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Improving Robustness: In Situ Generation of a Pd(0) Catalyst for the Cyanation of Aryl Bromides

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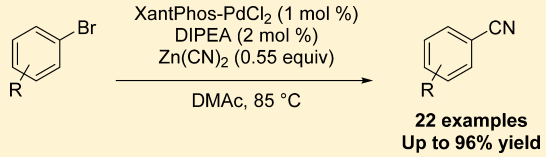
Supporting Information

ABSTRACT: Conditions have been developed for the palladium-catalyzed cyanation of aryl bromides utilizing the air-stable XantPhos-$PdCl_2$ precatalyst. By employing a trialkylamine as a reducing agent, the active Pd(0) species is generated in situ, alleviating the need to employ the air-sensitive $Pd_2(dba)_3$. Twenty-two substituted benzonitriles have been synthesized using this method.



Substituted benzonitriles are an important class of compounds that both serve as starting materials for a variety of synthetic transformations[1] and are present in active pharmaceutical ingredients.[2] Traditional methods to rapidly access benzonitriles, such as the Sandmeyer or Rosenmund−von Braun reaction, require harsh reaction conditions such as high reaction temperatures. As a result, the palladium-catalyzed cyanation[3] of aryl halides has become the preferred method for the installation of an aryl nitrile moiety. Several different cyanide sources have been reported in the literature for use in palladium-catalyzed reactions. NaCN and KCN are generally avoided on large scale due to their inherent toxicity. $K_4Fe(CN)_6$[4] is a low toxicity cyanide source, but cyanation reactions employing this reagent typically require long reactions at temperatures greater than 100 °C, thus increasing the risk of decomposition of the starting material.[5] Zinc cyanide, on the other hand, is approximately ten times less toxic than the sodium and potassium cyanide salts.[6] As a result, zinc cyanide is the most widely used cyanide source in palladium-catalyzed cyanations.[7]

The majority of palladium-catalyzed cyanations employ tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) as the palladium catalyst. However, the use of this Pd(0) complex is less than ideal. Pd(0) complexes have limited stability outside of a glovebox as they oxidize to Pd(II) species. Furthermore, commercially available $Pd_2(dba)_3$ has been shown to contain up to 40% palladium nanoparticles, leading to variability in the amount of active palladium involved in a reaction.[5,8] In addition to these concerns, the dibenzylideneacetone (dba) ligand can compete with another ligand to bind palladium, and after the reaction, dba removal can be problematic. In terms of practicality on a process scale,[9] the use of a well-defined, air-stable Pd(II) precatalyst would be greatly preferred over a Pd(0) species.

There have been several examples reported in the literature employing Pd(II) species in cyanation reactions with $Zn(CN)_2$;[10−14] these methods are not without their limitations. The main drawback associated is the manner in which Pd(II) is reduced to the catalytically active Pd(0) species. One method to reduce palladium required preformation of Pd(0) by the addition of $Zn(Et)_2$, a pyrophoric dialkylzinc reagent.[10] Similarly, up to 20 mol % Zn dust, which may need to be activated, can be added as a reductant to generate Pd(0).[11] The heterogeneous nature of the reaction, due to the addition of the typically insoluble Zn dust and the relatively insoluble $Zn(CN)_2$, could cause problems with mass transfer in larger scale reactions. Furthermore, additional steps would be required to remove the zinc dust at the end of the reaction. Lastly, the addition of 1−10 wt % of polymethylhydrosiloxane (PMHS) protects palladium from oxidation, allowing the use of $Pd(OAc)_2$ in a reaction open to the air.[12] Although effective in this transformation, a PMHS/Pd catalytic system is also capable of reducing aromatic nitro groups to amines, and therefore the method can be limited by reduction of the substrate.[13]

Recently, the Buchwald group published an improved procedure[14] for the cyanation of aryl halides under mild reaction conditions by employing 2−5 mol % *t*-BuXPhos-Pd-G3. Although effective, the need to synthesize a palladacycle precatalyst with an expensive, proprietary ligand limits the ability to perform this reaction on scale. The biphasic system employed, such that cyanide slowly diffuses into the organic phase, introduces an additional parameter that could cause issues on scale.

We sought to develop a general procedure for the cyanation of aryl bromides employing an air-stable, ligated Pd(II) precatalyst that could be easily reduced in situ to an active Pd(0) species without requiring preformation. Initially, we envisioned that a bulky ligand with a large bite angle would be required to promote reductive elimination of the benzonitrile.[15] Preliminary experiments showed that when XantPhos[16] was combined with $Pd_2(dba)_3$, full conversion of 4-bromoanisole (**1**) was achieved with a slight excess of $Zn(CN)_2$ in dimethylacetamide (DMAc) at 85 °C. Unsurprisingly,

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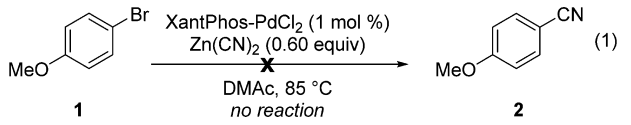
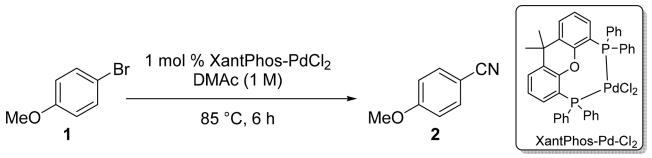
attempted replacement of $Pd_2(dba)_3$ with commercially available XantPhos−$PdCl_2$ resulted in no conversion of the aryl bromide, presumably because the Pd(II) precursor does not undergo reduction to the active Pd(0) species under these conditions (eq 1).



We next tested the ability of various bases to reduce XantPhos−$PdCl_2$ to the active Pd(0) catalyst (Table 1).

Table 1. Optimization of the Cyanation with XantPhos-$PdCl_2$[a]



entry	base (mol %)	equiv of $Zn(CN)_2$	SM[b]	product[b]
1	CsOAc (4%)	0.60	97.3	02.7
2	KOAc (4%)	0.60	66.4	33.6
3	K_2CO_3 (4%)	0.60	69.2	30.8
4	NEt_3 (4%)	0.60	00.3	99.7
5	DIPEA (4%)	0.60	00.1	99.9
6	NEt_3 (2%)	0.55	00.5	99.5
7	**DIPEA (2%)**	**0.55**	**00.3**	**99.7**
8	DIPEA (2%)	0.60	00.6	99.4
9	NEt_3 (1%)	0.60	12.4	87.6
10	DIPEA (1%)	0.60	89.7	10.3
11	dioxane as solvent	0.55	61.3	38.7
12	toluene as solvent	0.55	88.0	12.0
13	MeTHF as solvent	0.55	66.3	33.7
14	$(PPh_3)_2PdCl_2$	0.55	100	0.00
15	DPEPhos−$PdCl_2$	0.55	83.7	16.3
16	DPPF−$PdCl_2$	0.55	82.6	17.4

[a]Reaction conditions: 4-Bromoanisole (1.0 mmol), $Zn(CN)_2$ (0.55−0.60 equiv), XantPhos-$PdCl_2$ (0.01 equiv), base (0.01−0.04 equiv), DMAc. DIPEA is *N,N*-diisopropylethylamine. NEt_3 is triethylamine. [b]Conversion determined by ratio of the HPLC areas of 4-bromoanisole and 4-methoxybenzonitrile

Because complete conversion was observed with 0.5 mol % of $Pd_2(dba)_3$ (1 mol % Pd loading), optimization was conducted with 1 mol % XantPhos−$PdCl_2$. Inorganic and amine bases were initially screened at a 4:1 ratio of base/palladium. CsOAc was not effective at facilitating the cyanation (entry 1); however, two different potassium salts (KOAc and K_2CO_3) provided moderate levels of conversion after 6 h (entries 2−3). Presumably, the modest conversion can be attributed to the low solubility of these bases in DMAc. With 4 mol % of *N,N*-diisopropylethylamine (DIPEA) and triethylamine (NEt_3), complete conversion to the desired nitrile was achieved with 0.60 equiv $Zn(CN)_2$ (entries 4−5). Decreasing the amount of these two organic bases to 2 mol % still afforded complete conversion to the desired product (entries 6−8), and the amount of $Zn(CN)_2$ can be reduced to 0.55 equiv without affecting the efficiency of the conversion (entry 7). Employing 1 mol % of DIPEA and NEt_3 resulted in diminshed levels of conversion to the desired product, suggesting that a 2:1 base/palladium ratio was necessary for the desired reaction (entries 9−10).

To ensure optimal reaction conditions were determined, XantPhos−$PdCl_2$ was tested in different solvents (Table 1, entries 11−13). None of these solvents performed superior to DMAc, presumably because of the decreased solubility of the $Zn(CN)_2$. Several other single component palladium chloride precatalysts were tested under the optimized conditions (Table 1, entries 14−16). These precatalysts performed poorly relative to XantPhos−$PdCl_2$, where the highest conversion to product was only 17 AP.

While NEt_3 and DIPEA were equally as effective at facilitating the desired transformation, DIPEA was chosen to investigate the substrate scope. A representative set of aryl bromides were subjected to the general conditions to afford the corresponding benzonitriles (Table 2), with all of the reactions conducted at greater than 1 g scale. Electron-withdrawing (entries 1−7), electron-donating, (entries 8−12), and electron-neutral (entries 13−15) aryl bromides provided the desired products in yields of up to 96%. The mild reaction conditions are demonstrated by the tolerance of nitrile, ester, ketone, nitro, and amine functional groups on the aromatic ring. The electrophilic compatibility of the cyanation was tested by subjecting an array of aryl (pseudo)halides to the reaction conditions (entry 15). Phenyl triflate and iodobenzene afforded the benzonitrile product in high yield, whereas phenyl tosylate and chlorobenzene were unreactive under the reaction conditions. Electron-poor aryl chlorides show some reactivity under the reaction conditions as demonstrated by the formation of 6% of the dinitrile product in the cyanation of **3g** (entry 7). Although 91% conversion was observed for the styrenyl bromide **3i**, polymerization of the product was observed, attributing to the low isolated yield (entry 10).

A variety of heteroaryl bromides were also subjected to the optimized reaction conditions (Table 3). Seven different heterocyclic bromides afforded the desired cyanation products in yields of up to 93%. Nitrogen-containing heterocycles such as quinoline (entry 1), isoquinoline (entry 2), pyridine (entries 3−4), and indole (entry 5) were successful coupling partners in the cyanation. Five-membered heterocyclic bromides, furan and thiophene (entries 6 and 7), provided the corresponding products in yields of 63% and 79%, respectively.

Attempts to elucidate the mechanism for the reduction of XantPhos−$PdCl_2$ to the active Pd(0) catalyst by ^{31}P NMR were unsuccessful, presumably because of the instability of the Pd(0) species. However, the kinetics of the $Pd_2(dba)_3$/XantPhos and XantPhos−$PdCl_2$/DIPEA systems were measured for three different substrates: an electron-withdrawing (4-bromobenzonitrile), an electron-neutral (bromobenzene), and an electron-donating aryl bromide (4-bromoanisole). Linear kinetics were observed for the consumption of the aryl bromide starting material for all reactions, and there was no significant difference in the initial reaction rates between the three different substrates. A general trend was observed across the two catalytic systems (see Supporting Information for graph of kinetics) in which the cyanation with $Pd_2(dba)_3$/XantPhos was slightly faster in each case than the XantPhos−$PdCl_2$/DIPEA system. The difference in reaction rates between these two catalysts systems may be due to incomplete reduction of the Pd(II) precatalyst in the XantPhos−$PdCl_2$/DIPEA system.

In summary, we report the use of DIPEA as a mild, homogeneous reducing agent to facilitate the reduction of XantPhos−$PdCl_2$ to an active Pd(0) catalyst, which has enabled

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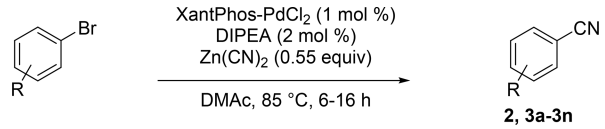
Table 2. Scope of the Cyanation with Aryl Bromides[a]



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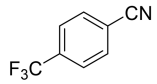
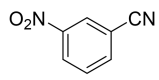
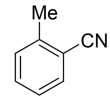
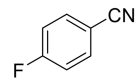
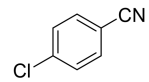
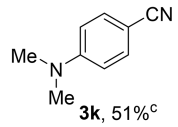
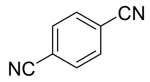
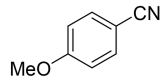
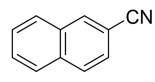
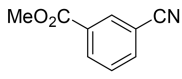
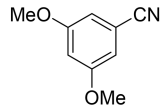
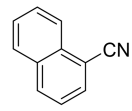
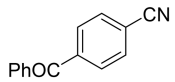
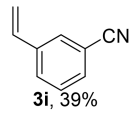
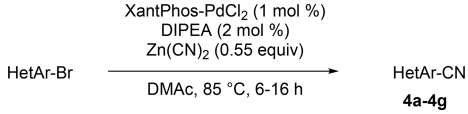
1	 **3a**, 90%	6	 **3f**, 86%	11	 **3j**, 60%
2	 **3b**, 82%	7	 **3g**, 84%[b]	12	 **3k**, 51%[c]
3	 **3c**, 92%	8	 **2**, 96%	13	 **3l**, 91%
4	 **3d**, 80%	9	 **3h**, 90%	14	 **3m**, 92%
5	 **3e**, 83%	10	 **3i**, 39%	15	 **3n** **X=OTf**, 84% **X=I**, 87% **X=Br**, 94% **X=Cl**, NR **X=OTs**, NR

[a]Reaction conditions: ArBr (7.0 mmol), $Zn(CN)_2$ (0.55 equiv), XantPhos $PdCl_2$ (0.01 equiv), DIPEA (0.02 equiv), DMAc (1 M). NR = no reaction. [b]6% of the dicyanated product was isolated. [c]53% conversion was observed with this substrate.

Table 3. Scope of the Cyanation with Heteroaryl Bromides[a]



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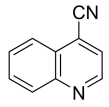
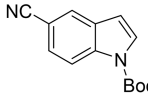
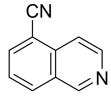
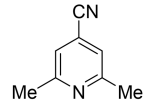
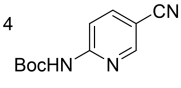
1	 **4a**, 93%	5	 **4e**, 85%
2	 **4b**, 81%	6	 **4f**, 63%
3	 **4c**, 73%	7	 **4g**, 79%
4	 **4d**, 75%		

[a]Reaction conditions: ArBr (7.0 mmol), $Zn(CN)_2$ (0.55 equiv), XantPhos $PdCl_2$ (0.01 equiv), DIPEA (0.02 equiv), DMAc (1 M).

a wide array of (hetero)aryl nitriles to be prepared in high yield. The developed methodology allows for the use of a well-defined and air-stable Pd(II) precursor for the cyanation of aryl bromides.

EXPERIMENTAL SECTION

General Considerations. All reagents were purchased from commercial sources. Standard benchtop techniques were employed for handling air-sensitive reagents. Melting points (°C) are uncorrected. NMR spectra were recorded on a 400 or 500 MHz spectrometer. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant *J* (Hz), and integration. Analytical thin-layer chromatography (TLC) was performed on TLC silica gel plates (0.25 mm) precoated with a fluorescent indicator. Visualization of the TLC plates was effected with ultraviolet light. Standard flash chromatography procedures were followed using 100−200 mesh silica gel. HRMS samples were run on the Thermo LTQ-Orbitrap with Acquity Classic inlet.

General Procedure for the Cyanation. To a 20 mL scintillation vial with a stir bar were added XantPhos−$PdCl_2$ (53 mg, 0.07 mmol, 0.01 equiv), (hetero)aryl bromide (7 mmol), and zinc cyanide (461 mg, 3.85 mmol, 0.55 equiv). The vial was capped with a pressure relief septa and evacuated and purged with N_2 five times. Degassed *N*,*N*-dimethylacetamide (7 mL) (degassed by sparging N_2) was added along with degassed *N*,*N*-diisopropylethylamine (24 μL, 0.138 mmol, 0.02 equiv), all under N_2. The reaction mixture was heated to 85 °C until complete conversion was observed, as judged by HPLC. The reaction mixture was cooled to rt, and 20 mL of a 10:2:88 (NaCl, K_2CO_3, H_2O, wt %) solution was added followed by EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organics were washed with H_2O (20 mL) and dried (Na_2SO_4). After concentrating in vacuo, the crude

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product was purified by flash column chromatography to yield the desired product.

*4-Methoxybenzonitrile (**2**).* The title compound was obtained as a white solid in 96% yield (894 mg). Mp 57−60 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60−7.57 (m, 2H), 6.97−6.92 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 162.8, 133.9, 119.2, 114.7, 103.9, 55.5. Physical and spectral data were in accordance with literature data.[22]

*4-(Trifluoromethyl)benzonitrile (**3a**).* The title compound was obtained as an off-white solid in 90% yield (1080 mg). Mp 36−38 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, J = 10.0 Hz, 2 H), 7.79 (d, J = 10.0 Hz, 2 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 134.5 (q, J = 41.8 Hz), 132.2, 126.2 (q, J = 5.0 Hz), 123.1 (q, J = 338.8 Hz), 117.5, 116.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ −63.5. Physical and spectral data were in accordance with literature data.[17]

*4-Fluorobenzonitrile (**3b**).* The title compound was obtained as a white solid in 82% yield (696 mg). Mp 34−36 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (dd, J = 12.5, 7.5 Hz, 2 H), 7.21 (dd, J = 12.5, 12.5 Hz, 2 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 165.1 (d, J = 320 Hz), 134.7 (d, J = 10.0 Hz), 118.1, 116.9 (d, J = 28.8 Hz), 108.6 (d, J = 5.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ −102.4. Physical and spectral data were in accordance with literature data.[18]

*Terephthalonitrile (**3c**).* The title compound was obtained as a white solid in 83% yield (1202 mg). Mp 222−224 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.08 (s, 4H); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 133.2, 117.5, 115.7. Physical and spectral data were in accordance with literature data.[19]

*Methyl-3-cyanobenzoate (**3d**).* The title compound was obtained as a white solid in 80% yield (902 mg). Mp 59−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (dt, 1H, J = 1.7, 0.8 Hz), 8.28 (dt, 1H, J = 7.9, 1.5 Hz), 7.85 (dt, 1H, J = 7.8, 1.4 Hz), 7.60 (t, 1H, J = 7.8 Hz), 3.97 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.0, 135.9, 133.6, 133.2, 131.3, 129.4, 117.8, 112.9, 52.6. Physical and spectral data were in accordance with literature data.

*4-Benzoylbenzonitrile (**3e**).* The title compound was obtained as a white solid in 83% yield (1202 mg). Mp 111−113 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91−7.86 (m, 2H), 7.79 (m, 4H), 7.69−7.61 (m, 1H), 7.54−7.50 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 195.0, 141.2, 136.3, 133.3, 132.2, 130.2, 130.0, 128.6, 118.0, 115.6. Physical and spectral data were in accordance with literature data.[20]

*3-Nitrobenzonitrile (**3f**).* The title compound was obtained as a white solid in 86% yield (889 mg). Mp 112−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (t, 1H J = 1.8 Hz), 8.49 (ddd, 1H, J = 8.3, 2.3, 1.0 Hz), 8.01 (dt, 1H, J = 7.8, 1.3 Hz), 7.75 (t, 1H, J = 8.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 148.2, 137.6, 130.6, 127.5, 127.2, 116.5, 114.1. Physical and spectral data were in accordance with literature data.[21]

*4-Chlorobenzonitrile (**3g**).* The title compound was obtained as a white solid in 84% yield (813 mg). Mp 90−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63−7.60 (m, 2H), 7.49−7.46 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 139.5, 133.3, 129.6, 117.9, 110.7. Physical and spectral data were in accordance with literature data.[22]

*3,5-Dimethoxybenzonitrile (**3h**).* The title compound was obtained as a white solid in 90% yield (1027 mg). Mp 84−86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.76 (d, J = 2.3 H, 2H), 6.65 (t, J = 2.3 Hz, 1H), 3.81 (s, 6H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 160.9, 118.7, 113.4, 109.8, 105.6, 55.6. Physical and spectral data were in accordance with literature data.[14]

*3-Vinylbenzonitrile (**3i**).* The title compound was obtained as a colorless oil in 39% yield (280 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59−7.57 (m, 2 H), 7.52 (d, J = 10.0 Hz, 1 H), 7.42 (t, J = 10.0 Hz, 1 H), 6.68 (ds, J = 17.5, 12.5 Hz, 1 H), 5.81 (d, J = 17.5 Hz, 1 H), 5.38 (d, J = 12.5 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 138.7, 134.8, 131.1, 130.4, 129.8, 129.4, 118.8, 116.6, 112.8. Physical and spectral data were in accordance with literature data.[23]

*2-Methylbenzonitrile (**3j**).* The title compound was obtained as a colorless oil in 60% yield (488 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (dd, J = 10.0, 1.0 Hz, 1 H) 7.50 (td, J = 10.0, 1.0 Hz, 1 H), 7.34−7.27 (m, 2 H), 2.57 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 141.9, 132.7, 132.5, 130.2, 126.2, 118.2, 112.8, 20.5. Physical and spectral data were in accordance with literature data.[17]

*4-(N,N-Dimethylamino)benzonitrile (**3k**).* The title compound was obtained as a white solid in 51% yield (523 mg). Mp 73−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 2H, J = 8.8 Hz), 6.64 (d, 2H, J = 9.1 Hz), 3.04 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 152.4, 133.3, 120.7, 111.4, 97.3, 39.9. Physical and spectral data were in accordance with literature data.[25]

*2-Cyanonaphthalene (**3l**).* The title compound was obtained as a white solid in 91% yield (975 mg). Mp 62−64 °C. ^{1}H NMR (CDCl3, 400 MHz): δ = 8.21 (s, 1H), 7.94−7.86 (m, 3H), 7.68−7.57 (m, 3H); ^{13}C NMR (CDCl3, 100 MHz): δ = 134.5, 134.0, 132.1, 129.1, 128.9, 128.3, 128.0, 127.6, 126.2, 119.2, 109.2. Physical and spectral data were in accordance with literature data.[24]

*1-Cyanonaphthalene (**3m**).* The title compound was obtained as a white solid in 91% yield (978 mg). Mp 34−36 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, 1H, J = 8.3 Hz), 8.10 (d, 1H, J = 8.3 Hz), 7.96−7.93 (m, 2H), 7.72 (ddd, 1H, J = 8.3, 7.1, 1.3 Hz), 7.66−7.62 (m, 1H), 7.55 (dd, 1H, J = 8.3, 7.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 133.0, 132.6, 132.3, 132.0, 128.4, 128.3, 127.3, 124.7, 124.6, 117.6, 109.8. Physical and spectral data were in accordance with literature data.[25]

*Benzonitrile (**3n**).* The title compound was obtained as a white solid in 94% yield (678 mg) from bromobenzene. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, 1H, J = 8.3 Hz), 8.10 (d, 1H, J = 8.3 Hz), 7.96−7.93 (m, 2H), 7.72 (ddd, 1H, J = 8.3, 7.1, 1.3 Hz), 7.66−7.62 (m, 1H), 7.55 (dd, 1H, J = 8.3, 7.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 133.0, 132.6, 132.3, 132.0, 128.4, 128.3, 127.3, 124.7, 124.6, 117.6, 109.8. Physical and spectral data were in accordance with literature data.[19]

*4-Cyanoquinoline (**4a**).* The title compound was obtained as a white solid in 93% yield (1003 mg). Mp 103−106 °C. ^{1}H NMR (CDCl3, 400 MHz): δ = 9.00 (d, 1H, J = 4.3 Hz), 8.18−8.13 (m, 2H), 7.83 (ddd, 1H, J = 8.4, 7.0, 1.5 Hz), 7.70−7.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4, 147.9, 131.3, 130.3, 129.3, 125.7, 124.9, 124.9, 118.7, 115.5. Physical and spectral data were in accordance with literature data.[26]

*6-Cyanoisoquinoline (**4b**).* The title compound was obtained as a white solid in 83% yield (1202 mg). Mp 137−140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.32 (d, J = 1 Hz, 1H), 8.69 (d, J = 5.8 Hz, 1H), 8.2 ppm (m, 1H), 8.08 (dd, J = 7.2 Hz, 1.1 Hz, 1H), 7.95 (m, 1H), 7.66 (dd, J = 8.3 Hz, 7.3 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 152.9, 145.4, 136.4, 135.0, 132.7, 127.7, 126.5, 117.4, 116.3, 109.4; IR (neat) 3092, 3064, 2224, 1615, 1494, 1373, 1029, 824, 765 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{10}H_7N_2$ $[M + H]^+$ 155.06037, found 155.06013.

*4-Cyano-2,6-lutidine (**4c**).* The title compound was obtained as a white solid in 73% yield (675 mg). Mp 81−84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (s, 2H), 2.58 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.3, 121.7, 120.7, 116.9, 24.4. Physical and spectral data were in accordance with literature data.[21]

*tert-Butyl 5-Cyanopyridin-2-ylcarbamate (**4d**).* The title compound was obtained as a white solid in 75% yield (1145 mg). Mp 190−192 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.10 (s, br, 1 H), 8.63 (s, 1 H), 8.18 (d, J = 8.0 Hz 1 H), 7.93 (dd, J = 8.0, 4.0 Hz 1 H), 1.59 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.1, 151.7, 141.4, 116.9, 112.2, 103.4, 82.5, 28.2; IR (neat) 3181, 3067, 2980, 2230, 1723, 1524, 1256, 1150, 770 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{11}H_{14}N_3O_2$ $[M + H]^+$ 220.10805, found 220.10782.

*tert-Butyl 5-cyano-1H-indole-1-carboxylate (**4e**).* The title compound was obtained as a white solid in 85% yield (1441 mg). Mp 125−127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, J = 8.6 Hz, 1 H), 7.9 (dd, J = 1.5 Hz, 0.8 Hz, 1 H), 7.71 (d, J = 3.8 Hz, 1H), 7.56 (dd, J = 8.7 Hz, 1.4 Hz, 1H), 6.63 (dd, J = 3.8 Hz, 0.8 Hz, 1H), 1.69 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 148.9, 137.0, 130.4, 128.0, 127.2, 125.7, 119.7, 115.9, 106.8, 106.0, 84.8, 28.0. Physical and spectral data were in accordance with literature data.[27]

*Furan-3-carbonitrile (**4f**).* The title compound was obtained as a brown solid in 63% yield (408 mg). Mp 26−28 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (t, J = 1.5 Hz, 1 H), 7.53 (t, J = 2.0 Hz, 1 H), 6.66 (t, J = 2.0 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 149.7,

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144.1, 113.1, 111.1, 97.9. Physical and spectral data were in accordance with literature data.[28]

*Thiophene-3-carbonitrile (**4g**).* The title compound was obtained as a yellow oil in 79% yield (604 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (dd, J = 5.0, 1.5 Hz, 1 H), 7.46 (dd, J = 10.0, 3.0 Hz, 1 H), 7.33 (dd, J = 10.0, 1.5 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 135.5, 128.7, 127.4, 115.2, 110.7. Physical and spectral data were in accordance with literature data.[18]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01003.

Kinetic data, copies of ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

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■ REFERENCES

(1) Subramanian, L. R. Product Class 5: Nitriles. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Georg Thieme Verlag: Stuttgart, NY, 2014; Vol. *19*, pp 79−94.

(2) Kleemann, A.; Engle, J.; Kutscher, B.; Reichert, D. *Pharmaceutical substances: syntheses, patents, applications*, 4th ed.; Georg Thieme Verlag: Stuttgart, NY, 2001.

(3) For recent reviews of palladium-catalyzed cyanations, see: (a) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049. (b) Takagi, K. Palladium-Catalyzed Cross-Coupling Involving α-Hetero-Substituted Organometals: Palladium-Catalyzed Cross-Coupling Involving Metal Cyanides. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002. (c) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, *2003*, 3513.

(4) For recent cyanations with $K_4[Fe(CN)_6]$, see: (a) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 648. (b) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508. (c) Schareina, T.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2004**, *689*, 4576. (d) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388.

(5) Ryberg, P. *Org. Process Res. Dev.* **2008**, *12*, 540.

(6) Senecal, T. D.; Shu, W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 10035.

(7) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177.

(8) Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302.

(9) For examples of cyanations on scale, see: (a) Burg, F.; Egger, J.; Deutsch, J.; Guimond, N. *Org. Process Res. Dev.* **2016**, *20*, 1540. (b) Utsugi, M.; Ozawa, H.; Toyofuku, E.; Hatsuda, M. *Org. Process Res. Dev.* **2014**, *18*, 693. (c) Yu, H.; Richey, R. N.; Miller, W. D.; Xu, J.; May, S. A. *J. Org. Chem.* **2011**, *76*, 665.

(10) For recent examples of cyanations with $Zn(Et)_2$, see: (a) Hu, X. E. Melanin Concentrating Hormone Antagonists. WO 2008/001160 A1. 3 Jan 2008. (b) Hu, X. E. Melanin Concentrating Hormone Antagonists. WO 2005/033063 A2. 14 April 2005.

(11) For recent examples of cyanations with Zn dust, see: (a) Shapiro, R.; Taylor, E. D. G.; Zimmerman, W. T. Method For Preparing N-Phenylpyrazole-1-Carboxamides. WO 2006/062979 A1. 15 June 2006. (b) Jones, L. H.; Middleton, D. S.; Mowbray, C. E.; Newman, S. D.; Williams, D. H. Chemical Compounds. WO 2006/067587 A2. 29 June 2006. (c) Littke, A.; Soumeillant, M.; Kaltenbach, R. F., III; Cherney, R. J.; Tarby, C. M.; Kiau, S. *Org. Lett.* **2007**, *9*, 1711. (d) Shevlin, M. *Tetrahedron Lett.* **2010**, *51*, 4833.

(12) Martin, M. T.; Liu, B.; Cooley, B. E., Jr.; Eaddy, J. F. *Tetrahedron Lett.* **2007**, *48*, 2555.

(13) Rahaim, R. J.; Maleczka, R. E., Jr. *Org. Lett.* **2005**, *7*, 5087.

(14) Cohen, D. T.; Buchwald, S. L. *Org. Lett.* **2015**, *17*, 202.

(15) (a) Erhardt, S.; Grushin, V. V.; Kilpatrick, A. H.; Macgregor, S. A.; Marshall, W. J.; Roe, D. C. *J. Am. Chem. Soc.* **2008**, *130*, 4828. (b) Dobbs, K. D.; Marshall, W. J.; Grushin, V. V. *J. Am. Chem. Soc.* **2007**, *129*, 30. (c) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661.

(16) For examples of the cyanation of aryl halides with XantPhos, see: (a) Pitts, M. R.; McCormack, P.; Whittall, J. *Tetrahedron* **2006**, *62*, 4705. (b) Scott, J. S.; Brocklehurst, K. J.; Brown, H. S.; Clarke, D. S.; Coe, H.; Groombridge, S. D.; Laber, D.; MacFaul, P. A.; McKerrecher, D.; Schofield, P. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3175.

(17) Noh, J.-H.; Kim, J. *J. Org. Chem.* **2015**, *80*, 11624.

(18) Zou, T.; Yu, X.; Feng, X.; Bao, M. *Chem. Commun.* **2015**, *51*, 10714.

(19) Zheng, S.; Yu, C.; Shen, Z. *Org. Lett.* **2012**, *14*, 3644.

(20) Chang, S.; Jin, Y.; Zhang, X. R.; Sun, Y. B. *Tetrahedron Lett.* **2016**, *57*, 2017.

(21) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389.

(22) Hatsuda, M.; Seki, M. *Tetrahedron* **2005**, *61*, 9908.

(23) Schedler, M.; Wang, D.-S.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 2585.

(24) Hughes, T. V.; Cava, M. P. *J. Org. Chem.* **1999**, *64*, 313.

(25) Anbarasan, P.; Neumann, H.; Beller, M. *Chem. - Eur. J.* **2010**, *16*, 4725.

(26) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 648.

(27) Seggio, A.; Priem, G.; Chevallier, G.; Mongin, F. *Synthesis* **2009**, *2009*, 3617.

(28) Cantillo, D.; Kappe, C. O. *J. Org. Chem.* **2013**, *78*, 10567.

DOI: 10.1021/acs.joc.7b01003
J. Org. Chem. 2017, 82, 7040−7044