Practical and Scalable Synthesis of a Benzonitrile Derivative via Palladium-Catalyzed Cyanation with Potassium Ferrocyanide

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Supporting Information

ABSTRACT: A practical and reproducible synthetic method for the preparation of a benzonitrile derivative (1) from an aryl bromide (2) via Pd-catalyzed cyanation was established with dimethylacetamide (DMAc)-toluene as a mixed solvent. Optimization was examined by a design of experiments (DoE) technique to enhance reaction conversion and reduce the dimeric impurity 3, and desired benzonitrile derivative 1 was successfully obtained in high yields with excellent quality control on a 117 kg scale.

INTRODUCTION

Benzonitrile derivatives are valuable components of agrochemicals, fine chemicals, and pharmaceuticals.¹ They are widely used in active pharmaceutical ingredients (APIs) and their synthetic intermediates. Benzonitrile derivative 1 is a key synthetic intermediate of our API.² A medicinal chemistry route is shown in Scheme 1. This method has two main drawbacks: its multistep nature and the use of cryogenic equipment. This prompted us to devise a short synthetic method via userfriendly reactions.

Pd-catalyzed cyanation is a practical approach for synthesizing benzonitrile derivatives from the corresponding aryl halides and triflates.³ The reaction has received considerable attention following Takagi's discovery of Pd-catalyzed cyanation with KCN in 1973.⁴ Various cyanide sources have been developed, such as NaCN, Zn(CN)₂, TMSCN, and acetone cyanohydrin, but these reagents are toxic and difficult to handle on an industrial scale. In 2004, Beller and co-workers described a Pdcatalyzed cyanation using $K_4[Fe(CN)_6]$, which is inexpensive and also used as a food additive, as a nontoxic cyanide source.^{5,6} Despite these advantages, only a few examples of this reaction have been reported on a manufacturing scale. Cyanide potentially deactivates the catalyst. Thus, heterogeneous conditions in which the cyanide source is insoluble are generally required, which increases the difficulty of the transformation on a large scale. Herein, we describe the application of $K_4[Fe(CN)_6]$ for the preparation of target compound 1. We further explain how we overcame these difficulties and controlled the quality of 1 by modifying the method, effectively optimizing the reaction conditions with DoE studies and accomplishing the manufacturing of 1 on a >100 kg scale.

RESULTS AND DISCUSSION

Initial Screening. Compound 1 was obtained using Weissman's conditions as a preliminary guide, but two major issues arose during the Pd-catalyzed cyanation with K_4 [Fe-

 $(CN)_6]\cdot 3H_2O$ (Scheme 2).⁷ First, the reaction stalled irreproducibly (88–100% conversion), and reprocessing was necessary for completion after work-up. Second, byproduct homodimer 3 was formed in the reaction (up to 0.53 area %, HPLC) and was difficult to remove during purification, resulting in the presence of a derivative of 3 in the final API.

To improve the reaction conversion and avoid the use of the patented ligand XPhos, we first screened several alternative ligands. As depicted in Table 1, aryl phosphine ligands were effective at promoting the desired transformation, but the cyanation of our substrate proceeded very slowly without them (entry 2).⁷ A comparison of the results for the different ligands, most notably with respect to the formation of **3** and other impurities, indicated that $P(o-tol)_3$ is equivalent to XPhos in this reaction (entry 7 vs entry 1, respectively).

Improvement of Reaction Reproducibility. Reproducibility remained an issue, however. We speculated that this lack of reproducibility was due to catalyst deactivation. Grushin and co-workers reported that catalyst deactivation in Pd-catalyzed cyanation reactions results from the transformation of the Pd(II) complex to inactive species such as $[ArPd(CN)_3]^-$, $[HPd(CN)_3]^-$, and $[Pd(CN)_4]^{2-8,9}$ via oxidation of Pd(0) and the presence of a high concentration of the cyanide source in the reaction solution.^{8e}

The effect of oxygen and other additives on the cyanation reaction to produce 1 was then investigated, and the results are presented in Table 2.^{3a,10} As air inhibited the cyanation, it did not prevent the reaction under inert atmosphere (entry 1 vs entry 2). The combination of Zn (4 mol %) and Zn(OAc)₂ (4 mol %) as a reducing agent induced completion of the reaction^{10b} but afforded a higher amount of 3 (0.47 area %) under a nitrogen atmosphere with an oxygen concentration of <0.5% (entries 5 and 6).¹¹ Other agents also gave disappointing

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Scheme 1. Medicinal chemistry route for the synthesis of benzonitrile derivative 1



Scheme 2. Initial conditions for Pd-catalyzed cyanation



Table 1. Ligand screening^a



^{*a*}Conditions: **2** (100-mg scale), magnetic stirring. All reagents were charged followed by a nitrogen purge. ^{*b*}Conversion was calculated from the HPLC area. ^{*c*}Detected by HPLC.

Table 2. Effect of oxygen and additives a

entry	additives (mol %)	${^{O_2}}^b$ (%)	time (h)	conversion ^{c,d} (%)	3 ^c (area %)
1	none	21	8	64	0.50
2	none	< 0.5	3	100	0.32
3	Zn (4), Zn(OAc) ₂ (4)	21	8	95	0.48
4	PMHS (10 wt %) ^{e}	21	2	18	6.73
5	Et ₃ SiH (10)	21	2	16	1.19
6	Zn (4), Zn(OAc) ₂ (4)	<0.5	2	100	0.47

^{*a*}Conditions: **2** (1 g scale), $Pd(OAc)_2$ (1 mol %), $P(o-tol)_3$ (1 mol %), $K_4[Fe(CN)_6]\cdot 3H_2O$ (0.8 equiv), DMAc (8 v/w), 135 °C, magnetic stirring. ^{*b*}Oxygen concentration in the gaseous phase. ^{*c*}Detected by HPLC. ^{*d*}Conversion was calculated from the HPLC area. ^{*e*}PMHS: polymethylhydrosilane.

results. The need to carefully control the oxygen concentration was not desirable for the manufacturing process.

Therefore, we focused next on the concentration of the cyanide source as another catalyst deactivator. Frech reported that an excess of $K_4[Fe(CN)_6]$ leads to catalyst deactivation.^{8e} Thus, we reduced the concentration of the cyanide source by adding toluene as an antisolvent for $K_4[Fe(CN)_6]$ (Table 3).

Table 3. Effect of toluene^a

entry	solvent (v/w)	temp (°C)	time (h)	conversion ^{<i>b,c</i>} (%)	3 ^b (area %)
1	DMAc (6)	125	2	100	0.33
2	toluene (6)	110	24	6	nd ^d
3	DMAc (4), toluene (2)	125	2	100	0.11

^{*a*}Conditions: **2** (2-g scale), $Pd(OAc)_2$ (2 mol %), $P(o-tol)_3$ (2 mol %), $K_4[Fe(CN)_6]$ ·3H₂O (0.4 equiv), Na_2CO_3 (1 equiv), magnetic stirring under a nitrogen atmosphere. ^{*b*}Detected by HPLC. ^{*c*}Conversion was calculated from the HPLC area. ^{*d*}nd: not detected.

While the reaction proceeded sluggishly with only 6% conversion at 110 °C when toluene was used exclusively as the solvent (entry 2), the reaction was reproducible in a mixed solvent of DMAc-toluene. Furthermore, the addition of toluene reduced the formation of **3** (entry 3). As a result, the conditions adopted for the reaction included the use of DMAc-toluene under O₂ <1%. The irreproducible results in DMAc were likely due to oxygen.¹²⁻¹⁴

OPTIMIZATION

DoE Studies. Our interest was then directed towards the optimization of this cyanation process in order to improve the reaction conversion and reduce the formation of byproduct 3. DoE is an excellent statistical tool for estimating the main effects and interactions of several factors in a reaction in order to truly determine the optimized values and robust ranges.¹⁵ In our previous studies, it was found that the mole fraction of $Pd(OAc)_2$ and $P(o-tol)_3$ and the composition ratio of toluene in the DMAc-toluene have an impact on the conversion and formation of 3.¹⁶ Therefore, a Box–Behnken design was

employed considering these three parameters (Table 4, entries 1-14).^{15,17} The ranges were selected based on the results of our initial studies (Pd(OAc)₂: 0.5–2.0 mol %, P(*o*-tol)₃: 0.25–2.25 mol %, and toluene: 16–50 vol %).

Table 4. DoE studies^a

entry	Pd(OAc) ₂ (mol %)	P(<i>o</i> -tol) ₃ (mol %)	toluene (vol %)	conversion ^{b,c} (%)	3 ^b (area %
1	0.5	1.25	16	100	0.46
2	2.0	1.25	16	100	0.32
3	0.5	1.25	50	79.1	0.13
4	2.0	1.25	50	99.6	0.12
5	0.5	0.25	33	79.1	0.29
6	2.0	0.25	33	97.7	0.15
7	0.5	2.25	33	99.9	0.34
8	2.0	2.25	33	100	0.16
9	1.25	0.25	16	93.4	0.47
10	1.25	0.25	50	81.1	0.10
11	1.25	2.25	16	99.9	0.31
12	1.25	2.25	50	90.6	0.08
13	1.25	1.25	33	99.9	0.22
14	1.25	1.25	33	100	0.18

^{*a*}Conditions: **2** (4 g scale), $K_4[Fe(CN)_6] \cdot 3H_2O$ (0.4 equiv), Na_2CO_3 (1 equiv), DMAc-toluene (6 v/w), 125 °C, 8 h, magnetic stirring. These experiments were performed with vigorous stirring using a magnetic stirring tip in a test tube. ^{*b*}Detected by HPLC. ^{*c*}Conversion was calculated from the HPLC area.

The outcomes were analyzed using the JMP 10.0.2 software package.¹⁸ With respect to conversion, beneficial effects of increasing the mole fraction of $Pd(OAc)_2$ and $P(o-tol)_3$ and decreasing the toluene ratio were confirmed. On the other hand, with regard to the formation of **3**, it was found that increasing the toluene ratio and mole fraction of $Pd(OAc)_2$ was beneficial (Figure 1). These conflicting results were overlapped in Figure 2 in order to find the optimized conditions; they were ($Pd(OAc)_2$: 1.9 mol %, $P(o-tol)_3$: 1.9 mol %, and toluene: 43 vol %). In fact, excellent results were obtained using these conditions (8 h, 100% conversion, **3**: 0.07 area %).

Scale-up Studies with a Stirring Impeller. Unfortunately, we found that the optimized conditions using magnetic



(b) byproduct 3 (left: Pd(OAc)₂-P(o-tol)₃, middle: Pd(OAc)₂-toluene, right: P(o-tol)₃-toluene)

Figure 1. Three-dimensional contour plots showing the conversion, byproduct 3 level, mole fraction of $Pd(OAc)_2$ and $P(o-tol)_3$, and the toluene composition in the toluene–DMAc mixed solvent.



Figure 2. Overlays of graphical analyses showing the vol % of toluene, mol % of $Pd(OAc)_2$, reaction conversion, and formation of byproduct 3 (P(*o*-tol)₃: 1.9 mol %). The zone within the red area (conversion) corresponds to 95–100% conversion; the line, 99% conversion. The zone within the blue area (dimer) represents 0.12–0.20 area %; the line, 0.15 area %. The circle represents the optimized conditions (Pd(OAc)₂: 1.9 mol %, toluene: 43 vol %; see Supporting Information).

stirring were not appropriate for larger scale reactions with impeller stirring (8 h, 65% conversion, 3: 0.22 area %). It was hypothesized that the use of the different stirring methods affected the reactive surface area (particle size) of $K_4[Fe-(CN)_6]$. As the cyanation proceeds, the surfaces of $K_4[Fe-(CN)_6]$ particles might be converted to a less reactive cyanide species. With magnetic stirring, however, the $K_4[Fe(CN)_6]$ particles are generally ground by the tip, thus exposing fresh reactive surfaces that can promote the cyanation. An impeller would not affect the $K_4[Fe(CN)_6]$ particles in this manner, and therefore no new reactive surfaces would be exposed as the reaction progressed.

In fact, the particle size distribution of $K_4[Fe(CN)_6]$ ·3H₂O was a critical factor for the reaction. Weissman reported that $K_4[Fe(CN)_6]$ ·3H₂O with a mean particle size of 312 μ m with a D90 (maximum particle diameter below which 90% of the sample exists) of <509 μ m provided good results, while $K_4[Fe(CN)_6]$ ·3H₂O with a mean particle size of 464 μ m and D90 <822 μ m afforded only 5% conversion to their desired benzonitrile after 10 h.⁷ In our case, milled $K_4[Fe(CN)_6]$ ·3H₂O was initially used (mean particle size: ~87.6 μ m, D90: ~188.7 μ m), but it was found that $K_4[Fe(CN)_6]$ ·3H₂O with a mean particle size of ~227 μ m and D90 of ~496 μ m exhibited similar reactivity, and it was commercially available.

Subsequently, the in situ particle size of $K_4[Fe(CN)_6]$ in the DMAc-toluene mixed solvent stirred with an impeller was investigated. A slurry of $K_4[Fe(CN)_6]\cdot 3H_2O$ in each of three different DMAc-toluene solvent mixtures (0, 33, and 43 vol % toluene) was heated to 85 °C, and the chord length distribution (CLD) of the particles (square weight) was measured using a focused beam reflectance measurement (FBRM) probe (see Supporting Information). Notably, the CLD of the particles in the 43 vol % toluene solution was larger than that in the 100% DMAc solution (Figure 3). While the results of the abovementioned DoE studies using magnetic stirring were not

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Figure 3. Overlays of chord length distribution (CLD) plots for K_4 [Fe(CN)₆] (2.4 g) in 0, 33, and 43 vol % toluene in DMAc (30 mL) at 85 °C (square weight).

completely applicable to the reactions using overhead stirring, it was concluded that the CLD data for the <43 vol % toluene in DMAc reaction should be relevant because the results obtained under these conditions with impeller stirring were similar to those obtained when using $K_4[Fe(CN)_6]$ of an appropriate particle size with magnetic stirring.¹⁹ Further CLD analyses of $K_4[Fe(CN)_6]$ particles in different solvent mixtures with impeller stirring then revealed that 33 vol % toluene afforded a CLD for $K_4[Fe(CN)_6]$ that was similar to that in DMAc. The optimum conditions for impeller stirring were thus determined to be $Pd(OAc)_2$, 2 mol %; $P(o-tol)_3$, 2 mol % for 8 h, and using these conditions, the target compound 1 was obtained with \geq 99% conversion, while 3 was formed with 0.18 area %.

MANUFACTURING

To ensure scalability, we confirmed the reaction conditions with a vessel similar to the reactor on a 50 g scale. Slow heating during scale-up did not affect catalyst deactivation in spite of the early introduction of the catalyst and cyanide source at 25 $^{\circ}$ C.²⁰ After completion, the reaction was filtered to remove the catalyst and inorganic salts.²¹ The filtrate was washed with water and extracted with toluene. The combined extracts were concentrated, and **1** was obtained by crystallization from isopropyl alcohol (IPA)–water incorporating *N*-methyl thiourea as a palladium scavenger in 84% yield.

Finally, a series of scale-up studies led to reproducible manufacture of 1 in high yields with excellent quality on 48.2 kg and 116.6 kg scales, regardless of the impeller type (Table 5).

CONCLUSION

In conclusion, we developed a practical and reproducible Pdcatalyzed cyanation in DMAc-toluene while simultaneously controlling the formation of byproduct **3**. Using DoE studies, the ideal concentration range for $Pd(OAc)_2$ and $P(o-tol)_3$ and fraction of toluene in the mixed solvent were identified. A high percentage of toluene was, however, found not to be appropriate when using impeller stirring because of the in situ particle size of $K_4[Fe(CN)_6]$, as revealed using CLD analysis with FBRM. As a result of this effort, we accomplished the manufacturing of 1 in high yield and high quality on a 117 kg scale.

EXPERIMENTAL SECTION

General Information. Solvents and reagents were used without purification or drying. ¹H and ¹³C NMR spectra were acquired on a Bruker spectrometer at frequencies of 400 and 100 MHz, respectively. Infrared spectra were acquired on a PerkinElmer Spectrum One spectrometer. Mass spectra were recorded on a Waters ZQ-2000 mass spectrometer. HPLC chromatograms were recorded on a Shimadzu LC-10 system. Optical rotations were recorded on a PerkinElmer polarimeter 341. Reaction calorimetry was performed using a Mettler Toledo RC1e vessel and Omnical SuperCRC calorimeter. Chord length distributions were measured by a Mettler Toledo FBRM S-400 probe.

4-{(2S)-4-[(1R)-1-Phenylethyl]morpholin-2-yl}benzonitrile (1). A deoxygenated solution of 2.1 kg of $Pd(OAc)_2$ (9.2 mol) and 2.8 kg of P(o-tol)₃ (9.2 mol) in 302.7 kg of DMAc was added to a deoxygenated suspension of 160.4 kg of 2 (463.2 mol), 78.1 kg of K₄[Fe(CN)₆]·3H₂O (184.9 mol, PSD: mean size ~ 227 μ m, D90 ~ 496 μ m), 49.0 kg of Na₂CO₃ (463.2 mol) in 277.1 kg of toluene, and 305.0 kg of DMAc at 25 °C (measured O_2 : 0.2–0.4%). The resulting suspension was heated to 120-130 °C over 1 h and stirred for 9 h at 125 °C (bubbling nitrogen from the bottom of the vessel every 1 h).²² After cooling, the reaction mixture was filtered and washed with 277.2 kg of toluene. The filtrate was washed with 640 kg of water. The aqueous layer was extracted with 277.0 kg of toluene, and the combined organic layers were washed with 320 kg of water and concentrated to 480 L. To the concentrate was added 753.0 kg of IPA, and the resulting mixture was concentrated to 400 L. The concentrate was combined with 768.4 kg of IPA, and the mixture was heated to 60 °C and treated with 16.1 kg of activated charcoal. The resulting mixture was filtered through a Celite pad, and the residue was washed with 251.3 kg of IPA. The filtrate was concentrated to 400 L and combined with 260 kg of IPA, and to the resulting solution was treated with 6.4 kg of *N*-methyl thiourea. The mixture was stirred at 55 °C until dissolved. The product crystallized at 40 °C. After cooling to 20 °C, 800 kg of water was dropped into the slurry. The slurry was aged over 1 h and filtered, and the filter cake was washed with a solution of 125.8 kg of IPA and 320 kg of water and dried at 60 °C under reduced pressure to afford 1 as a white solid (116.6 kg, yield 86%, purity 99.4 area %).

IR (ATR): 2802, 2229, 1610, 1449, 1296, 1119, 1095, 1020, 956, 834, 759, 699, 565 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.66–7.61 (m, 2H), 7.51–7.45 (m, 2H), 7.37–7.24 (m, 5H), 4.65 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.94 (ddd, *J* = 11.3, 3.1, 1.8 Hz, 1H), 3.74 (ddd, *J* = 11.3, 11.3, 2.3 Hz, 1H), 3.38 (q, *J* = 6.7 Hz,1H), 3.09 (ddd, *J* = 11.3, 2.6, 2.3 Hz, 1H), 2.62 (dd, *J* = 11.5, 1.8 Hz, 1H), 2.14 (ddd, *J* = 11.5, 11.3, 3.1 Hz, 1H), 2.01

Table 5. Results on manufacturing scale a

				reaction		yield		
entry	2 scale (kg)	reactor (L)	impeller type	conversion ^{b,c} (%)	3 ^c (area %)	kg	%	purity ^b (%)
1	68.0	1000	Pfaudler	100	0.10	48.2	84	99.4
2	160.0	3000	anchor	100	0.17	116.6	86	99.4

^{*a*}Conditions: **2**, Pd(OAc)₂ (2 mol %), P(*o*-tol)₃ (2 mol %), K₄[Fe(CN)₆]-3H₂O (0.4 equiv), Na₂CO₃ (1 equiv), DMAc-toluene (toluene 33 vol %, 6 v/w), 125 °C, 8 h. ^{*b*}Detected by HPLC. ^{*c*}Conversion was calculated from the HPLC area.

(dd, J = 11.3, 10.2 Hz, 1H), 1.40 (d, J = 6.7 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 146.0, 143.2, 132.1, 128.3, 127.6, 127.1, 126.8, 118.8, 111.3, 77.5, 67.2, 65.0, 57.3, 50.5, 19.5. LRMS (ESI) m/z: calcd for C₁₉H₂₀N₂O [M + H]⁺ 293, found 293. [α]²⁰_D +50.7° (c 2.36, CHCl₃).

(2S)-2-(4-Bromophenyl)-4-[(1R)-1-phenylethyl]morpholine (2). IR (ATR): 2801, 1601, 1487, 1450, 1294, 1118, 1098, 1069, 1008, 957, 917, 809, 758, 699, 550 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.50–7.44 (m, 2H), 7.36–7.21 (m, 7H), 7.14 (d, *J* = 8.4 Hz, 2H), 4.56 (dd, *J* = 10.2, 2.3 Hz, 1H), 3.91 (ddd, *J* = 11.3, 3.1, 1.8 Hz, 1H), 3.73 (ddd, *J* = 11.3, 1.3, 2.3 Hz, 1H), 3.35 (q, *J* = 6.7 Hz, 1H), 3.07 (ddd, *J* = 11.3, 2.6, 2.3 Hz, 1H), 2.59 (dd, *J* = 11.5, 1.8 Hz, 1H), 2.12 (ddd, *J* = 11.5, 11.3, 3.1 Hz, 1H), 2.03 (dd, *J* = 11.3, 10.2 Hz, 1H), 1.36 (d, *J* = 6.7 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 143.4, 139.8, 131.3, 128.3, 127.9, 127.6, 127.1, 121.5, 77.7, 67.2, 65.1, 57.6, 50.7, 19.6. LRMS (ESI) *m*/*z*: calcd for C₁₈H₂₀BrNO [M + H]⁺ 346, found 346. [α]²⁰_D +44.5° (*c* 2.00, EtOH).

 $\begin{array}{l} (25,2'5)-2,2'-Biphenyl-4,4'-diylbis\{4-[(1R)-1-phenylethyl]-morpholine\} (3). IR (ATR): 2796, 1741, 1492, 1452, 1288, 1121, 1098, 957, 807, 760, 700, 552 cm^{-1}. ^{1}H NMR (400 MHz, CDCl_3): <math display="inline">\delta$ 7.59–7.54 (m, 4H), 7.47–7.42 (m, 4H), 7.35–7.23 (m, 10H), 7.14 (d, *J* = 8.4 Hz, 4H), 4.65 (dd, *J* = 10.2, 2.3 Hz, 2H), 3.94 (ddd, *J* = 11.3, 3.1, 1.8 Hz, 2H), 3.76 (ddd, *J* = 11.3, 11.3, 2.3 Hz, 2H), 3.37 (q, *J* = 6.7 Hz, 2H), 3.16 (ddd, *J* = 11.3, 2.6, 2.3 Hz, 2H), 2.61 (dd, *J* = 11.5, 1.8 Hz, 2H), 2.22–2.09 (m, 4H), 1.38 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 143.6, 140.3, 139.8, 128.3, 127.6, 127.0, 127.0, 126.7, 78.2, 67.3, 65.2, 57.7, 50.8, 19.7. LRMS (ESI) *m*/*z*: calcd for C₃₆H₄₀N₂O₂ [M + H]⁺ 533, found 533. [α]²⁰_D +68.0° (*c* 4.83, CHCl_3).

ASSOCIATED CONTENT

Supporting Information

Experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs. org.

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Notes

The authors declare no competing financial interest.

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(9) Frech reported that $[Pd(CN)_4]^{2-}$ formed slowly using $K_4[Fe(CN)_6]$ as a cyanide source in ref 8e.

(10) (a) Martin, M. T.; Liu, B.; Cooley, B. E., Jr.; Eaddy, J. F. Tetrahedron Lett. 2007, 48, 2555–2557. (b) Chidambaram, R. Tetrahedron Lett. 2004, 45, 1441–1444. (c) Ren, Y.; Liu, Z.; He, S.; Zhao, S.; Wang, J.; Niu, R.; Yin, W. Org. Process Res. Dev. 2009, 13, 764–768.

(11) For a review on the synthesis of biaryls with zinc, see: Hassan, J.; Sevignon, M.; Gozzi, C.; Schultz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.

(12) The effect of toluene was unclear, but it worked as expected; in addition, it also worked as a degassing agent during refluxing. Degassing due to refluxing toluene may prolong the catalyst life. According to Merritt, dissolved oxygen should be purged under refluxing; see: Merritt, J. M.; Buser, J. Y.; Campbell, A. N.; Fennell, J. W.; Kallman, N. J.; Koenig, T. M.; Moursy, H.; Pietz, M. A.; Scully, N.; Singh, U. K. Org. Process Res. Dev. **2014**, *18*, 246–256.

(13) In our earlier studies, we observed uneven results using different batches of **2** in DMAc. It was thought that impurities in **2** which may have increased the solubility of the cyanide source were causing catalyst deactivation, but critical impurities for catalyst deactivation were not identified. In addition, it should be noted that in the case of $K_4[Fe(CN)_6]\cdot 3H_2O$, unlike that of $Zn(CN)_2$, NaCl, 1-phenetylamine, and 4 did not hinder the reaction. For the catalyst deactivation using $Zn(CN)_2$ with NaCl and dimethylamine, see: Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C. Org. Lett. **2004**, *6*, 3723–3725.

(14) In our kinetic studies using reaction calorimeter SuperCRC, the trend of catalytic deactivation in the cyanation with 1.0 equiv of $K_4[Fe(CN)_6]\cdot 3H_2O$ was not observed. The studies described that $K_4[Fe(CN)_6]\cdot 3H_2O$ accelerated the cyanation than the catalyst, which may suggest that mass transfer of $K_4[Fe(CN)_6]$ is rate-limiting step. The reaction stalled using 0.2 equiv of $K_4[Fe(CN)_6]\cdot 3H_2O$ at ~70% conversion. For our kinetics studies, see Supporting Information.

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(15) For an example of a book about DoE, see: Carlson, R.; Carlson, R. *Design and Optimization in Organic Synthesis*, 2nd ed.; Elsevier: Amsterdam, 2005.

(16) The stirring was carried out under a fast impeller speed because it was critical for the reaction. Byproduct **3** increased under a slow impeller speed, and its formation depended on the mixing efficiency in the reactor. Although the amount of water also had a great impact on reaction rate, we did not further investigate for avoiding increase of the cyanide source.

(17) Box, G. E. P.; Behnken, D. W. Ann. Math. Stat. 1960, 31, 838-864.

 $(18)\ We\ used\ JMP\ 10.0.2\ (SAS)\ and\ STAVEX\ (Aicos)\ as\ statistical\ analysis\ software.$

(19) We did not have enough time to re-examine the DoE studies using overhead stirring.

(20) Some papers suggested that early addition of the cyanide source causes catalyst deactivation; see: Ryberg, P. *Org. Process Res. Dev.* **2008**, *12*, 540–543 and ref 10c.

(21) Free cyanide was not detected in the corresponding filtrate by ion chromatography (detectable limit <0.5 ppm). An analytical method using ion chromatography was referred to ref 13. The residue was disposed of as toxic waste.

(22) It was observed that heavy inorganic salts (e.g., $K_4[Fe(CN)_6]$) remained at the bottom of the vessel just below the impeller, even with vigorous overhead stirring. We thus were concerned about the mixing efficiency and clogging of the reactor by these salts during the workup.