



## Sulfate additives generate robust and highly active palladium catalysts for the cyanation of aryl chlorides

Michael Shevlin\*

Department of Process Research, Merck and Co., Inc., PO Box 2000, Rahway, NJ 07065, United States

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### ABSTRACT

The use of sulfate additives such as  $\text{H}_2\text{SO}_4$  greatly increases the reactivity of palladium catalysts for the cyanation of aryl and heteroaryl chlorides and renders them more robust toward adventitious air. Using this method, a wide variety of aromatic and heteroaromatic nitriles were prepared in high yield.

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The cyanation of aryl halides is a powerful method for preparing complex substituted benzonitriles.<sup>1</sup> Although this chemistry is well-established with aryl iodides, bromides, and triflates, aryl chlorides offer potential advantages due to their wider availability and lower cost.<sup>2</sup>

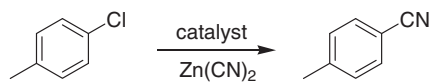
However, the cyanation of aryl chlorides is a particularly difficult transformation, as oxidative insertion into aryl–Cl bonds is slower than insertion into iodides, bromides, or triflates.<sup>3</sup> The coupling partner cyanide is a potent catalyst poison,<sup>4</sup> and it has been suggested that the catalyst is particularly vulnerable to cyanide poisoning at the beginning of the reaction as it enters the catalytic cycle.<sup>5</sup> To mitigate catalyst poisoning, many published procedures employ poorly soluble cyanide sources like  $\text{Zn}(\text{CN})_2$  and  $\text{K}_4[\text{Fe}(\text{CN})_6]$ .<sup>6</sup> As the reaction progresses, however, the halide liberated from the substrate solubilizes cyanide as the mixed salt  $\text{Zn}(\text{CN})\text{X}$ .<sup>7</sup> Thus, there arises a delicate balance between having a coordinatively unsaturated catalyst, as is required for facile Ar–Cl insertion but which may be vulnerable to cyanide poisoning, and having a long-lived catalyst which may be slow to insert into the Ar–Cl bond.<sup>8</sup>

Several recent reports describe the cyanation of aryl chlorides;<sup>9</sup> however, they tend to require high reaction temperatures, high catalyst loadings, or have a limited substrate scope. In this Letter, we report a new and highly active catalyst system for the cyanation of aryl and heteroaryl chlorides which is capable of delivering

high yields at low catalyst loadings and relatively mild temperatures.

We began our investigation by examining the palladium-catalyzed cyanation of model substrate 4-chlorotoluene with zinc cyanide (Table 1). We first examined the  $\text{Pd}(\text{OAc})_2$  complexes of a number of ligands known to oxidatively insert into aryl chlorides (Table 1, entries 1–6). Unfortunately, we observed virtually no

**Table 1**  
Initial catalyst screening<sup>a</sup>



Entry	Pd source	Ligand	Yield <sup>b</sup>
1	$\text{Pd}(\text{OAc})_2$	1	3
2	$\text{Pd}(\text{OAc})_2$	2	0
3	$\text{Pd}(\text{OAc})_2$	3 <sup>c</sup>	7
4	$\text{Pd}(\text{OAc})_2$	4	0
5	$\text{Pd}(\text{OAc})_2$	5	2
6	$\text{Pd}(\text{OAc})_2$	6	78
7	$[(\text{allyl})\text{PdCl}]_2$	1	44
8	$[(\text{allyl})\text{PdCl}]_2$	2	29
9	$[(\text{allyl})\text{PdCl}]_2$	3 <sup>c</sup>	15
10	$[(\text{allyl})\text{PdCl}]_2$	4	50
11	$[(\text{allyl})\text{PdCl}]_2$	5	65
12	$[(\text{allyl})\text{PdCl}]_2$	6	82

<sup>a</sup> Reaction conditions: 5% Pd, 10% ligand, 10% Zn, 0.6 equiv  $\text{Zn}(\text{CN})_2$ , DMA (0.2 M substrate), 120 °C, 18 h.

<sup>b</sup> Yield determined by HPLC assay versus authentic product standard.

<sup>c</sup> 5% ligand used.

\* Tel.: +1 732 594 0538.

E-mail address: [michael\\_shevlin@merck.com](mailto:michael_shevlin@merck.com)

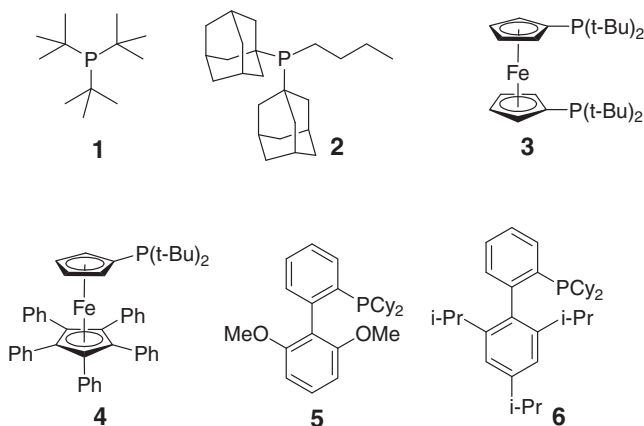


Figure 1. Ligands screened.

product formation with trialkylphosphines **1** and **2**, bidentate ferrocenylphosphine **3**, monodentate ferrocenylphosphine **4**,<sup>10</sup> or dialkylbiaryl phosphine **5** (Fig. 1).<sup>11</sup> Gratifyingly, dialkylbiaryl phosphine **6**<sup>12</sup> (XPhos) gave the desired product in 78% yield. We also examined the more reactive palladium precursor [(allyl)PdCl]<sub>2</sub> (Table 1, entries 7–12) and observed uniformly higher yields. When this precursor was combined with ligand **6**, the product could be obtained in 82% yield.

Interestingly, Pd/XPhos catalysts have been previously reported to give poor results in aryl chloride cyanations<sup>9c</sup>. We believe that this apparent discrepancy can be attributed to a critical difference in experimental setup. As shown in Eq. (1), pre-mixing the ligand and metal precursor in the reaction solvent prior to introduction into the reaction mixture containing cyanide gave the desired product in 78% yield, while adding ligand, metal precursor, and other reagents to the reaction at the same time gave only 48% yield. We postulate that this loss of activity arises from competition between the poorly soluble ligand XPhos and cyanide for binding to the palladium precursor. Thus, pre-mixing the ligand and metal precursor leads to increased amounts of the desired phosphine–palladium complex relative to catalytically inactive palladium–cyanide complexes.<sup>4</sup>

Encouraged by these initial results, we attempted to scale up the reaction with a few electronically diverse aryl chlorides (Eq. (2)). Excellent yields were obtained with 4-chlorotoluene, 2-chloroanisole, and 1-chloro-3-nitrobenzene. Unfortunately, these reactions only proceeded to high conversion when run in a glovebox, and consistently stalled at low conversion using standard vacuum line techniques. While the [(allyl)PdCl]<sub>2</sub> precursor gave a particularly active catalyst, it also appeared to be so air-sensitive that it was impractical for common use. Additives such as Zn dust, BHT, and Ph<sub>3</sub>PO<sup>13</sup> did not improve the poor performance outside the glovebox. We sought to improve the robustness of the catalyst system by examining a number of different palladium precursors run with standard vacuum line techniques (Table 2, entries 1–5).

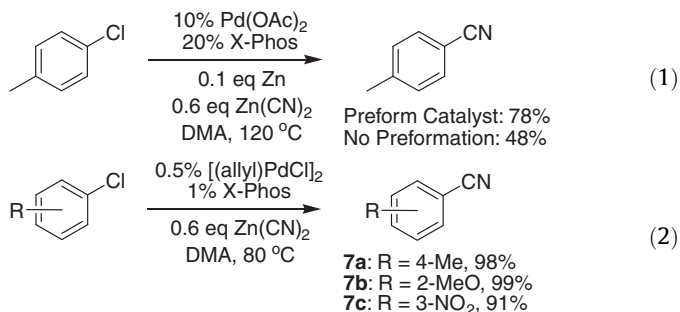


Table 2  
Catalyst optimization<sup>a</sup>

Entry	% Pd	Pd source	Additive <sup>b</sup>	Yield <sup>c</sup>
1	1	[(allyl)PdCl] <sub>2</sub>	—	12 <sup>d</sup>
2	1	Pd(OAc) <sub>2</sub>	—	1 <sup>d</sup>
3	1	Pd(TFA) <sub>2</sub>	—	13 <sup>d</sup>
4	1	Pd <sub>2</sub> (dba) <sub>3</sub> ·CHCl <sub>3</sub>	—	8 <sup>d</sup>
5	1	PdSO <sub>4</sub> ·2H <sub>2</sub> O	—	86 <sup>d</sup>
6	1	Pd(OAc) <sub>2</sub>	2 H <sub>2</sub> O	14
7	1	Pd(OAc) <sub>2</sub>	(Me <sub>4</sub> N) <sub>2</sub> SO <sub>4</sub>	>99
8	1	Pd(OAc) <sub>2</sub>	Cs <sub>2</sub> SO <sub>4</sub>	21
9	1	Pd(OAc) <sub>2</sub>	(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub>	37
10	1	Pd(OAc) <sub>2</sub>	(Et <sub>3</sub> NH) <sub>2</sub> SO <sub>4</sub>	85
11	1	Pd(OAc) <sub>2</sub>	KHSO <sub>4</sub>	99
12	0.5	Pd(OAc) <sub>2</sub>	HBf <sub>4</sub> ·OEt <sub>2</sub>	24
13	0.5	Pd(OAc) <sub>2</sub>	2 HBf <sub>4</sub> ·OEt <sub>2</sub>	73
14	0.5	Pd(OAc) <sub>2</sub>	(Me <sub>4</sub> N) <sub>2</sub> SO <sub>4</sub> + 2 HBf <sub>4</sub> ·OEt <sub>2</sub>	99
15	0.5	Pd(OAc) <sub>2</sub>	H <sub>2</sub> SO <sub>4</sub>	>99

<sup>a</sup> Reaction conditions: Pd/XPhos (1:2), 2% Zn, 0.6 equiv Zn(CN)<sub>2</sub>, DMA (0.2 M substrate), 120 °C, 18 h.

<sup>b</sup> Additive stoichiometry relative to Pd.

<sup>c</sup> Yield determined by HPLC assay versus authentic product standard.

<sup>d</sup> Reaction performed outside glovebox using standard vacuum line techniques.

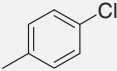
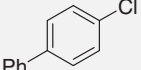
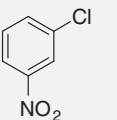
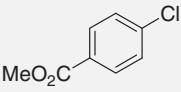
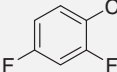
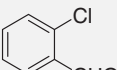
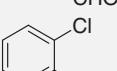
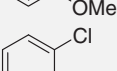
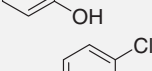
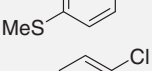
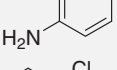
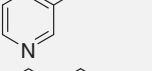
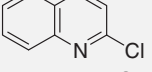
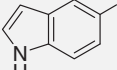
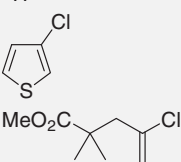
As we observed previously, the [(allyl)PdCl]<sub>2</sub>-based catalyst stalled at only 12% yield (entry 1). Other standard palladium precursors such as Pd(OAc)<sub>2</sub>, Pd(TFA)<sub>2</sub>, and Pd<sub>2</sub>(dba)<sub>3</sub> gave similar results (entries 2–4). Interestingly, PdSO<sub>4</sub>·2H<sub>2</sub>O furnished the product in 86% yield (entry 5). To the best of our knowledge, only a single report on the use of this palladium precursor has appeared in the cross-coupling literature.<sup>14</sup> In this case, however, it was employed for high aqueous solubility and no novel reactivity was observed.<sup>15</sup> Unfortunately, further experiments revealed a large variability in performance with different lots of palladium sulfate.<sup>16</sup> PdSO<sub>4</sub>·2H<sub>2</sub>O is poorly soluble in DMA, and lots that were slower to dissolve during catalyst formation tended to give poor results, presumably due to poor ligand–metal complex formation.

In order to better understand the unusual combination of high reactivity and catalyst longevity conferred by PdSO<sub>4</sub>·2H<sub>2</sub>O, we conducted experiments with Pd(OAc)<sub>2</sub> and various additives (Table 2, entries 6–15). In the presence of two catalyst equivalents of water, (entry 6), the reaction gave poor performance. Upon the addition of (Me<sub>4</sub>N)<sub>2</sub>SO<sub>4</sub>, however, we observed a near-quantitative yield of the desired product (entry 7). Cautioned by a recent report on the potential liability of tetraalkylammonium salts in cyanations,<sup>4</sup> we sought another source of sulfate. Inorganic sulfate salts such as Cs<sub>2</sub>SO<sub>4</sub> and (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> (entries 8 and 9) were poorly soluble and gave a poor yield of the product. Soluble triethylammonium sulfate (entry 10) furnished the product in 85% yield, and KHSO<sub>4</sub>, despite its poor solubility in DMA, gave a nearly quantitative yield of product (entry 11).

Intrigued by this result, we probed the effects of added acid, since KHSO<sub>4</sub> has a pK<sub>a</sub> = 1.92. One catalyst equivalent of tetrafluoroboric acid provided a low yield of the product, but two catalyst equivalents of acid gave a respectable 73% yield of the product (entries 12 and 13). Combining acid and sulfate gave the product in near-quantitative yield. While this could be accomplished with soluble sources of strong acid and sulfate (entry 14), it was operationally simpler to use concentrated sulfuric acid, which gave identical results (entry 15).

With optimized conditions in hand, we proceeded to investigate the scope of the transformation with this catalyst system (Table 3).<sup>17</sup> Electron-neutral and electron-poor aryl chlorides furnished the corresponding nitriles in excellent yield (entries 1–5). A

**Table 3**  
Substrate scope<sup>a</sup>

Entry	Substrate	Product	% Pd	Yield <sup>b</sup> (%)
1		<b>8a</b>	1	99
2		<b>8b</b>	1	99 <sup>c</sup>
3		<b>8c</b>	1	>99
4		<b>8d</b>	1	97
5		<b>8e</b>	1	95
6		<b>8f</b>	1	60
7		<b>8g</b>	1	>99
8		<b>8h</b>	2	98
9		<b>8i</b>	2	83
10		<b>8j</b>	3	60
11		<b>8k</b>	1	94
12		<b>8l</b>	1	92
13		<b>8m</b>	2	91
14		<b>8n</b>	2	78
15		<b>8o</b>	5	65 <sup>d</sup>

<sup>a</sup> Reaction conditions: Pd(OAc)<sub>2</sub>/XPhos/H<sub>2</sub>SO<sub>4</sub> (1:2:1), 0.6 equiv Zn(CN)<sub>2</sub>, 4% Zn, DMA (0.2 M substrate), 120 °C, 2 h.

<sup>b</sup> Yield determined by HPLC assay versus authentic product standard.

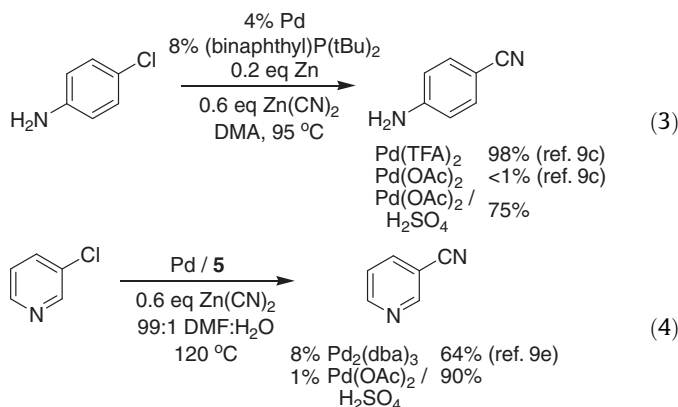
<sup>c</sup> 95% Isolated yield.

<sup>d</sup> 48% Isolated yield.

respectable yield could even be obtained with 2-chlorobenzaldehyde (entry 6), though significant losses due to thermal decomposition were observed. Electron-rich benzonitriles could also be obtained in good to excellent yield, although sometimes additional catalyst was necessary for good conversion (entries 7–10). Similarly, a number of heterocyclic substrates gave the corresponding heteroaryl nitriles in good to excellent yield (entries 11–14). Nota-

bly, sulfur-containing substrates (entries 9 and 14) were well-tolerated. We also examined the cyanation of a vinyl chloride (entry 15); the corresponding acrylonitrile was obtained in moderate yield.<sup>18</sup> To the best of our knowledge, this is the first example of catalytic cyanation of a vinyl chloride.<sup>19</sup>

We also investigated the scope of the palladium sulfate precursor across other ligands by comparison with other cyanation conditions reported in the literature. Catalyst preformation and sulfate activation of a (binaphthyl)P(<sup>t</sup>Bu)<sub>2</sub>-based catalyst provided a marked reactivity enhancement in the cyanation of 4-chloroaniline when compared to palladium acetate alone, though for this challenging substrate it could not quite match the palladium trifluoroacetate precursor (Eq. (3)).<sup>9c</sup> Likewise, preformation and sulfate activation of a Pd(OAc)<sub>2</sub>/5 catalyst provided higher yield and markedly reduced catalyst loading compared to Pd<sub>2</sub>(dba)<sub>3</sub>/5 (Eq. (4)).<sup>9e</sup>



In conclusion, we have discovered a highly active and robust catalyst system for the cyanation of aryl chlorides. The reported catalyst preformation and sulfate activation method gives highly active catalysts with a number of different ligands. Experiments are currently underway to understand the role of sulfuric acid in catalyst activation and to test the applicability of this catalyst system to other reaction classes.<sup>20</sup>

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2010.07.045](https://doi.org/10.1016/j.tetlet.2010.07.045).

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16. Yields ranged from 0% to 86% with different lots of PdSO<sub>4</sub>·2H<sub>2</sub>O.
17. *General procedure for cyanation of aryl chlorides:* Anhydrous DMA was sparged with a gentle stream of N<sub>2</sub> for 30 min prior to use. A 50 mM solution of H<sub>2</sub>SO<sub>4</sub> was prepared with 10 mL DMA and 26.8 μL concd H<sub>2</sub>SO<sub>4</sub> and sparged with N<sub>2</sub> for 10 min. To an 8 mL vial equipped with a magnetic stirbar and septum cap were added Pd(OAc)<sub>2</sub> (22.5 mg, 100 μmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (95.3 mg, 200 μmol). The vial was evacuated and filled with N<sub>2</sub> three times, purged with a gentle stream of N<sub>2</sub> for 10 min, H<sub>2</sub>SO<sub>4</sub> (2.0 mL, 50 mM in DMA) was added, and the catalyst mixture was stirred in an oil bath at 80 °C for 30 min to give a homogeneous coffee-brown solution. To a 100 mL two-neck round-bottomed flask were added Zn dust (13.1 mg, 200 μmol, 10 micron), Zn(CN)<sub>2</sub> (352.3 mg, 3.0 mmol), and 4-chlorobiphenyl (940 mg, 5.0 mmol). The flask was equipped with a magnetic stirbar, septum, and gas inlet, evacuated and filled with N<sub>2</sub> three times, and purged with N<sub>2</sub> for 10 min. DMA (20 mL) and catalyst solution (1.0 mL, 50 μmol Pd, 1% loading) were added and the flask was stirred in an oil bath at 120 °C for 1 h. Quantitative HPLC analysis using authentic 2-cyanobiphenyl purchased from Acros indicates 100% assay yield. The reaction mixture was added to 200 mL H<sub>2</sub>O and 20 mL saturated NaCl was added. The aqueous layer was extracted with 3 × MTBE, combined organics were dried over MgSO<sub>4</sub> and concentrated. The residue was purified via silica gel chromatography (2–20% EtOAc in hexane) to give a white solid (851 mg, 95%). Spectroscopic data match those previously reported in the literature; GC/MS (EI) calcd for C<sub>13</sub>H<sub>9</sub>N (M<sup>+</sup>): 179.07, found: 179.05.
18. A little material was lost due to product volatility with unoptimized workup conditions.
19. For stoichiometric cobalt-mediated cyanation of vinyl chlorides, see Stuhl, L. S. *J. Org. Chem.* **1985**, *50*, 3934–3936.
20. Investigation of the mechanistic effects of sulfuric acid on the catalyst system has been hampered by the poor solubility of the ligand in polar aprotic solvents and the heterogeneity of the reaction mixture. It does not appear that sulfuric acid markedly changes the nature of the ligand–metal complex, as no change in the <sup>31</sup>P NMR signal is observed upon its addition. It also does not appear that the ligand–metal complex is reduced to palladium(0) prior to introduction to the reaction mixture, as no signal corresponding to the ligand oxide is observed in the <sup>31</sup>P NMR spectrum. By comparison, the ligand triphenylphosphine spontaneously reduces its Pd(OAc)<sub>2</sub> complex to Pd(0). See Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009–3013.