

Zinc Cyanide – First Update

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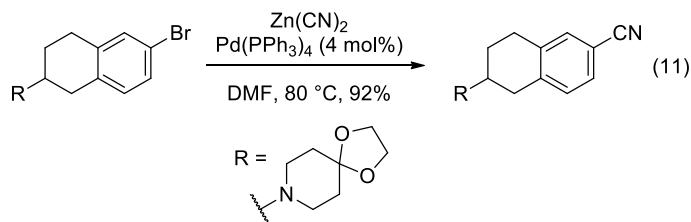
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Transition-Metal-Catalyzed Cyanation of Aryl Halides and Pseudohalides with Zinc Cyanide

Zinc cyanide has become one of the most attractive reagents for transition-metal-catalyzed cyanation of aryl halides and pseudohalides.

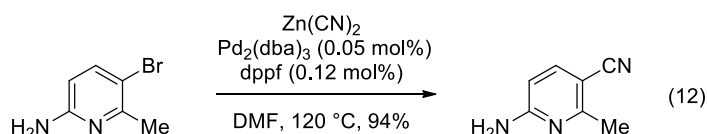
Zinc cyanide has low solubility in most organic solvents and water, which prevents poisoning of the metal catalyst by high concentration of cyanide ions, allowing for low catalyst loading and high turnover numbers. As an added advantage, zinc cyanide has low toxicity when compared with other metal cyanides. Thus, it is not surprising that at present zinc cyanide is one of the most widely used cyanating reagents in pharmaceutical development.²⁵⁻²⁷

Over the past two decades, many catalytic systems have been developed for efficient cyanation of aryl halides and pseudohalides using zinc cyanide. The first example of a palladium-catalyzed cyanation of aryl bromides and iodides was reported by Tschaen and co-workers in 1994 (eq 11).^{27,28} They found that among other commonly used metal cyanides, zinc cyanide gave the best results as a consequence of low concentration of free cyanide ions. Later, Gundersen developed a Pd-catalyzed cyanation of chloropurines under similar reaction condition.²⁹



Subsequently, Maligres and co-workers investigated the effect of phosphine ligands on Pd-catalyzed cyanation of aryl bromides with zinc cyanide (eq 12).³⁰ Dppf was found to be the best ligand among all phosphines tested. The developed catalytic system was highly robust and the reaction could be conducted on a 4 kg scale at low catalyst loading.

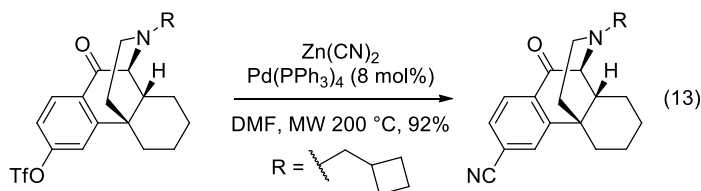
Maddaford and co-workers developed a Pd-catalyzed cyanation of aryl bromides and iodides with zinc cyanide at room temperature using bulky and electron-donating *t*-Bu₃P ligand.³¹



May and co-workers disclosed a practical Pd-catalyzed cyanation of aryl halides using Pd/C as catalyst, dppf as ligand and zinc cyanide as cyanide source.³² Activated aryl chlorides were converted into the corresponding nitriles in good yields.

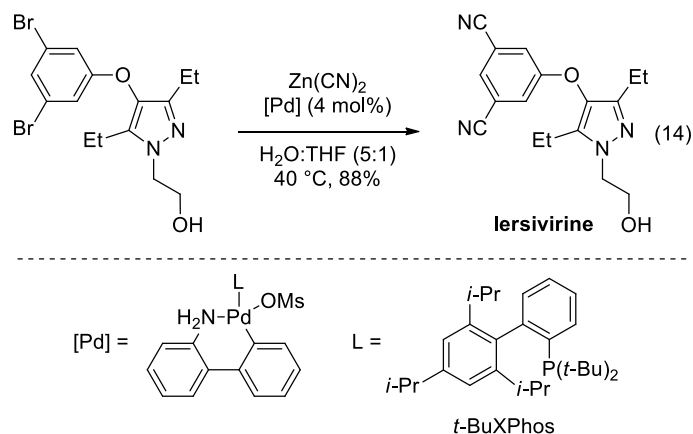
Hallberg reported the first microwave-assisted Pd-catalyzed cyanation of aryl and vinyl bromides with zinc cyanide.³³ Sequential [3+2] cycloaddition with sodium azide produced the corresponding tetrazole.

Neumeyer reported the microwave-assisted Pd-catalyzed cyanation of aryl triflates with zinc cyanide to efficiently provide key intermediates for the synthesis of selective opioid receptor ligands (eq 13).³⁴



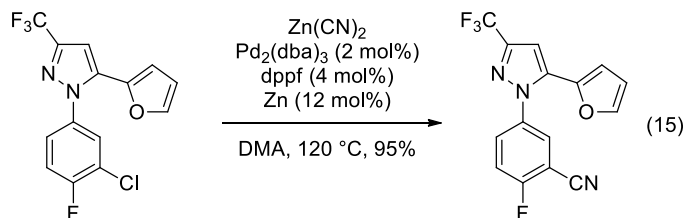
The Buchwald group reported a mild method for a Pd-catalyzed cyanation of aryl bromides and triflates using zinc cyanide in aqueous media (eq 14).³⁵ The protocol was suitable for the cross-coupling of a wide range of aryl and heteroaryl bromides at room temperature. The catalytic system uses a palladacycle precatalyst with a sterically-hindered, electron-rich phosphine ligand. Lersivirine, a reverse transcriptase inhibitor, was synthesized by this method.

Later, Wisniewski and co-workers at Bristol-Myers Squibb reported a similar process using an air-stable, commercially-available $\text{PdCl}_2(\text{Xantphos})$ precatalyst, triethylamine or diisopropylethylamine (DIPEA) as reducing agent and zinc cyanide as cyanide source.³⁶ The catalytic system showed good functional group tolerance. A wide range of electronically-diverse aryl bromides as well as an iodide and a triflate could be cross-coupled to give the corresponding nitriles in high yields.



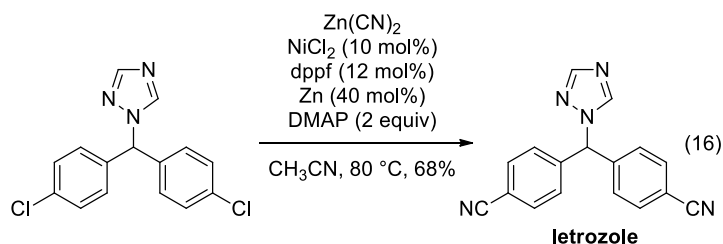
Jin reported the first Pd-catalyzed cyanation of aryl chlorides with zinc cyanide and catalytic amount of zinc (eq 15).³⁷ Both electron-deficient and deactivated, electron-rich aryl chlorides gave high yields of the cross-coupling products.

Littke and co-workers developed two catalytic systems for cyanation of aryl and heteroaryl chlorides using zinc cyanide.³⁸ A system based on $\text{Pd}(\text{TFA})_2$ and $(\text{binaphthyl})\text{P}(t\text{-Bu})_2$ works well for electron-rich and neutral aryl chlorides, while $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$ is well-suited for cross-coupling of heteroaryl and electron-deficient aryl chlorides.



The Liu group reported a Ni-catalyzed cyanation of aryl chlorides with zinc cyanide under mild conditions (eq 16).³⁹ Preliminary mechanistic studies suggest the key role of DMAP to facilitate transmetallation by activating zinc cyanide. The method was applied to the synthesis of letrozole, a nonsteroidal aromatase inhibitor.

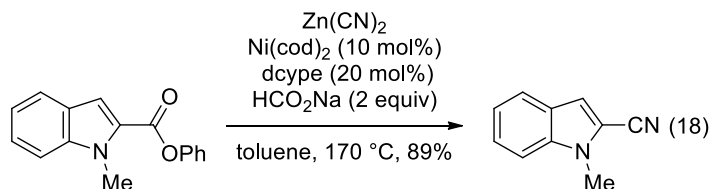
Independently, the Beller group reported a similar process using air-stable (*o*-tol)Ni(Xantphos) as precatalyst and zinc cyanide as cyanide source.⁴⁰ Room temperature cyanation of a wide range of heteroaryl chlorides can be achieved by this method.



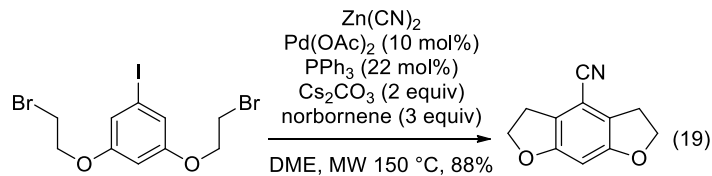
We have reported the first example of decarbonylative cyanation of amides (eq 17).⁴¹ We found zinc cyanide to be a key cyanide source in this process. The reaction shows good functional group tolerance. Electronically-diverse aryl, heteroaryl and vinyl nitriles are readily accessible under the reaction conditions. Furthermore, isotopically-labeled ¹³C nitriles can be synthesized by this method.



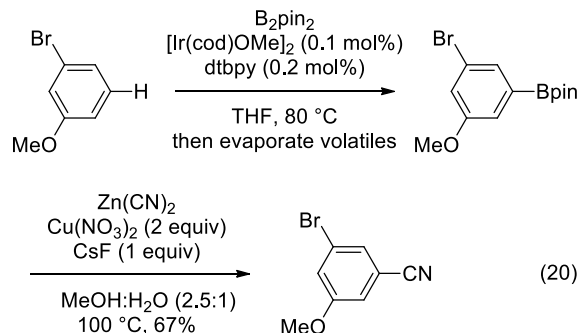
Independently, the Rueping group reported a similar method for decarbonylative cyanation of esters and amides using nickel catalysis and zinc cyanide as cyanide source (eq 18).⁴² Under their conditions, aroyl cyanides can also be converted to the corresponding aryl nitriles.



The Lautens group developed a Pd-catalyzed tandem C–H activation, alkylation, cyanation using zinc cyanide as a cyanating reagent (eq 19).⁴³ The protocol allows for a one-step synthesis of complex polycyclic benzonitriles in good yields.



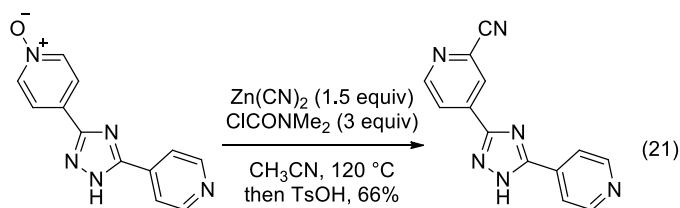
The Hartwig group reported a Cu-mediated cyanation of aryl boronic acids and boronate esters with zinc cyanide (eq 20).⁴⁴ The mild reaction conditions and very good functional group tolerance of this method are noteworthy. The precursor aryl boronic esters were easily synthesized by Ir-catalyzed meta-C–H borylation of 1,3-di-substituted arenes with high regioselectivity.



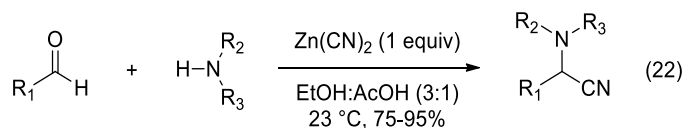
Zinc Cyanide as a Nucleophile or Lewis Acid

In addition to the transition-metal-catalyzed cross-coupling, zinc cyanide has been commonly used as a nucleophile and Lewis acid.

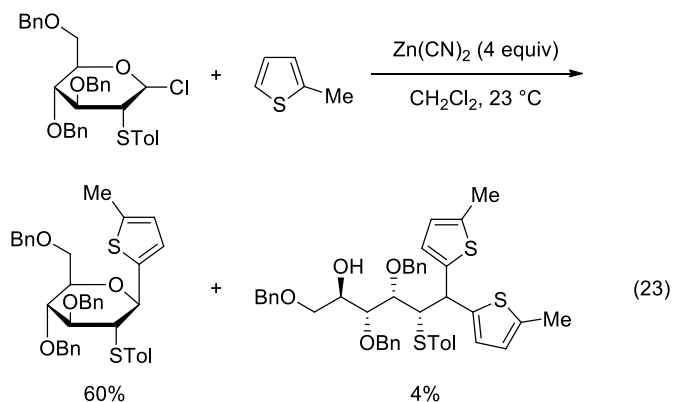
Yamamoto reported zinc cyanide as a cyanating reagent in the synthesis of 2-cyanopyridines from the corresponding pyridine N-oxides (eq 21).⁴⁵ The protocol was applied to the synthesis of FYX-051, a xanthine oxidoreductase inhibitor.



Shah reported a one-pot Strecker reaction using zinc cyanide as a cyanide source (eq 22).⁴⁶ Using this method, α -aminonitriles can be prepared by condensation of aldehydes, amines and zinc cyanide at room temperature in high yields.

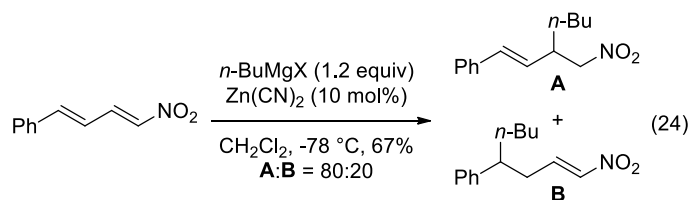


Smoliakova demonstrated that zinc cyanide can be used as a Lewis acid in Friedel-Crafts reactions of 2-thio-2-*S*-(aryl)pyranosyl chlorides to afford *C*- β -D-glucopyranosides with high selectivity (eq 23).⁴⁷ Importantly, under these conditions only trace amounts of the undesired open-chain side product were formed. In contrast, the more commonly used SnCl_4 gave predominantly open-chain products even at lower temperatures.

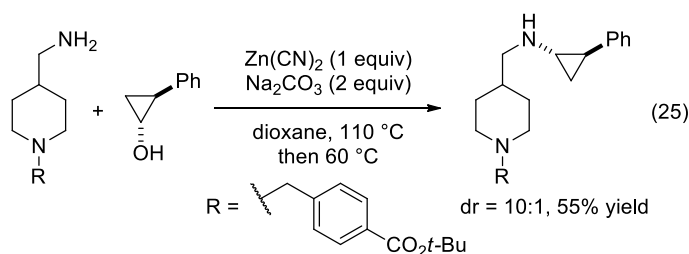


Dieter reported the synthesis of 1,2,3-trisubstituted cyclopropanes with high regio- and stereoselectivity by nucleophilic addition/cyclization of organozinc and Grignard reagents to γ,δ -epoxy- α,β -unsaturated Michael acceptors using catalytic zinc cyanide.⁴⁸

The same group also discovered that catalytic zinc cyanide promotes 1,4-conjugate additions of Grignard reagents to nitrodienes with high regioselectivity (eq 24).⁴⁹



The Rousseaux group reported a stereocontrolled synthesis of cyclopropylamines from cyclopropanols via zinc homoenolates (eq 25).⁵⁰ Zinc cyanide was identified as the optimal zinc salt. The utility of this protocol was showcased in the synthesis of a lysine demethylase 1 inhibitor, GSK2879552.



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