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General and Mild Nickel-Catalyzed Cyanation of Aryl/Heteroaryl Chlorides with $Zn(CN)_2$: Key Roles of DMAP

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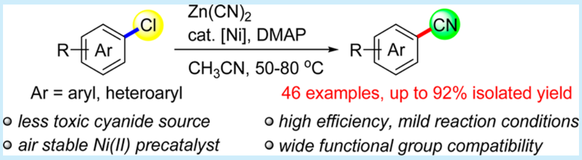
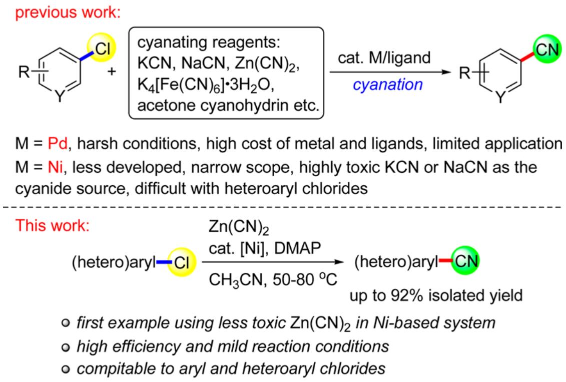
Supporting Information



ABSTRACT: A new and general nickel-catalyzed cyanation of hetero(aryl) chlorides using less toxic $Zn(CN)_2$ as the cyanide source has been developed. The reaction relies on the use of inexpensive $NiCl_2{\cdot}6H_2O$/dppf/Zn as the catalytic system and DMAP as the additive, allowing the cyanation to occur under mild reaction conditions (50−80 °C) with wide functional group tolerance. DMAP was found to be crucial for successful transformation, and the reaction likely proceeds via a Ni(0)/Ni(II) catalysis based on mechanistic studies. The method was also successfully extended to aryl bromides and aryl iodides.

Aromatic nitriles are common structural motifs found in organic materials, natural products, pharmaceuticals, and agrochemicals.[1] They also serve as versatile building blocks for the synthesis of heterocycles, as well as precursors for amides, amines, carboxylic acids, aldehydes, ketones, and alcohols.[2] The classical methods for preparing aryl nitriles involve diazotization of anilines followed by the Sandmeyer reaction,[3] and the Rosenmund−von Braun reaction where a stoichiometric amount of copper(I) cyanide is heated with an aryl iodide at high temperatures (≥150 °C).[4] All these reactions occur either under harsh reaction conditions and/or with limited scope. Transition-metal-catalyzed cyanation of aryl halides represents one of the most promising methods for the synthesis of aryl nitriles. Extensive research has been devoted to Pd-catalyzed cyanation of aryl halides, and remarkable improvements in terms of efficiency and practicality have been achieved in this field over the past 30 years.[1] Despite much progress, Pd-catalyzed cyanation of aryl chlorides,[5] the least expensive and the most widely available aryl halides, still remains as a formidable task. The known methods generally require high reaction temperatures (120−160 °C),[5d,e,g−i] and only a few of them are capable to catalyze the cyanation of nonactivated aryl chlorides. Recently, Pd complexes of electron-rich, bulky phosphine ligands such as Buchwald biaryl ligand (binaphthyl)P(t-Bu)$_2$[5f] or indole-based phosphine ligand CM-phos[5c] were found to promote the cyanation of aryl chlorides under milder reaction conditions. Nevertheless, the high cost of Pd metal coupled with the ancillary ligands led chemists to consider the first-row metal complex for such reactions.[6] In this context, nickel-based catalysts are highly attractive not only due to their low cost but also because of their high reactivity toward the activation of relatively inert substrates such as aryl chlorides and sulfonates. However, nickel-catalyzed cyanation reactions have far less been developed. In 1973, Cassar reported the first nickel-catalyzed cyanation of aryl halides with NaCN in EtOH,[7] since then, only very limited reports are precedent.[8] To date, most Ni-catalyzed cyanation reactions use highly toxic KCN or NaCN as the cyanide source with certain drawbacks, such as limited substrate scope,[8] poor reproducibility,[9] with carcinogenic HMPA as the solvent,[8b,d,e] under microwave irradiation at high reaction temperatures,[8c] etc. In addition, the cyanation of heteroaryl chlorides remains problematic and examples are quite rare.[8d] These situations prompted us to explore a mild, robust, and efficient Ni-based catalytic system for cyanation reactions, especially using less toxic cyanating agents. In this letter, we report the first example of Ni-catalyzed cyanation of aromatic chlorides with $Zn(CN)_2$. The reaction proceeds at moderate temperatures with air-stable and inexpensive nickel(II) salts as the precatalyst, allowing the cyanation of aryl and heteroaryl chlorides with wide functional group compatibility (Scheme 1). DMAP was found to be crucial for the reaction efficiency, and the reaction likely proceeds via a Ni(0)/Ni(II) catalysis based on mechanistic studies. The method was also successfully extended to aryl bromides and aryl iodides.

Scheme 1. Transition-Metal-Catalyzed Cyanation of Aryl/Heteroaryl Chlorides



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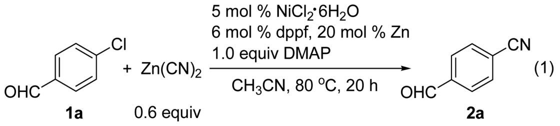
The challenge in Pd- or Ni-catalyzed cyanations is to avoid catalyst poisoning. The use of zinc cyanide has been widely spread in Pd-catalyzed cyanation reactions since it is significantly less toxic compared to a sodium or potassium cyanide source.[5a,f,i] It also exhibits low solubility in most organic solvents, which is beneficial for maintaining a low cyanide concentration and preventing catalyst deactivation. We initially investigated the nickel-catalyzed reactions of 4-chlorobenzaldehyde **1a** with $Zn(CN)_2$. However, either no reaction or small amounts of the desired nitrile was observed in most of the experiments, possibly due to the poor solubility of $Zn(CN)_2$. After tremendous effort in the optimization studies, including the effects of the nickel source, reducing agents, base, additives, reaction temperature, and solvents,[10] we found that the additive 4-(dimethylamino)pyridine (DMAP) played key roles in the effective transformation. Thus, in the presence of 1.0 equiv of DMAP, the desired 4-formylbenzonitrile **2a** could be obtained in 89% yield catalyzed by 5 mol % $NiCl_2·6H_2O$, 6 mol % dppf, and 20 mol % activated zinc flakes in CH_3CN at 80 °C (Table 1, entry 1). Interestingly, no cyanide ion-induced benzoin condensation was observed, indicating that the current process is mild and selective. Without DMAP, only 12% of **2a** was obtained (entry 2). In the absence of dppf, only a trace of **2a** was observed (entry 3). NiI_2 also displayed efficient catalytic activity, while $Ni(acac)_2$ failed to give the desired product (entries 4−5). The effects of ligands on the reaction course were also examined (entries 6−9), among them, a bidentate ligand Xantphos with a large bite angle ($\beta = 111°$) showed comparable activity with that of dppf. Notably, a monodentate ligand PPh_3, which has been used in Ni-catalyzed cyanation of aryl halides with NaCN or KCN,[7,8b,d−g] was ineffective in this reaction (entry 7). As the bases are often used to promote cyanide dissociation,[5b] different bases were examined. It was found that K_2CO_3 could also be used for effective reactions to give **2a** in moderate yield (entry 11). The results suggest that DMAP may have a similar impact on cyanide ion dissociation. Lowering the reaction temperature to 60 °C led to a marked decrease in the yield of **2a** (entry 12). A slightly higher yield of 92% was achieved by using 0.8 equiv of $Zn(CN)_2$ (entry 14). Interestingly, $Ni(COD)_2$ also showed excellent catalytic reactivity (entry 15). Control experiments run without either nickel or zinc catalyst resulted in no formation of **2a**.

Table 1. Optimization of the Reaction Conditions[a]



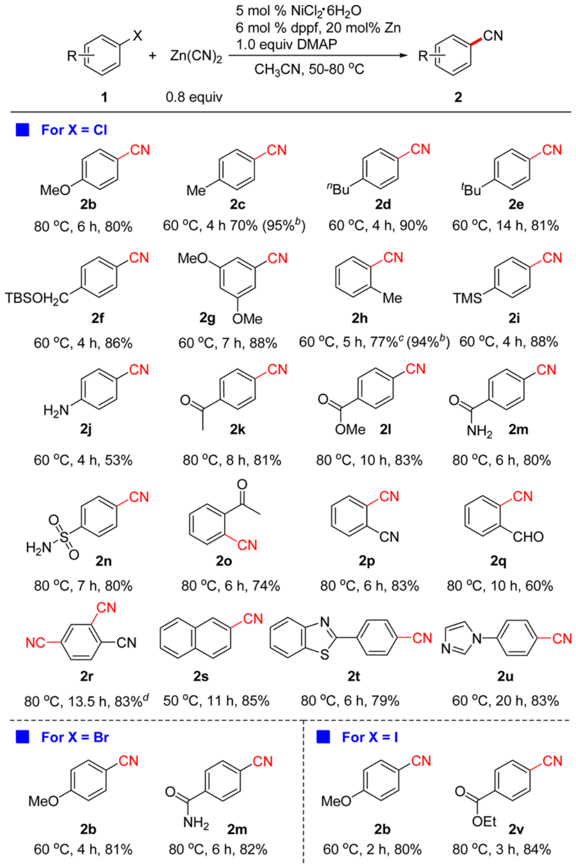
1a **2a** (1)

entry	deviation from conditions shown in eq 1	yield (%)[b]
1	none	89
2	no DMAP	12 (75)
3	no dppf	2 (86)
4	NiI_2 instead of $NiCl_2·6H_2O$	81
5	$Ni(acac)_2$ instead of $NiCl_2·6H_2O$	– (78)
6	10 mol % $PMePh_2$ instead of 6 mol % dppf	67
7	10 mol % PPh_3 instead of 6 mol % dppf	10 (61)
8	dppb instead of dppf	45
9	Xantphos instead of dppf	84
10	DMF instead of CH_3CN	74
11	K_2CO_3 instead of DMAP	64
12	60 °C instead of 80 °C	22
13	50 mol % DMAP was used	51
14	**0.8 equiv of $Zn(CN)_2$ was used**	**92**
15	$Ni(COD)_2$ instead of $NiCl_2·6H_2O$, and without Zn	90[c]

[a]All reactions were carried out on 1.0 mmol scale in a sealed Schlenk tube. [b]Isolated yields. Yields of recovered **1a** are in parentheses. [c]0.8 equiv of $Zn(CN)_2$ was used.

We chose the reaction conditions shown in Table 1, entry 14 as the standard catalytic system for further development. A series of aryl chlorides were first used as the substrates to test the generality of the reaction (Scheme 2). During this process, we found that the reaction was influenced significantly by the nature of aryl substituents. For example, deactivated aryl chlorides such as 1-chloro-4-methoxybenzene underwent cyanation smoothly at 80 °C to afford **2b** in 80% yield. However, when 1-chloro-4-methylbenzene was used as the substrate, only 37% nitrile **2c** was obtained at 80 °C, and the side products of 1-*p*-tolylethanone derived from the addition of aryl nickel intermediate to CH_3CN (4%) as well as homocoupled biaryl (1%) were also observed. It appeared likely that, at higher reaction temperature, the side reactions became competitive with the desired transformation in some electron-rich aryl chlorides, thereby deactivating the nickel catalyst. This led us to consider performing the reaction under milder reaction conditions. Gratifyingly, a high yield of the desired aryl nitrile **2c** could be achieved by lowering the reaction temperature to 60 °C. This result contrasted with the reaction of activated aryl chlorides such as 4-chlorobenzaldehyde, in which a

Scheme 2. Scope of Ni-Catalyzed Cyanation of Aryl Halides[a]



[a]Isolated yields. All reactions were carried out on 1 mmol scale in CH_3CN (5 mL) in a sealed Schlenk tube. [b]NMR yields. [c]10 mol % $NiCl_2·6H_2O$, 12 mol % dppf, 40 mol % Zn and CH_3CN (10 mL) were used. [d]2,4-Dichlorobenzonitrile was used as the substrate. 10 mol % $NiCl_2·6H_2O$, 12 mol % dppf, 40 mol % Zn, 2.0 equiv of DMAP, 1.6 equiv of $Zn(CN)_2$, and CH_3CN (10 mL) were used.

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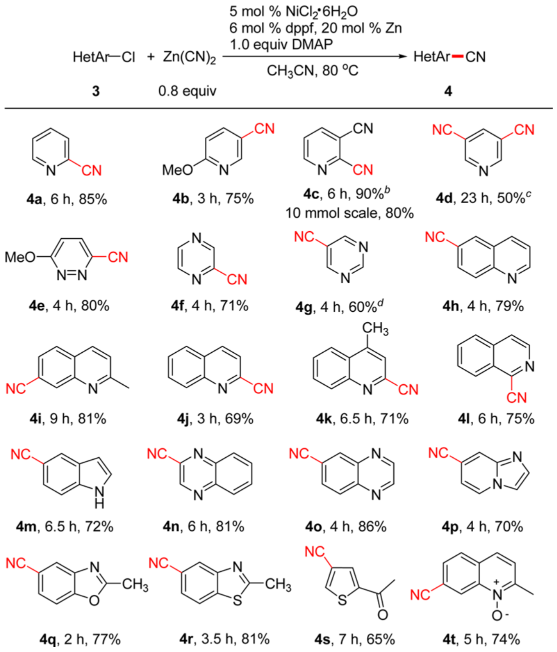
poor product yield was observed at 60 °C (Table 1, entry 12). These observations also indicated that oxidative addition of the Ar−Cl bond may not be the rate-determining step since activated aryl chlorides are typically more reactive toward oxidative addition.[11] The differences in reactivity of these substrates might be attributed to the effectiveness of the subsequent transmetalation/reductive elimination to form Ar−CN with electron-donating aryl groups, thus allowing the cross-coupling of electron-rich aryl chlorides to proceed at a lower reaction temperature. Cyanation of 1-chloro-4-methoxybenzene at 60 °C was then examined; as expected, a good product yield (**2b**, 6 h, 88%) could also be achieved at this temperature. This is in line with our assumption. A recent study by Hartwig et al. revealed that an arylpalladium cyanide complex containing an electron-donating aryl group underwent reductive elimination much faster than that containing an electron-withdrawing aryl group.[12] Similar electronic effects may also be involved in our system. Similarly, *n*-Bu, *t*-Bu, TBSOCH$_2$, and 3,5-di(MeO)-substituted aryl chlorides gave the corresponding nitriles **2d**−**2g** in high yields at 60 °C. In the case of sterically hindered 1-chloro-2-methylbenzene, the reaction appeared to work well only by doubling the amounts of $NiCl_2 \cdot 6H_2O$, dppf, and Zn under dilute conditions (**2h**). Trimethylsilyl-substituted aryl chloride was cyanated successfully (**2i**). The highly challenging 4-chloroaniline with a free amino group could also be cyanated (**2j**). A series of electron-withdrawing group-substituted aryl chlorides underwent the cyanation efficiently (**2k**−**2q**). Common functional groups such as keto, ester, amide, sulfonamide, nitrile, aldehydo groups were well tolerated under the standard reaction conditions. Especially, aryl chlorides with a hindered *ortho*-substituent were well suited (**2o**−**2q**). Double cyanation of 2,4-dichlorobenzonitrile could also be achieved (**2r**). Interestingly, efficient cyanation of 2-chloronaphthalene could occur at a lower temperature of 50 °C (**2s**). Aryl chlorides featuring a heterocycle ring at the *para*-position were well accommodated (**2t** and **2u**). In addition to aryl chlorides, aryl bromides and iodides also coupled well with Zn(CN)$_2$, and both electron-donating and -withdrawing substituents on the aryl rings were tolerated.

Given the prevalence and wide utility of heterocycles in pharmaceuticals, we then turned our attention to exploring the cyanation of heteroaryl chlorides. We were pleased to see that the current nickel-based catalytic system is highly efficient and general for cyanation of a wide variety of heteroaryl chlorides (Scheme 3). For example, reactions of 2-chloropyridine (**4a**) or pyridines bearing MeO (**4b**) or cyano (**4c**) functionalities with Zn(CN)$_2$ gave the desired nitriles in 75−90% yields. Both chlorides on 3,5-dichloropyridine could be cyanated (**4d**). Heterocycles with two nitrogen atoms such as pyridazine (**4e**), pyrazine (**4f**), and pyrimidine (**4g**) turned out to be also perfect substrates. Chloro quinolines or isoquinoline reacted efficiently (**4h**−**4l**). Unprotected indole bearing a free *N*-H group was well tolerated (**4m**). Quinoxaline (**4n** and **4o**), imidazo[1,2-*a*]-pyridine (**4p**), and benzo[*d*]oxazole (**4q**) were also suitable. Sulfur-containing heterocycles such as benzo[*d*]thiazole (**4r**) and thiophene (**4s**) worked efficiently, indicating that the catalyst did not become deactivated. Interestingly, *N*-oxides such as 7-chloro-2-methylquinoline 1-oxide could also be cyanated (**4t**).

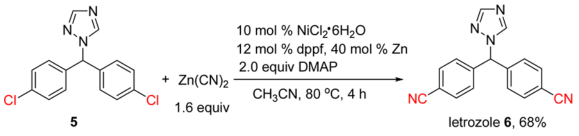
The practicality of this method was demonstrated by a gram-scale study (**4c**, 80% yield, see Scheme 3). In addition, Letrozole, a nonsteroidal aromatase inhibitor used for the treatment of hormonally responsive breast cancer,[13] was prepared in good yield by this Ni-catalyzed cyanation (Scheme 4). Thus, the present method can be used for the late-stage functionalization of medicinally relevant compounds.

Scheme 3. Scope of Ni-Catalyzed Cyanation of Heteroaryl Chlorides[a]



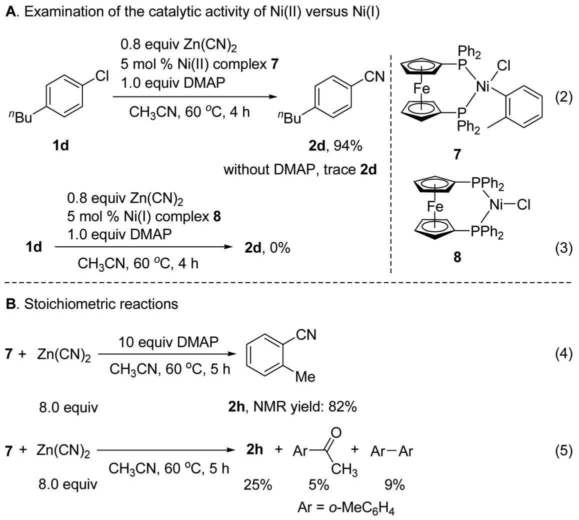
[a]Isolated yields. All reactions were carried out on 1 mmol scale in CH$_3$CN (5 mL) in a sealed Schlenk tube. [b]2-Chloronicotinonitrile was used as the substrate. [c]10 mol % $NiCl_2 \cdot 6H_2O$, 12 mol % dppf, 40 mol % Zn, 2.0 equiv DMAP, 1.6 equiv Zn(CN)$_2$ and CH$_3$CN (10 mL) were used. [d]CH$_3$CN (10 mL) was used.

Scheme 4. Synthesis of Letrozole



For nickel-catalyzed cross-coupling reactions, both Ni(0)/Ni(II) and Ni(I)/Ni(III) redox cycles[14] have been proposed to be possible reaction pathways. To understand the mechanism, the complexes of air stable [(dppf)Ni(II)(Cl)(*o*-MeC$_6$H$_4$)] **7**[15] and [(dppf)Ni(I)Cl] **8**[14a] were prepared. It was found that Ni(II) complex **7** showed excellent catalytic activity to form **2d** in 94% yield, whereas Ni(I) complex **8** failed to catalyze the reaction (Scheme 5, eqs 2 and 3). These results strongly support the Ni(0)/Ni(II) reaction pathway. It should be noted that, in the absence of DMAP, only a trace of **2d** was observed. The results emphasized the crucial role of DMAP. The stoichiometric reactions of Ni(II) complex **7** with Zn(CN)$_2$ were also investigated. The reaction proceeded efficiently in the presence of 10 equiv of DMAP to give **2h** in 82% yield (Scheme 5, eq 4). However, in the absence of DMAP, only 25% of **2h** was obtained, together with small amounts of side products (Scheme 5, eq 5). The results imply that Ni(II) complex **7** serves as the reaction intermediate, and DMAP may effect the activation of Zn(CN)$_2$ through coordination to form a DMAP−Zn(CN)$_2$ adduct and facilitating the transmetalation step.[16] To test whether the DMAP could be a coligand,[17] the catalytic activity of $NiCl_2(DMAP)_4 \cdot 2H_2O$ was evaluated.[18] Cyanation of **1d** catalyzed by this complex

Scheme 5. (A) Examination of the Catalytic Activity of Ni(II) versus Ni(I); (B) Stoichiometric Reactions



under the standard reaction conditions afforded a good yield of nitrile **2d**. These results imply that DMAP may also act as a coligand.

In summary, we have developed the first efficient and general Ni-catalyzed aromatic cyanation using less toxic $Zn(CN)_2$ as the cyanide source. The use of challenging hetero(aryl) chlorides as the substrates, air-stable and low-cost nickel salts as the precatalyst, normal phosphine as the ligand in conjunction with wide functional group tolerance, and mild reaction conditions makes this approach one of the most attractive and practical methods. Preliminary mechanistic studies indicate that a diphosphine-ligated arylnickel(II) chloride complex not only serves as the reaction intermediate but also displays high catalytic activity for this transformation. Further investigations on the detailed reaction mechanism and application of this chemistry are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00732.

Experimental details and spectroscopic data; X-ray crystallography of $NiCl_2(DMAP)_4 \cdot 2H_2O$ (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews, see: (a) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049. (b) Jones, L. H.; Summerhill, N. W.; Swain, N. A.; Mills, J. E. *MedChemComm* **2010**, *1*, 309.

(2) Larcok, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed.; VCH: New York, U.S.A, 1999.

(3) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2650.

(4) (a) Rosenmund, K. W.; Struck, E. *Ber. Dtsch. Chem. Ges. B* **1919**, *52*, 1749. (b) von Braun, J. V.; Manz, G. *Liebigs Ann. Chem.* **1931**, *488*, 111.

(5) For selected papers on palladium-catalyzed cyanation of aryl chlorides, see: (a) Cohen, D. T.; Buchwald, S. L. *Org. Lett.* **2015**, *17*, 202. (b) Senecal, T. D.; Shu, W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 10035. (c) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 648. (d) Schareina, T.; Jackstell, R.; Schulz, T.; Zapf, A.; Cotte, A.; Gotta, M.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 643. (e) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 1087. (f) Littke, A.; Soumeillant, M.; Kaltenbach, R. F., III; Cherney, R. J.; Tarby, C. M.; Kiau, S. *Org. Lett.* **2007**, *9*, 1711. (g) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem. - Eur. J.* **2003**, *9*, 1828. (h) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661. (i) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271.

(6) Copper was known to catalyze cyanation reactions; however, the scope has been limited to aryl iodides and bromides. For a review, see: Wen, Q.; Jin, J.; Zhang, L.; Luo, Y.; Lu, P.; Wang, Y. *Tetrahedron Lett.* **2014**, *55*, 1271.

(7) Cassar, L. *J. Organomet. Chem.* **1973**, *54*, C57.

(8) For nickel-catalyzed cyanation of aryl halides, see: (a) Moghaddam, F. M.; Tavakoli, G.; Rezvani, H. R. *Appl. Organomet. Chem.* **2014**, *28*, 750. (b) Sakakibara, Y.; Sasaki, K.; Okuda, F.; Hokimoto, A.; Ueda, T.; Sakai, M.; Takagi, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1013. (c) Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2003**, *68*, 9122. (d) Sakakibara, Y.; Ido, Y.; Sasaki, K.; Sakai, M.; Uchino, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2776. (e) Sakakibara, Y.; Okuda, F.; Shimobayashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1985. (f) Cassar, L.; Foà, M.; Montanari, F.; Marinelli, G. P. *J. Organomet. Chem.* **1979**, *173*, 335. (g) Cassar, L.; Ferrara, S.; Foá, M. *Homogeneous Catalysis II*", Adv. Chem. Ser. 132. *Adv. Chem. Ser.* **1974**, *132*, 252. For nickel-catalyzed cyanation of mesylates, see: (h) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895. For nickel-catalyzed cyanation of aryl triflates, see: (i) Chambers, M. R. I.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1365.

(9) See ref 12 in ref 8e.

(10) For optimization details, see the Supporting Information.

(11) (a) Foà, M.; Cassar, L. *J. Chem. Soc., Dalton Trans.* **1975**, 2572. (b) Green, R. A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2015**, *54*, 3768.

(12) Klinkenberg, J. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5758.

(13) Bhatnagar, A. S. *Breast Cancer Res. Treat.* **2007**, *105*, 7.

(14) For recent reports involving Ni(0)/Ni(II) catalysis, see: (a) Yin, G.; Kalvet, I.; Englert, U.; Schoenebeck, F. *J. Am. Chem. Soc.* **2015**, *137*, 4164. (b) Ge, S.; Green, R. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 1617. For recent reports involving Ni(I)/Ni(III) catalysis, see: (c) Jones, G. D.; McFarland, C.; Anderson, T. J.; Vicic, D. A. *Chem. Commun.* **2005**, 4211. (d) Guard, L. M.; Beromi, M. M.; Brudvig, G. W.; Hazari, N.; Vinyard, D. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 13352.

(15) (a) Standley, E. A.; Smith, S. J.; Müller, P.; Jamison, T. F. *Organometallics* **2014**, *33*, 2012. (b) Park, N. H.; Teverovskiy, G.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 220.

(16) Very recently, Ley et al. found that boronic esters could be activated by DMAP; see: Lima, F.; Kabeshov, M. A.; Tran, D. N.; Battilocchio, C.; Sedelmeier, J.; Sedelmeier, G.; Schenkel, B.; Ley, S. V. *Angew. Chem., Int. Ed.* **2016**, *55*, 14085.

(17) (a) Xiao, Y.-L.; Min, Q.-Q.; Xu, C.; Wang, R.-W.; Zhang, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 5837. (b) Wang, X.; Wang, S.; Xue, W.; Gong, H. *J. Am. Chem. Soc.* **2015**, *137*, 11562.

(18) See the Supporting Information for details.