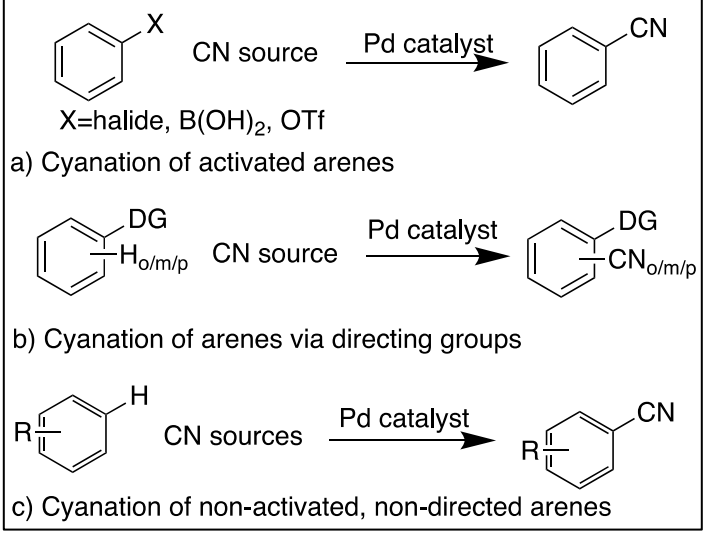
# RECENT ADVANCES IN PALLADIUM-CATALYZED CYANATION OF ARENES

Reported by Aliza N. Yazdani 27 April 2021

## INTRODUCTION

Nitriles—a common motif in natural products, pharmaceuticals, dyes, herbicides, and more — constitute an incredibly versatile functional group, capable of conversion to other functional groups such as aldehydes, amides, carboxyls, esters, amidines *etc*.[1-2] Introduction of a cyano group can be achieved on alkenes, alkynes, parrafins, heteroaryls, and arenes. For the cyanation of arenes, Palladium-based catalysts have shown the highest activity in three common categories: cyanation of activated arenes, directed C-H cyanation, and non-directed C-H cyanation. Palladium-based catalysts allow for the facile conversion of aryl halides to aryl nitriles (Scheme 1a). Additionally, for directed C-H cyanation, palladium catalysis allows for cyanation at the *ortho-, meta-*, and *para*-positions (Scheme 1b). Finally, palladium complexes can catalyze the non-directed C-H cyanation of arenes (Scheme 1c).

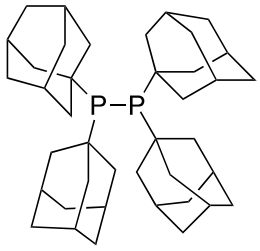
**Scheme 1.** The general arene cyanation reactions




## CYANATION OF ACTIVATED ARENES

The cyanation of activated arenes is the oldest method for producing aryl nitriles, dating back to in 1927, and the first palladium-catalyzed cyanation was reported in 1973 (Scheme 1a).[3-4] Recently, Beller and co-workers reported the first biphosphine ligand design for palladium-catalyzed functional group coupling.[5] Using tetraadamantylbiphosphine as the stable ligand with facile handling, the authors were able to demonstrate the cyanation of aryl chlorides and bromides (Scheme 2). In 2020, Baran reported a cyanation of aryl halides using palladium nanoparticles on a support of $Fe_3O_4$/chitosan/pumice hybrid beads as a catalyst.[6] This nanocatalyst provided high yields, good recyclability, and good stability.

**Scheme 2.** The structure of tetraadamantylbiphosphine (TABP)

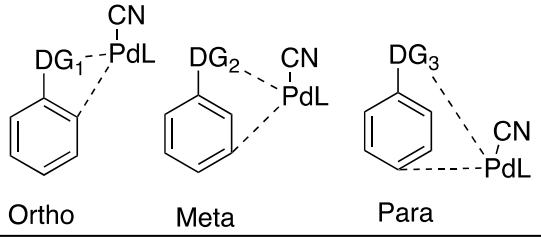



## CYANATION OF ARENES BY DIRECTING GROUP

C-H cyanation using directing groups has gained significant attention in recent years (Scheme 1b). By the use of a Lewis basic coordinating group, C-CN bonds be selectively introduced at the *ortho*-, *meta,* and *para*-positions (Scheme 3). In 2016, Shen and co-workers reported the *ortho*-cyanation of arenes using $Pd(OAc)_2$ as the catalyst, the eco-friendly α-iminonitrile as the cyanating agent, and pyridine as the

*ortho*-directing group.[7] Maiti and co-workers in 2017 developed a method for palladium-catalyzed remote *meta*-C-H cyanation using silyl-bridged directing groups and copper (I) cyanide as the cyanide source.[8] Finally, in 2020, the same authors developed an approach for palladium-catalyzed *para*-cyanation of arenes once again using silyl-bridged directing groups and copper (I) cyanide.[9] All studies showed excellent selectivity, good yields, and relatively mild conditions.

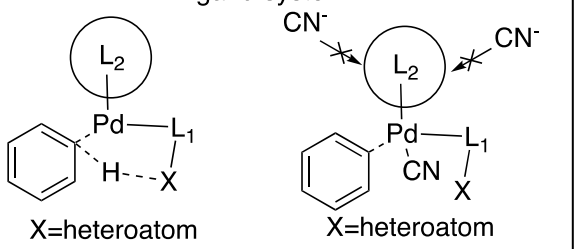
**Scheme 3.** The chelating scaffolds that afford cyanation at the *ortho*-, *meta*-, and *para*-positions




## CYANATION OF NON-DIRECTED ARENES BY LIGAND

C-H cyanation using directing groups requires either substrates with the directing group attached already or a directing group that can be easily introduced and removed.[10] A non-directed approach avoids these limitations and can activate sites that would otherwise be inactive (Scheme 1c). The two major challenges of the non-directed method are the reactivity of the catalyst and the high potential of free cyanide to strongly bind to the metal, poisoning the catalyst. One method that has shown promise in overcoming these challenges is the use of a dual ligand system (Scheme 4). One ligand promotes reactivity, often through hydrogen bonding with the reaction site (Scheme 4a). The other ligand blocks the metal center from free cyanide attack, typically by steric bulk and high electron-density (Scheme 4b). Recently, Ritter and co-workers developed an approach for non-directed C-H cyanation enabled by the combination of ligands *N*-acetyl-L-alanine and quinoxaline.[10] The authors show the application of this method through the late stage cyanation of a number of pharmaceutical products and other commercially available compounds.

**Scheme 4.** The roles of the ligands in a dual ligand system

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