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Research Article

Ni-Catalyzed Cyanation of (Hetero)Aryl Electrophiles Using the Nontoxic Cyanating Reagent $K_4[Fe(CN)_6]$

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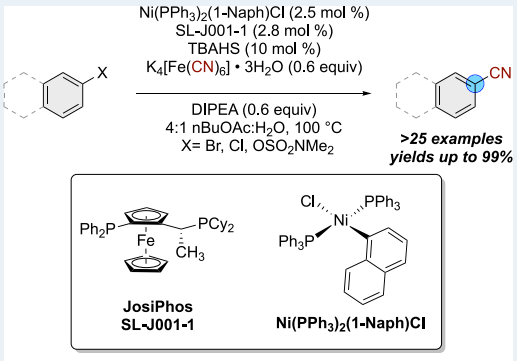
ABSTRACT: A Ni-catalyzed cyanation of aryl halides using potassium ferrocyanide ($K_4[Fe(CN)_6]$) as a nontoxic cyanide source has been developed. Key features of this method include the use of biphasic aqueous conditions to overcome the innate insolubility of $K_4[Fe(CN)_6]$ in organic solvents and the use of a bench-stable Ni(II) precatalyst combined with a commercially available JosiPhos ligand that enhances the practicality and scalability of this cyanation reaction. The inclusion of the acidic additive tetrabutylammonium hydrogen sulfate was found to improve the reaction rate and conversion. The initial scope of this Ni-catalyzed cyanation reaction was successfully demonstrated on a range of (hetero)aryl bromides, chlorides, and sulfamates using catalyst loadings as low as 2.5 mol %. This base-metal-catalyzed methodology was further translated to the decagram synthesis of a pharmaceutical intermediate, usurping the prior Pd-catalyzed process that employed a hazardous cyanide source and solvent pair ($Zn(CN)_2$, DMAc).



KEYWORDS: *Ni-catalysis, cyanation, nitriles, earth abundant catalysis, base metal catalysis*

INTRODUCTION

The implementation of sustainable base metal catalysis is rapidly emerging as a decisive goal in the manufacture of pharmaceuticals, agrochemicals, and fine chemicals.[1−8] Given the overwhelming success of Pd-based catalysts in industrially relevant transformations,[9−11] it is not surprising that significant effort has been put forth to identify base metal catalysts that can complement, or in some cases, replace this precious metal. In particular, nickel has emerged as a viable alternative in several Pd-catalyzed methods.[12] The implementation of Ni-based catalysts as surrogates to Pd-based catalysts has yielded more sustainable alternatives to classical transition metal catalyzed reactions such as Suzuki−Miyaura cross-couplings,[13−15] Buchwald−Hartwig aminations,[16,17] and C−X borylations.[18]

Another class of reactions that has successfully undergone the transition from Pd catalysis to Ni catalysis is the cyanation of (hetero)aryl electrophiles. Ni complexes supported by electron-rich phosphines have been demonstrated to mediate the incorporation of cyanide from $M(CN)_x$ salts, TMSCN, α-amino nitriles, and cyanohydrins into an impressive range of electrophiles.[19−31] While these systems offer improved sustainability over traditional Pd-catalyzed cyanation methodology,[32,33] these benefits are offset by the significant toxicity of the accompanying cyanating reagents. The preferred reagent for large scale manufacturing[34] is the nontoxic and inexpensive cyanide source potassium ferrocyanide $K_4[Fe(CN)_6]$,[35−38] originally pioneered by Beller et al.[39,40] for the Pd-catalyzed cyanation of aryl halides. In contrast, attempts to use potassium ferrocyanide with a Ni catalyst thus far have proven to be unsuccessful.[21]

The development of a Ni catalyst that is compatible with $K_4[Fe(CN)_6]$ to efficiently convert aryl electrophiles into benzonitriles would therefore represent a significant advancement in metal-catalyzed cyanations as a uniquely sustainable and safe method. Furthermore, since benzonitriles are proven pharmacophores that have been incorporated in several approved drugs (i.e., enzalutamide, crisaborole, escitalopram) and crop protection active ingredients such as the insecticide tetraniliprole and the fungicide isotianil (Figure 1), the development of a practical and scalable cyanation method using an earth abundant metal catalyst combined with a nontoxic cyanide source could have tangible benefits in the future manufacture of biologically active aryl nitriles.

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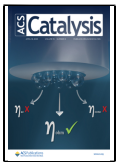

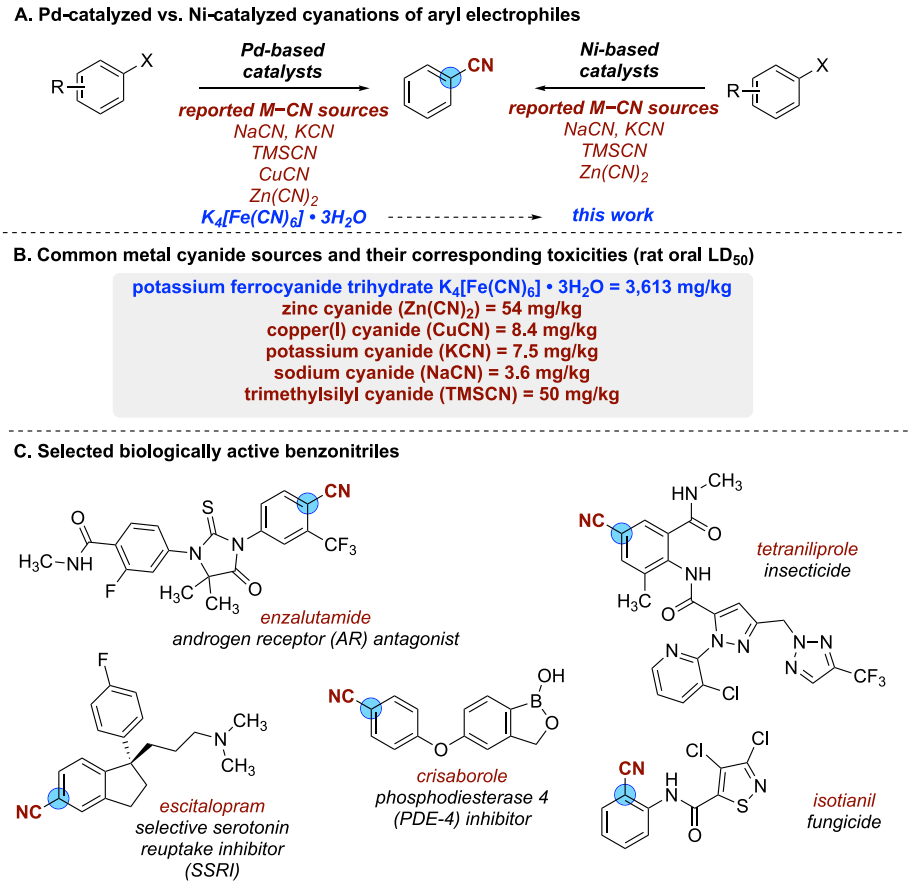

Figure 1. Pd-based and Ni-based catalytic cyanations with compatible metal cyanide sources, corresponding toxicity data, and representative biologically active benzonitriles.

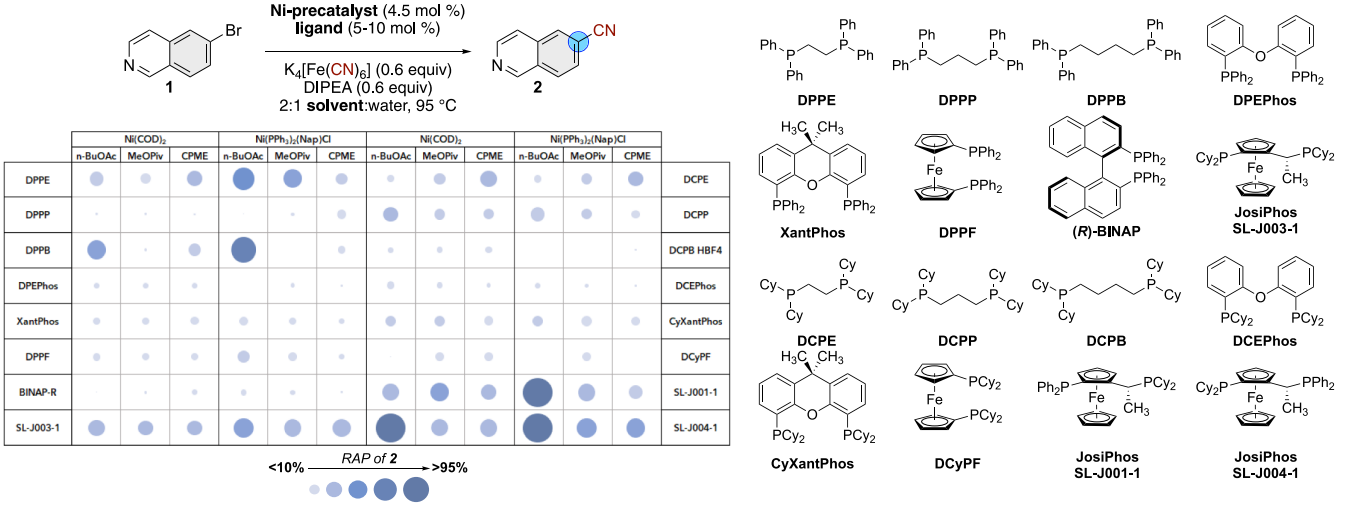

Figure 2. HTE trial for the Ni-catalyzed cyanation of 6-bromoisoquinoline (**1**) with $K_4[Fe(CN)_6]$ using two different Ni-precatalysts, three different solvents, and 16 different bidentate phosphine ligands. Color and size of the circles corresponds to relative area percent (RAP, area of product peak/total area of all peaks) × 100%) of **2** by UPLC-UV at 254 nm.

RESULTS AND DISCUSSION

Building upon our recent success on developing a Pd-catalyzed cyanation of aryl imidazolylsulfonates using $K_4[Fe(CN)_6]$,[41] the ongoing collaboration between the process department at Bristol Myers Squibb (BMS) and the Frantz lab at UTSA sought to identify a Ni-catalyzed cyanation of aryl electrophiles using $K_4[Fe(CN)_6]$ as a viable cyanide source. To accelerate this endeavor, we envisioned utilizing the efficiency of high-throughput experimentation (HTE)[42,43] to test an array of Ni-precatalysts, ancillary ligands, solvents, and additives to rapidly discover initial conditions that productively led to product formation. To overcome the exceedingly low solubility of $K_4[Fe(CN)_6]$ in most common organic solvents, we strategically focused on the use of aqueous biphasic conditions

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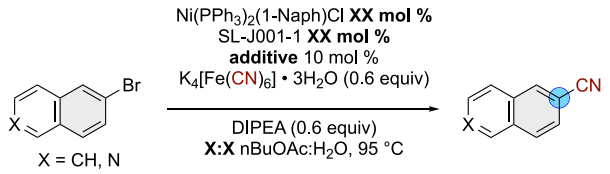
Table 1. Refined Optimization of the Ni-Catalyzed Cyanation Using $K_4[Fe(CN)_6]$ as the Cyanide Source



entry	X (0.5 mmol)	catalyst loading (mol %)	ligand loading (mol %)	DIPEA (equiv)	additive[a]	*n*BuOAc (mL)	water (mL)	5 h RAP[b] (%)	27 h RAP[b] (%)
1	N	4.5	5.0	0.6	-	1.0	0.5	65	95
2	CH	4.5	5.0	0.6	-	1.0	0.5	26	84
3	CH	4.5	5.0	-	-	1.0	0.5	35	60
4	CH	4.5	5.0	-	AcOH	1.0	0.5	16	21
5	CH	4.5	5.0	0.6	AcOH	1.0	0.5	47	91
6	CH	4.5	5.0	0.6	TBAHS	1.0	0.5	67	>95
7	CH	4.5	5.0	0.6	TBAHS	2.4	0.6	>95	>95
8	CH	2.5	2.8	0.6	TBAHS	2.4	0.6	>95	>95
9[c]	CH	2.5	2.8	0.6	TBAHS	2.4	0.6	53[d]	94[e]

[a]AcOH = acetic acid; TBAHS = tetrabutylammonium hydrogen sulfate. [b]RAP = relative area percent reported as a ratio of product to starting material as determined by UPLC analysis using UV detection at 220 nm. [c]Reaction set up outside of glovebox employing standard Schlenk techniques. [d]RAP at 6 h reaction time point. [e]RAP at 24 h reaction time point.

in our preliminary screening efforts. We also established a unified goal to identify an air stable Ni-precatalyst in combination with a commercially available ancillary ligand that would translate into a practical method suitable for a broad range of applications both in academia and industry.

$Ni(PPh_3)_2(1\text{-Naph})Cl$ is an air stable complex that has limited precedence as a cyanation catalyst with NaCN.[44] Additionally, this complex has been demonstrated as a precatalyst for other Ni-catalyzed cross-couplings.[45] To decouple ligand exchange from catalytic activity, we also opted to include the air sensitive complex $Ni(COD)_2$ as a well-established Ni(0) source in our experimental design. Two water-miscible organic solvents, DMAc and dioxane, were chosen along with 24 different phosphine-based ancillary ligands, water as a cosolvent, and 0.6 equiv of $K_4[Fe(CN)_6]$. Triethylamine (0.6 equiv) was also added as a weak base based on numerous reports of palladium-catalyzed cyanations using $K_4[Fe(CN)_6]$ that required a base additive. The results of this preliminary 96-well HTE endeavor are summarized in the Supporting Information. While proof of concept reactivity was achieved, < 30% conversion of the aryl imidazolylsulfonate starting material was observed.

For the next round of high-throughput experimentation we expanded our survey to include a combination of water miscible and immiscible organic solvents (biphasic conditions) in combination with the top 8 ancillary phosphine-based ligands from the previous ligand survey. We were surprised to observe a pronounced solvent and ligand effect, as *n*-BuOAc provided exceptional conversion and clean reaction profile to the corresponding aryl nitrile when JosiPhos SL-J004-1 (>95% conversion) was used as the ancillary ligand. Similar results were observed when we switched to aryl bromide 6-bromoisoquinoline (**1**).

To understand the generality of the observed solvent effect, we expanded our experimental design to include 16 bisphosphine ligands in *n*-butyl acetate, methyl pivalate (MeOPiv), and cyclopentylmethyl ether (CPME). Despite their similar dielectric constants (5.01 and 4.76, respectively), *n*-BuOAc dramatically outperformed CPME in nearly all cases (Figure 2). The sterically encumbered ester solvent MeOPiv, which is more recalcitrant to hydrolysis, also displayed inferior performance to *n*-BuOAc.

Several catalyst systems with precedented reactivity with alternative cyanating reagents displayed moderate ((DPPB)-Ni) to poor ((XantPhos)Ni, (DPPF)Ni) reactivity when employing potassium ferrocyanide. Only the JosiPhos family of ligands (SL-J001-1, SL-J004-1) provided significant conversion of **1** to **2**, highlighting the value of high-throughput experimentation as a tool to identify novel catalyst systems (see Supporting Information for additional details regarding all HTE efforts).

Subsequent translation of the optimal conditions identified by HTE (*n*-BuOAc, JosiPhos SL-J001−1, and $Ni(PPh_3)_2(1\text{-Naph})Cl$ as the precatalyst) on 0.5 mmol scale encouragingly provided similar performance to what was observed on 0.01 mmol scale (Table 1, entry 1). However, a simple substrate switch to the less electronically activated 2-bromonaphthalene displayed attenuated reactivity and was thus subjected to further optimization (entry 2). The requirement of a weak amine base was also validated during these studies (entry 3) and is consistent with previous metal-catalyzed cyanations using $K_4[Fe(CN)_6]$.[39] Additional studies also demonstrate a kinetic dependence on the rate of product formation based on the amount of DIPEA added, however, all reactions proceeded to completion at the 24 h time point (see Supporting Information for details). Further optimization studies with additional additives also proved fruitful. While acetic acid was ineffective in the absence of base (entry 4), the combination of acid and tertiary amine base displayed superior reactivity to base alone (entries 3 vs 5). These results may also help explain the superiority of n-BuOAc as solvent as it may undergo fractional hydrolysis to produce small amounts of acetic acid in situ that also facilitates catalyst turnover. The acidic additive tetrabutylammonium hydrogen sulfate (TBAHS) proved to be even more effective, furnishing the desired benzonitrile product in >95% conversion after 27 h. Further dilution of the reaction solvent improved the reaction rate (entry 7) which permitted reduction of the catalyst loading to 2.5 mol % (entry 8). Gratifyingly, these reactions conditions proved to be robust enough to permit standard laboratory Schlenk technique,

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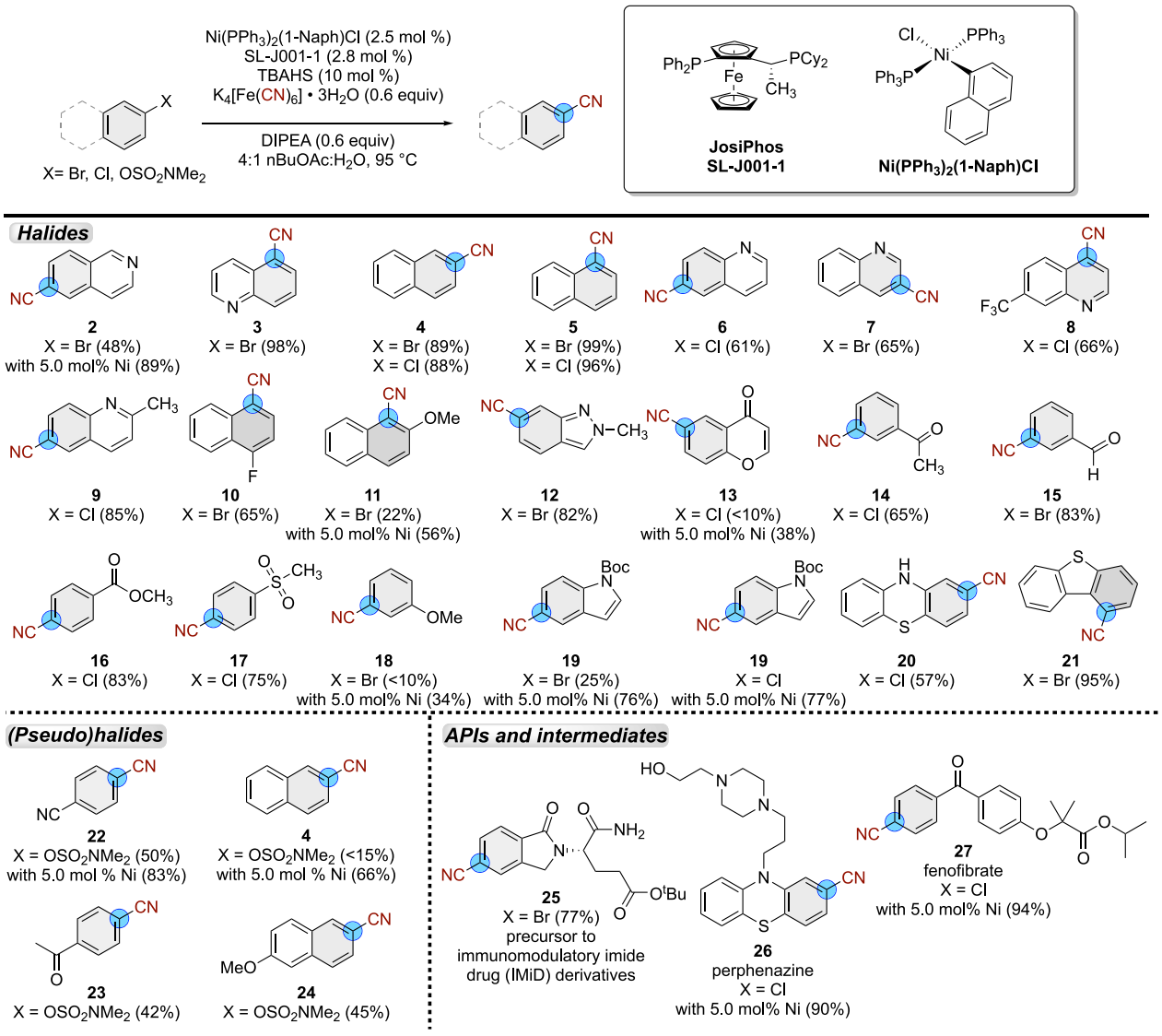

Figure 3. Preliminary substrate scope for the Ni-catalyzed cyanation of aryl electrophiles using $K_4[Fe(CN)_6]$ under biphasic reaction conditions using standard Schlenk techniques. Yields reported in parentheses are isolated yields.

reaching full conversion even outside of the glovebox (albeit with diminished reaction kinetics). Furthermore, motivated by the positive impacts resulting from these additional optimization studies, we rescreened several Ni-precatalysts and solvents. While $Ni(COD)_2$ displayed comparable results, $Ni(PPh_3)_2$(1-Naph)Cl was superior to other Ni(II)-precatalysts surveyed. Unexpectantly, the addition of TBAHS further expanded the scope of compatible solvents beyond *n*-BuOAc to include MeOPiv, CPME, anisole, and MIBK which all demonstrated high conversions. The results of these rescreening efforts are conveyed in the Supporting Information.

Having identified suitable reaction conditions, we next sought to probe the generality of this method with a diverse array of (hetero)aryl electrophiles. The results of these efforts are presented in Figure 3, which reveals some discernible trends with respect to the leaving group, substrate electronics and overall yield. In general, both aryl chlorides and bromides perform equally well in this Ni-catalyzed cyanation in head-to-head comparisons (i.e., **4**, **5**, and **19**). However, the electronic properties of the electrophile do display a perceptible trend, with electron poor substrates (i.e., **14**, **15**, **16**, and **17**) providing better yields overall than electron rich electrophiles (i.e., **11** and **13**). We were delighted by the general functional group tolerability of the method with ketones (**14**), aldehydes (**15**), esters (**16**), sulfones (**17**), unprotected anilines (**20**), thioethers (**21**), primary amides (**25**), and unprotected alcohols (**26**) all proving to be compatible with this catalytic process. The electrophile scope was also expanded to include aryl sulfamates to provide benzonitrile derivatives **4** and **22**–**24** in comparable yields to the corresponding aryl halides. In addition, the method was successfully demonstrated on two aryl chloride containing active pharmaceutical ingredients (APIs), perphenazine (**26**) and fenofibrate (**27**), in high yields using 5 mol % of the Ni(II)-precatalyst in each case. During these efforts, we identified substrates where little to no conversion of the starting aryl electrophile was observed by HPLC under the current reaction conditions. Additional details regarding these unreactive substrates can be found in the Supporting Information (Figure S13).

To further demonstrate the practicality of this Ni-catalyzed cyanation method, we performed a Ni-catalyzed cyanation reaction on a 15-g scale using aryl bromide **28** (Figure 4). In

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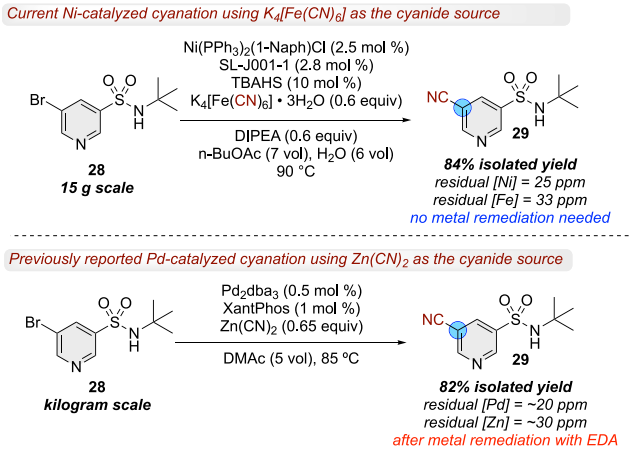


Figure 4. Ni-catalyzed vs Pd-catalyzed cyanation of (hetero)aryl bromide **28** at scale.

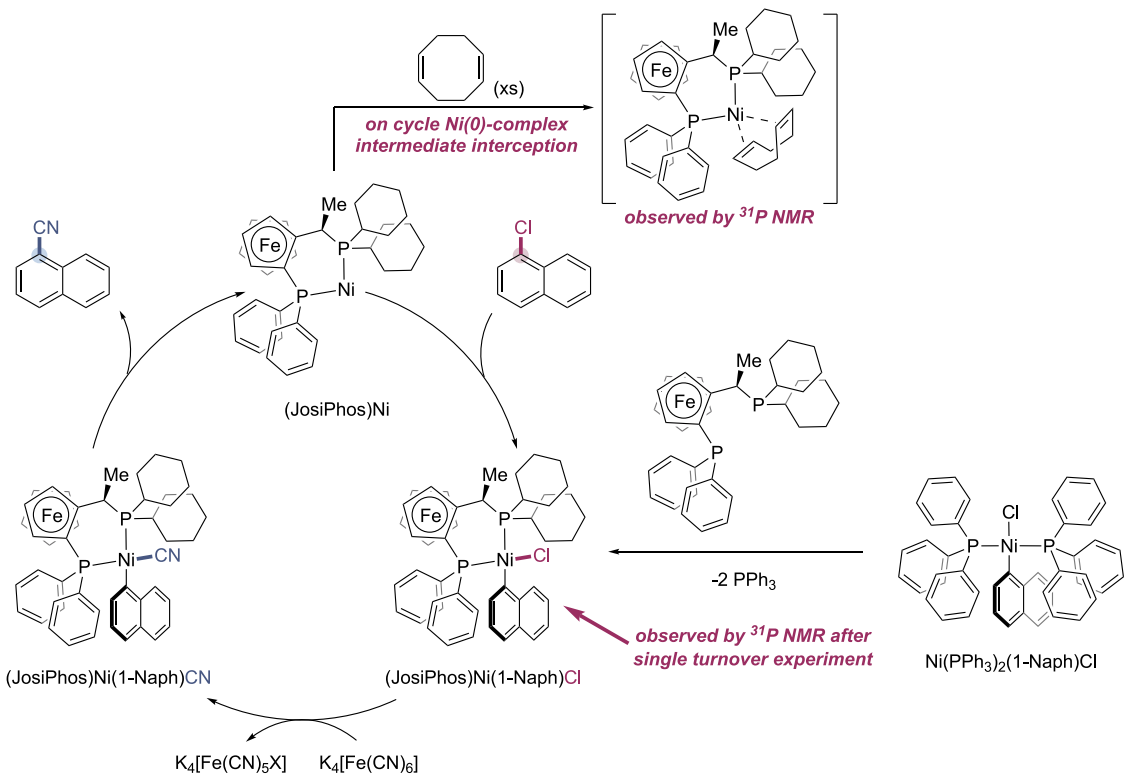
conversion of **28** to the corresponding nitrile **29** in the synthesis of BMS-919373, a potent inhibitor of atrial-specific ultrarapid delayed rectifier potassium current (I_{Kur}) enzyme for the potential treatment of atrial fibrillation (AF), a Pd-catalyzed cyanation using $Zn(CN)_2$ as the cyanide source was previously developed to install the requisite cyano group on the pyridine ring using DMAc as the solvent (Figure 4).[46] Prior to isolation via crystallization, the workup required the addition of ethylene diamine (EDA) as a scavenger for both Pd and Zn to achieve residual metal concentrations of ~20 ppm and ~30 ppm, respectively, in the final product. In comparison, the Ni-catalyzed version using $K_4[Fe(CN)_6]$ provided the desired aryl nitrile **29** in comparable isolated yield (84% vs 82%) via crystallization from *n*-BuOAc/heptane with residual Ni and Fe concentrations of 25 and 33 ppm, respectively, without any metal scavenger required. Although catalyst loadings were higher using nickel, additional advantages were realized over the Pd-catalyzed version including the use of two green solvents (*n*-BuOAc and water) instead of DMAc and the nontoxic cyanide source $K_4[Fe(CN)_6]$ in place of toxic $Zn(CN)_2$.[47]

We sought to further understand the elementary steps of the catalytic cycle using ^{31}P NMR (see Supporting Information). In the cyanation of 1-chloronaphthalene, (JosiPhos)Ni(1-Napth)Cl was observed to be the resting state of the catalyst. Heating this complex under the reaction conditions in the presence of excess 1,5-cyclooctadiene (COD) resulted in the formation of **5** and (JosiPhos)Ni (COD). On the basis of these experiments, we propose the catalytic cycle described in Scheme 1. Ligand exchange between $Ni(PPh_3)_2(1\text{-Naph})Cl$ and JosiPhos (SL-J001-1) generates (JosiPhos)Ni(1-Napth)Cl which undergoes turnover-limiting transmetalation with $K_4[Fe(CN)_6]$. Reductive elimination to generate 1-cyanonaphthalene and (JosiPhos)Ni(0) and oxidative addition to 1-chloronaphthalene regenerates the resting state of the catalyst. For alternative aryl (pseudo)halide electrophiles, the (JosiPhos)Ni(1-Naph)Cl precatalyst undergoes a single turnover to liberate **5** before engaging with the substrate. While optimization studies point to the beneficial impact of the inclusion of tetrabutylammonium hydrogen sulfate and diisopropylethylamine, currently the precise role of base and acid remain the subject of further study.

CONCLUSION

In conclusion, we have developed a Ni-catalyzed cyanation of aryl electrophiles using $K_4[Fe(CN)_6]$ as an inexpensive and nontoxic cyanide source. Salient features of the method include

Scheme 1. Proposed Mechanism for the Ni-Catalyzed Cyanation of Aryl Electrophiles with $K_4[Fe(CN)_6]$



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the use of an air-stable Ni(II)-precatalyst and a commercially available ancillary ligand to generate an active catalyst capable of producing the corresponding benzonitrile products in good overall yields using catalyst loadings as low at 2.5 mol %. Current efforts include a detailed mechanistic analysis on the roles that both amine base and TBAHS play in promoting this Ni-catalyzed cyanation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.5c00158.

All experiment procedures, structures of ligands screened, optimization studies, tabulated HTE data, characterization data of all compounds, photographs of experimental setup, list of common cyanating agents and oral toxicities, list of unreactive substrates, mechanistic studies, and NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Bullock, R. M.; Chen, J. G.; Gagliardi, L.; Chirik, P. J.; Farha, O. K.; Hendon, C. H.; Jones, C. W.; Keith, J. A.; Klosin, J.; Minteer, S. D.; et al. Using nature's blueprint to expand catalysis with Earth-abundant metals. *Science* **2020**, *369*, 6505.

(2) Kment, S.; Bakandritsos, A.; Tantis, I.; Kmentova, H.; Zuo, Y.; Henrotte, O.; Naldoni, A.; Otyepka, M.; Varma, R. S.; Zboril, R. Single Atom Catalysts Based on Earth-Abundant Metals for Energy-Related Applications. *Chem. Rev.* **2024**, *124* (21), 11767−11847.

(3) Hayler, J. D.; Leahy, D. K.; Simmons, E. M. A Pharmaceutical Industry Perspective on Sustainable Metal Catalysis. *Organometallics* **2019**, *38*, 36−46.

(4) Chirik, P.; Morris, R. Getting Down to Earth: The Renaissance of Catalysis with Abundant Metals. *Acc. Chem. Res.* **2015**, *48*, 2495.

(5) Zhao, H.; Ravn, A. K.; Haibach, M. C.; Engle, K. M.; Johansson Seechurn, C. C. C. Diversification of Pharmaceutical Manufacturing Processes: Taking the Plunge into the Non-PGM Catalyst Pool. *ACS Catal.* **2024**, *14*, 9708−9733.

(6) Clapson, M. L.; Durfy, C. S.; Facchinato, D.; Drover, M. W. Base metal chemistry and catalysis. *Cell Rep. Phys. Sci.* **2023**, *4*, 101548.

(7) Wheelhouse, K. M. P.; Webster, R. L.; Beutner, G. L. Advances and Applications in Catalysis with Earth-Abundant Metals. *Org. Process Res. Dev.* **2023**, *27*, 1157−1159.

(8) Chirik, P. J.; Engle, K. M.; Simmons, E. M.; Wisniewski, S. R. Collaboration as a Key to Advance Capabilities for Earth-Abundant Metal Catalysis. *Org. Process Res. Dev.L* **2023**, *27*, 1160−1184.

(9) Magano, J.; Dunetz, J. R. Large-scale applications of transition metal-catalyzed couplings for the synthesis of pharmaceuticals. *Chem. Rev.* **2011**, *111*, 2177−2250.

(10) Devendar, P.; Qu, R. Y.; Kang, W. M.; He, B.; Yang, G. F. Palladium-Catalyzed Cross-Coupling Reactions: A Powerful Tool for the Synthesis of Agrochemicals. *J. Agric. Food Chem.* **2018**, *66*, 8914−8934.

(11) Farina, V. How to Develop Organometallic Catalytic Reactions in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2023**, *27*, 831−846.

(12) Chernyshev, V. M.; Ananikov, V. P. Nickel and Palladium Catalysis: Stronger Demand than Ever. *ACS Catal.* **2022**, *12*, 1180−1200.

(13) Goldfogel, M. J.; Guo, X.; Meléndez Matos, J. L.; Gurak, J. A.; Joannou, M. V.; Moffat, W. B.; Simmons, E. M.; Wisniewski, S. R. Advancing Base-Metal Catalysis: Development of a Screening Method for Nickel-Catalyzed Suzuki−Miyaura Reactions of Pharmaceutically Relevant Heterocycles. *Org. Process Res. Dev.* **2022**, *26*, 785−794.

(14) Haibach, M. C.; Ickes, A. R.; Tcyrulnikov, S.; Shekhar, S.; Monfette, S.; Swiatowiec, R.; Kotecki, B. J.; Wang, J.; Wall, A. L.; Henry, R. F.; et al. Enabling Suzuki-Miyaura coupling of Lewis-basic arylboronic esters with a nonprecious metal catalyst. *Chem. Sci.* **2022**, *13*, 12906−12912.

(15) Yang, J.; Neary, M. C.; Diao, T. ProPhos: A Ligand for Promoting Nickel-Catalyzed Suzuki-Miyaura Coupling Inspired by Mechanistic Insights into Transmetalation. *J. Am. Chem. Soc.* **2024**, *146*, 6360−6368.

(16) Villatoro, R. S.; Belfield, J. R.; Arman, H. D.; Hernandez, L. W.; Simmons, E. M.; Garlets, Z. J.; Wisniewski, S. R.; Coombs, J. R.; Frantz, D. E. General Method for Ni-Catalyzed C−N Cross-

Couplings of (Hetero)Aryl Chlorides with Anilines and Aliphatic Amines under Homogeneous Conditions Using a Dual-Base Strategy. *Organometallics* **2023**, *42*, 3164−3172.
(17) Morrison, K. M.; Stradiotto, M. The development of cage phosphine'DalPhos' ligands to enable nickel-catalyzed cross-couplings of (hetero)aryl electrophiles. *Chem. Sci.* **2024**, *15*, 7394−7407.
(18) Munteanu, C.; Spiller, T. E.; Qiu, J.; DelMonte, A. J.; Wisniewski, S. R.; Simmons, E. M.; Frantz, D. E. Pd- and Ni-Based Systems for the Catalytic Borylation of Aryl (Pseudo)halides with B(2)(OH)(4). *J. Org. Chem.* **2020**, *85*, 10334−10349.
(19) Kanchana, U. S.; Mathew, T. V.; Anilkumar, G. Recent advances and prospects in the nickel- catalyzed cyanation. *J. Organomet. Chem.* **2020**, *920*, 121337.
(20) Porte, V.; Kollmus, P.; Serrano, E.; Santagostino, M. High-throughput Experimentation Enables the Development of a Nickel-catalyzed Cyanation Platform for (Hetero)aryl Halides. *Chem.—eur. J.* **2025**, *31*, No. e202403795.
(21) Beattie, D. D.; Schareina, T.; Beller, M. A room temperature cyanation of (hetero)aromatic chlorides by an air stable nickel(ii) XantPhos precatalyst and Zn(CN)(2). *Org. Biomol. Chem.* **2017**, *15*, 4291−4294.
(22) Cassar, L.; Foà, M.; Montanari, F.; Marinelli, G. P. Phase-transfer catalysis in the nickel-catalyzed cyanation of aryl halides. *J. Organomet. Chem.* **1979**, *173*, 335−339.
(23) Ahmad, M. S.; Zeng, B.; Qasim, R.; Zheng, D.; Zhang, Q.; Jin, Y.; Wang, Q.; Meguellati, K. Ni-Catalyzed Cyanation of (Hetero)aryl Halides with Acetonitrile as Cyano Source. *ACS Catal.* **2024**, *14*, 2350−2357.
(24) Ueda, Y.; Tsujimoto, N.; Yurino, T.; Tsurugi, H.; Mashima, K. Nickel-catalyzed cyanation of aryl halides and triflates using acetonitrile *via* C−CN bond cleavage assisted by 1,4-bis-(trimethylsilyl)-2,3,5,6-tetramethyl-1,4-dihydropyrazine. *Chem. Sci.* **2019**, *10*, 994−999.
(25) Chen, H.; Sun, S.; Liu, Y. A.; Liao, X. Nickel-Catalyzed Cyanation of Aryl Halides and Hydrocyanation of Alkynes via C−CN Bond Cleavage and Cyano Transfer. *ACS Catal.* **2020**, *10*, 1397−1405.
(26) Duran-Camacho, G.; Hethcox, J. C. Nickel-Catalyzed Cyanation of (Hetero)aryl Bromides Using DABAL-Me(3) as a Soluble Reductant. *Org. Lett.* **2022**, *24*, 8397−8400.
(27) Ma, J.; Liu, H.; He, X.; Chen, Z.; Liu, Y.; Hou, C.; Sun, Z.; Chu, W. Ni-Catalyzed C−H Cyanation of (Hetero)arenes with 2-Cyanoisothiazolidine 1,1-Dioxide as a Cyanation Reagent. *Org. Lett.* **2021**, *23*, 2868−2872.
(28) Yan, Y.; Wang, P.; Wang, Y.; Dong, J.; Li, G.; Wang, C.; Xue, D. Light-Triggered, Ni-Catalyzed Cyanation of Aryl Triflates with 1,4-Dicyanobenzene as the CN Source. *Org. Lett.* **2024**, *26*, 1370−1375.
(29) Mills, L. R.; Graham, J. M.; Patel, P.; Rousseaux, S. A. L. Ni-Catalyzed Reductive Cyanation of Aryl Halides and Phenol Derivatives via Transnitrilation. *J. Am. Chem. Soc.* **2019**, *141*, 19257−19262.
(30) Hethcox, J. C.; Sifri, R. J. Air-Tolerant Nickel-Catalyzed Cyanation of (Hetero)aryl Halides Enabled by Polymethylhydrosiloxane, a Green Reductant. *J. Org. Chem.* **2022**, *87*, 4951−4954.
(31) Cassar, L. A new nickel-catalyzed synthesis of aromatic nitriles. *J. Organomet. Chem.* **1973**, *54*, C57−C58.
(32) Yan, G.; Zhang, Y.; Wang, J. Recent Advances in the Synthesis of Aryl Nitrile Compounds. *RSC Adv.* **2017**, *359*, 4068−4105.
(33) Neetha, M.; Afsina, C. M. A.; Aneeja, T.; Anilkumar, G. Recent advances and prospects in the palladium-catalyzed cyanation of aryl halides. *RSC Adv.* **2020**, *10*, 33683−33699.
(34) Hartung, J.; Wang, X.; Song, Z. J.; Chen, Y.; Guo, F.; Li, Z. Pd-Catalyzed Cyanation of a Bromoaryl Carboxylate En Route to Etrumadenant: Robust Process with Low Catalyst Loading Enabled by Preactivation. *Org. Process Res. Dev.* **2022**, *26*, 3161−3165.
(35) Nauth, A. M.; Opatz, T. Non-toxic cyanide sources and cyanating agents. *Org. Bio. Chem.* **2019**, *17*, 11−23.
(36) Richardson, J.; Mutton, S. P. Improved Substrate Scope in the Potassium Hexacyanoferrate(II)-Based Cyanation for the Synthesis of Benzonitriles and Their Heterocyclic Analogues. *J. Org. Chem.* **2018**, *83*, 4922−4931.
(37) Yeung, P. Y.; Tsang, C. P.; Kwong, F. Y. Efficient cyanation of aryl bromides with K4[Fe(CN)6] catalyzed by a palladium-indolylphosphine complex. *Tetrahedron Lett.* **2011**, *52*, 7038−7041.
(38) Senecal, T. D.; Shu, W.; Buchwald, S. L. A General, Practical Palladium-Catalyzed Cyanation of (Hetero)Aryl Chlorides and Bromides. *Angew. Chem., Int. Ed.* **2013**, *125*, 10219−10223.
(39) Schareina, T.; Zapf, A.; Beller, M. Potassium hexacyanoferrate-(II)—a new cyanating agent for the palladium-catalyzed cyanation of aryl halides. *Chem. Commun.* **2004**, 1388−1389.
(40) Schareina, T.; Zapf, A.; Beller, M. Improving palladium-catalyzed cyanation of aryl halides: development of a state-of-the-art methodology using potassium hexacyanoferrate(II) as cyanating agent. *J. Organomet. Chem.* **2004**, *689*, 4576−4583.
(41) Frantz, D. E.; Albaneze-Walker, J.; Wilson, N. A.; Palmer, W. M.; Ganley, J. M.; Coombs, J. R.; Levorse, M. S. Palladium-Catalyzed Cyanations of Aryl Imidazolylsulfonates with K4[Fe(CN)6]: A Pragmatic Approach to Benzonitriles from Phenols. *Synthesis* **2024**, *56*, 2655−2662.
(42) Mennen, S. M.; Alhambra, C.; Allen, C. L.; Barberis, M.; Berritt, S.; Brandt, T. A.; Campbell, A. D.; Castañón, J.; Cherney, A. H.; Christensen, M.; et al. The Evolution of High-Throughput Experimentation in Pharmaceutical Development and Perspectives on the Future. *Org. Process Res. Dev.* **2019**, *23*, 1213−1242.
(43) Krska, S. W.; DiRocco, D. A.; Dreher, S. D.; Shevlin, M. The Evolution of Chemical High-Throughput Experimentation To Address Challenging Problems in Pharmaceutical Synthesis. *Acc. Chem. Res.* **2017**, *50*, 2976−2985.
(44) Cassar, L.; Ferrara, S.; Foá, M. Nickel-Catalyzed Cyanation of Aryl Halides; American Chemical Society: Washington DC, 1974, *Advances in Chemistry Series*, Vol. *132*, pp. 252−273
(45) Chen, C.; Yang, L.-M. Nickel(II)−aryl complexes as catalysts for the Suzuki cross-coupling reaction of chloroarenes and arylboronic acids. *Tetrahedron Lett.* **2007**, *48*, 2427−2430.
(46) Wisniewski, S. R.; Stevens, J. M.; Yu, M.; Fraunhoffer, K. J.; Romero, E. O.; Savage, S. A. Utilizing Native Directing Groups: Synthesis of a Selective I(Kur) Inhibitor, BMS-919373, via a Regioselective C-H Arylation. *J. Org. Chem.* **2019**, *84*, 4704−4714.
(47) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J. CHEM21 selection guide of classical- and less classical-solvents. *Green Chem.* **2016**, *18*, 288−296.

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