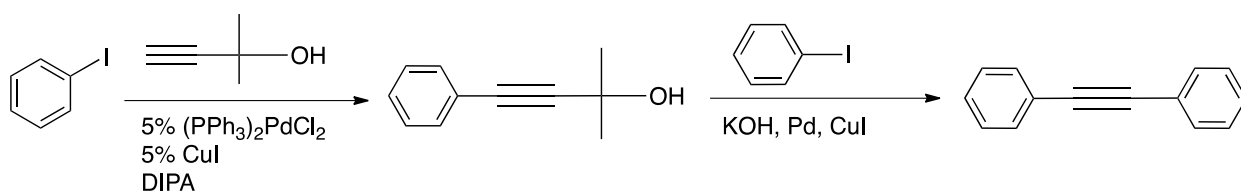
### 2.4 Applications

The Sonogashira reaction is used in the synthesis of various organic compounds and in the production of pharmaceuticals, agricultural chemicals, and natural products. For example, the reaction has been used to prepare Potassium Alkynylaryltrifluoroborates, which can then be used in Suzuki-Miyaura cross-coupling reactions.

The Sonogashira reaction which is used to form a Potassium Alkynylaryltrifluoroborate is shown preceding the Suzuki-Miyaura cross-coupling of the same Potassium Alkynylaryltrifluoroborate in the following reaction:<sup>8</sup>

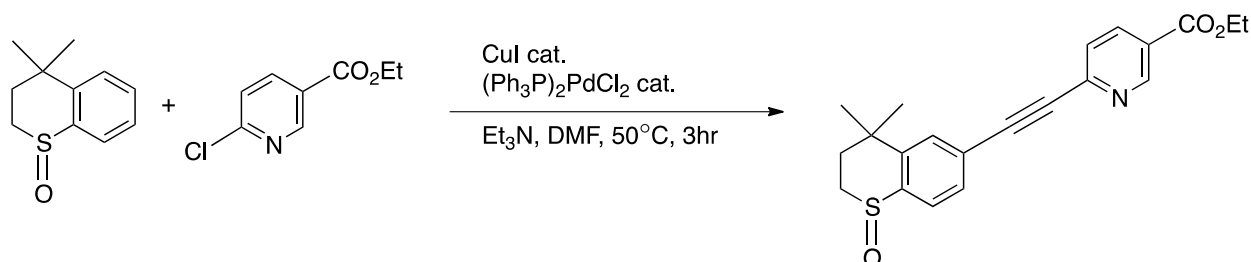


This reaction involves reacting a Haloaryltrifluoroborate with a terminal alkyne to form the Potassium Alkynylaryltrifluoroborates, which then can be used as a coupling partner in the Suzuki-Miyaura Coupling reaction. Along with this application of the Sonogashira reaction, the mechanism can also be used in the formation of Diarylalkynes, which are produced from terminal arylacetylenes. Tandem Sonogashira reactions have been used to first produce protected arylacetylenes, and then to produce Diarylalkynes from the protected arylacetylenes. The reaction is shown below:<sup>9</sup>

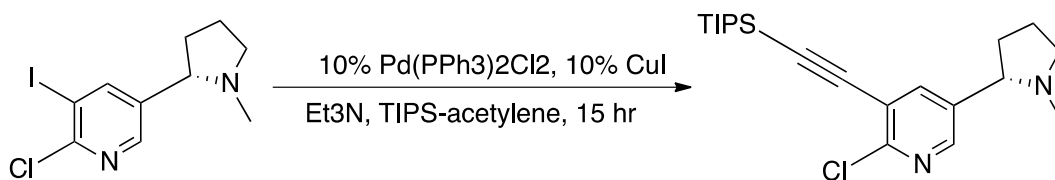


This reaction is applicable to organic synthesis of complex compounds, such as oligomers and polymers. These compounds have applications in electronics and optics.

Although, Sonogashira is useful in various fields of organic chemistry, it is also used in Biochemistry. Specifically, it is utilized in the formation of Tazarotene, which is used to treat acne and psoriasis. The reaction is shown below:<sup>10</sup>



Another common use for the Sonogashira reaction in Biochemistry is in the production of Altinicline or SIB-1508Y, which is used in treatments for Parkinson's disease. Altinicline is synthesized from nicotine molecules using multiple steps. One of these steps involves performing the Sonogashira coupling of a dihalonicotine and a triisopropylsilyl derivative to form a precursor for Altinicline. This reaction is shown below:<sup>11</sup>



### 3. Conclusion:

Since the discovery of the Sonogashira Coupling reaction in 1975, the procedure has been widely used and applied to many different scientific fields. It has proved to be one of the most popular methods for preparing conjugated enynes and aryl alkynes and is still being improved today. The reaction's impact can be seen in various fields, such as natural products chemistry, organic synthesis, pharmaceuticals, and optics technology. In the future, the Sonogashira reaction may be improved to be an even more applicable and efficient reaction.

## References:

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