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A facile microwave-assisted palladium-catalyzed cyanation of aryl chlorides

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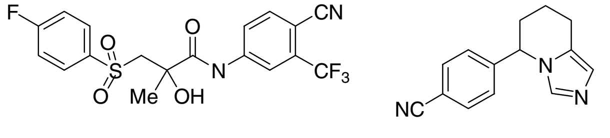
Abstract—We report an efficient method for the preparation of aryl nitriles from aryl chlorides under either microwave assisted or thermal conditions. A catalyst system comprising tris(dibenzylidene acetone)dipalladium ($Pd_2(dba)_3$) and 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine (S-Phos) is shown to effectively promote cyanation of various aryl chlorides with $Zn(CN)_2$ as the cyanide source.

Aryl nitriles are of great interest in the pharmaceutical arena both as par structures of new chemical entities and as synthetic intermediates. Two examples of marketed drugs that contain the benzonitrile functionality are Casodex, an antiandrogen and Arensin, a non-steroidal aromatase inhibitor (Fig. 1).[2]

The utility of aryl nitriles as synthetic intermediates is exemplified by many transformations including conversion to carboxylic acids, amides, amines, aldehydes, ketones, amide oximes, and tetrazoles.[3] As such, numerous reports have appeared divulging conditions for cyanation of aryl bromides and iodides[3–5] but only a few accounts to date have extended to aryl chlorides.[6,7] Maligres and co-workers reported that the combination of $Pd_2(dba)_3$ and 1,1′-bis(diphenylphosphino)ferrocene (DPPF) in wet DMF with $Zn(CN)_2$ as the cyanide source is a reliable procedure for the cyanation of various aryl bromides.[4] Following this report, Jin and Confalone described conditions for a palladium-catalyzed cyanation reaction of aryl chlorides that utilized $Pd_2(dba)_3$ and DPPF along with a catalytic amount of Zn with $Zn(CN)_2$ as the cyanide source.[6] Subsequently, Sundermeier and co-workers reported another catalyst system combining 1,5-bis(diphenylphosphino)pentane (DPPPE), $Pd(OAc)_2$, and TMEDA.[7] Both of these cyanation methods of aryl chlorides take 4–16 h to complete, depending on the substrate. In the latter case, the reaction is performed under thermal conditions in a sealed tube, rendering these reactions more difficult to scale.



Casodex (Zeneca)　Arensin (Ciba-Geigy)

Figure 1. Aryl nitriles of interest in clinical use.

Recently, we became interested in applying microwave-assisted conditions to convert aryl chlorides to aryl cyanides in our drug discovery program. Microwave irradiation is known to greatly accelerate reactions that are sluggish under thermal conditions.[8] Unfortunately, the two methods described above for the conversion of **1** to **2** were found to be ineffective in our hands when modified for microwave-assisted conditions (Table 1, entries 1 and 2). Although the factors underlying these failed attempts were unclear, a recent publication by Buchwald and co-workers prompted us to consider alternative phosphine ligands. In their work, S-Phos ligand was noted to possess 'unprecedented activity' in the coupling of aryl chlorides with various boronic acids and esters.[9] In addition, these coupling reactions can be performed with ppm levels of palladium. Indeed, when the DPPF ligand in entry 3 (Table 1) was replaced with the S-Phos ligand, cyanation of **1** with $Zn(CN)_2$ in the presence of 4 mol % $Pd_2(dba)_3$, 10 mol % S-Phos in

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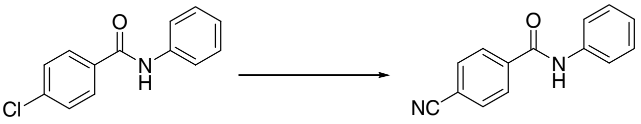
Table 1. Cyanation of 4-chlorobenzanilide



1 **2**

Entry	Ligand (mol%)	Palladium source	Solvent	Cyanide source	*T* (°C)[a]	*t* (min)	Yield (%)[b]
1	dppf	$Pd_2(dba)_3$	DMA	$Zn(CN)_2$/cat Zn	150	30	0
2	dpppe	$Pd(OAc)_2$	Toluene	KCN	150	30	0
3	dppf	$Pd_2(dba)_3$	wet DMF	$Zn(CN)_2$	150	30	0
4	NA	$Pd(PPh_3)_4$	DMF	$Zn(CN)_2$	150	30	0[8]
5	S-Phos	$Pd_2(dba)_3$	wet DMF	$Zn(CN)_2$	150	30	97

[a] All microwave reactions were performed on a Biotage Initiator.

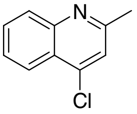
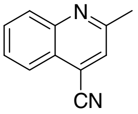
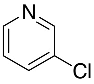
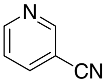
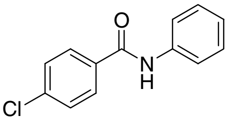
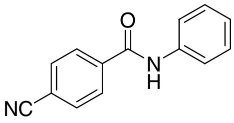
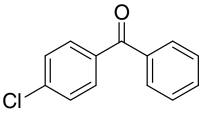
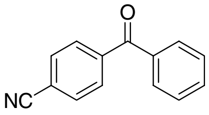
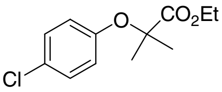
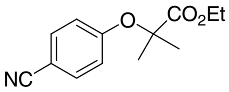
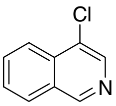
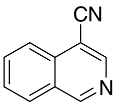
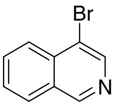
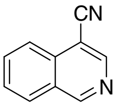
[b] Reactions were performed on 1 mmol scale.

wet DMF led to nearly quantitative conversion to nitrile **2** under microwave-assisted conditions (entry 5).

Delighted with these results, we decided to examine the scope of these new cyanation conditions by examining a wide array of electronically and structurally diverse substrates. As can be seen in Table 2, a substrate with an electron-donating group exhibited somewhat diminished yield of the product (entry 5), while those with electron withdrawing groups afforded excellent yield of products,

Table 2. Palladium(0)-S-Phos microwave-assisted cyanation of aryl chlorides

$$\text{Ar-X} \xrightarrow[\text{99:1 DMF:H}_2\text{O} \\ \text{microwave or thermal}]{\text{Zn(CN)}_2\text{, cat Pd}_2\text{(dba)}_3\text{, cat S-Phos}} \text{Ar-CN}$$

Entry	Ar-Cl	Product[a]	Yield (%)[b]	Yield (%)[c]
1			92	94
2			76	64
3			97	65
4			90	70
5			48	48
6			81	94
7[c]			81	94

[a] All products gave satisfactory NMR and MS data.

[b] Isolated microwave yield after column chromatography on silica.

[c] Isolated thermal yield after column chromatography on silica.

suggesting that the oxidative insertion step may be rate-limiting for less reactive chlorides. The cyanation of 3-chloropyridine (entry 2) also worked well under these conditions (76% isolated yield in 30 min), while a previously described attempt using KCN, $Pd(OAc)_2$, DPPPE and TMEDA[7] led to 48% isolated yield of 3-cyanopyridine after 16 h of heating. This new catalyst system is also amenable to thermal conditions, and comparable yields of products were obtained after 1 h of heating at 120 °C, underlying 'unprecedented activity' of this catalyst system previously reported by Buchwald.[9] Not surprisingly, these conditions can also be applied to the conversion of aryl bromides to aryl cyanides (entry 7, 81% yield under microwave-assisted conditions and 94% under thermal conditions).

In summary, we have shown that palladium-catalyzed cyanation of aryl chlorides can be performed readily by use of the commercially available S-Phos ligand under either microwave-assisted or thermal conditions.[10–12] The reaction is general for a variety of substrates and can also be applied to aryl bromides.

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10. General experimental conditions:
    Microwave: **1** (500 mg, 2.2 mmol), (79 mg, 009 mmol), S-Phos (89 mg, 0.2 mmol), $Zn(CN)_2$ (300 mg, 2.5 mmol) were dissolved in 10 mL 99:1 v/v DMF/H_2O in a 20 mL microwave vial. The solution was degassed with N_2 for 10 min before being capped and heated in the microwave reactor for 30 min at 150 °C. Once complete, the reaction was diluted with 1 N NaOH (40 mL) and EtOAc (100 mL). The EtOAc layer was removed, dried over $MgSO_4$, filtered, and concentrated giving rise to an oil. The oil was purified via silica gel chromatography (5–40% EtOAc/hexanes) and concentrated under reduced pressure to yield 462 mg (97%) of **2** as a white solid.
    Thermal: **1** (500 mg, 2.2 mmol), $Pd_2(dba)_3$ (79 mg, 009 mmol), S-Phos (89 mg, 0.2 mmol), $Zn(CN)_2$ (300 mg, 2.5 mmol) were dissolved in 20 mL 99:1 v/v DMF/H_2O. The solution was degassed with N_2 for 10 min before being heated to 120 °C for 1 h. Once complete, the reaction was purified as described above.
11. S-Phos ligand was purchased from Strem Chemicals Inc., 7 Mulliken Way, Dexter Industrial Park, Newburyport, MA 01950.
12. The catalyst loading for the microwave was lowered to 1 mol % $Pd_2(dba)_3$ and 2 mol % S-Phos for the conversion of **1** to **2** without any significant change in yield or reaction time.