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Nickel-Catalyzed Cyanation of Unactivated Alkyl Chlorides or Bromides with $Zn(CN)_2$

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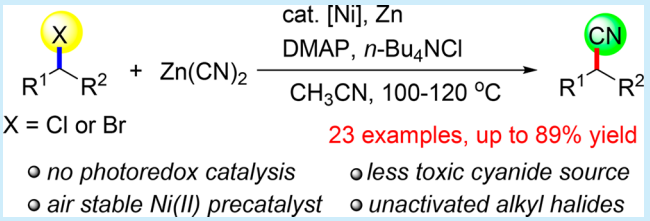
Supporting Information

ABSTRACT: A nickel-catalyzed cyanation of unactivated secondary alkyl chlorides or bromides using less toxic $Zn(CN)_2$ as the cyanide source has been developed. The reaction features the use of air-stable and inexpensive $NiCl_2 \cdot 6H_2O$ or $Ni(acac)_2$ as the precatalysts and offers an efficient synthesis of a broad range of alkyl nitriles. Cyanation of primary alkyl chlorides or bromides was also achieved by reaction with $Zn(CN)_2$ in the presence of n-Bu_4NCl without the need of nickel catalyst.



Nitriles are one of the most important building blocks for modern organic synthesis. For example, they can serve as precursors for amides, amines, carboxylic acids, aldehydes, ketones, and alcohols, etc.[1] Nitrile functionalities are also frequently found in natural products, pharmaceuticals, and agrochemicals[2] (Figure 1). Alkyl nitriles have been prepared

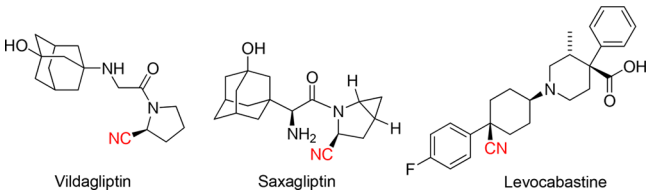


Figure 1. Representative bioactive cyano-containing compounds.

classically by nucleophilic substitutions of alkyl halides or pseudoalkyl halides with cyanide sources. However, in fact, the studies on the cyanation of secondary alkyl halides are quite rare, and the reported methods usually suffer from harsh reaction conditions (high temperature, long reaction time) and limited substrate scope.[3] Besides, in most of the cases, extremely poisonous NaCN or KCN was employed as the cyanating agent. Thus, the development of cyanation of alkyl halides using less toxic cyanating agents with high efficiency is highly desired. In this regard, transition-metal-catalyzed cross-coupling of alkyl halides with cyanide sources would be one of the most powerful and promising methods for the synthesis of alkyl nitriles. However, most research has focused on the metal-catalyzed cyanation of aryl halides,[4] while the cyanation of alkyl halides to alkyl nitriles is considerably less developed. This is possibly due to a number of challenges when alkyl halides, especially alkyl chlorides, are used as the coupling partners, such as a low tendency of oxidative addition, β-hydride elimination of alkylmetal intermediates, proto-demetalation, elimination of HX to form alkene byproducts, etc.[5] To the best of our knowledge, transition-metal-catalyzed cyanation of alkyl halides has been limited mainly to benzyl chlorides.[6] In 2015, Fu and co-workers reported an excellent work of photoinduced and copper-catalyzed cyanation of unactivated alkyl halides with TBACN (tetrabutylammonium cyanide) (Scheme 1).[7] The method required special photochemical equipment and expensive cyanating agent. Inspired by our recent studies on nickel-catalyzed cyanation of aryl/heteroaryl chlorides,[4k] we show here a mild, robust, and efficient Ni-based catalytic system for cyanation of alkyl halides using inexpensive and relatively less toxic $Zn(CN)_2$ (intra-

Scheme 1. Transition-Metal-Catalyzed Cyanation of Unactivated Alkyl Halides

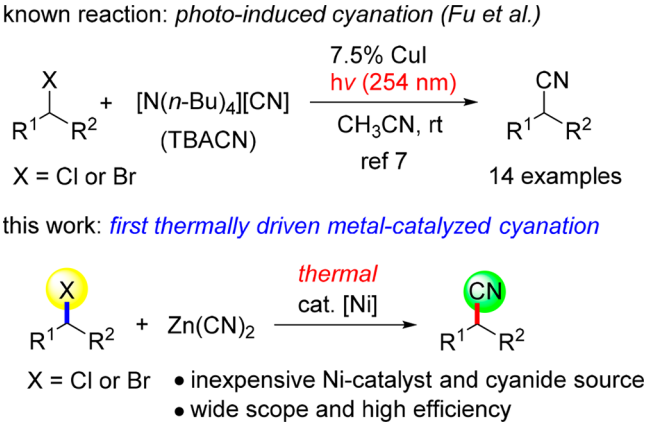


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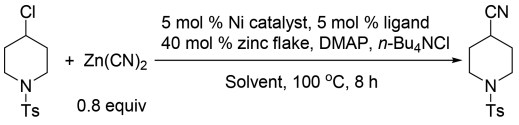
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand	DMAP (equiv)	*n*-Bu_4NCl (equiv)	solvent	yield[b] (%)
1	**$NiCl_2·6H_2O$**	**Xantphos**	**2.0**	**0.5**	**CH_3CN**	**86, 87**[c]
2	$NiCl_2·6H_2O$	Xantphos		0.5	CH_3CN	2 (97)
3	$NiCl_2·6H_2O$	Xantphos	2.0		CH_3CN	2 (98)
4	$NiCl_2·6H_2O$	Xantphos	1.5	0.5	CH_3CN	83 (6)
5	$NiCl_2·6H_2O$	Xantphos	2.0	0.25	CH_3CN	19 (78)
6	$NiCl_2$(DME)	Xantphos	2.0	0.5	CH_3CN	79
7	$Ni(acac)_2$	Xantphos	2.0	0.5	CH_3CN	77
8	$NiCl_2·6H_2O$	NiXantphos	2.0	0.5	CH_3CN	47 (40)
9	$NiCl_2·6H_2O$	dppf	2.0	0.5	CH_3CN	15 (76)
10	$NiCl_2·6H_2O$	bipyridine	2.0	0.5	CH_3CN	– (87)
11	$NiCl_2·6H_2O$	PCy_3[d]	2.0	0.5	CH_3CN	– (97)
12	$NiCl_2·6H_2O$	$PMePh_2$[d]	2.0	0.5	CH_3CN	– (92)
13[e]	$NiCl_2·6H_2O$	Xantphos	2.0	0.5	CH_3CN	– (99)
14[f]	$NiCl_2·6H_2O$	Xantphos	2.0	0.5	CH_3CN	85 (2)
15[g]	$NiCl_2·6H_2O$	Xantphos	2.0	0.5	CH_3CN	85
16	$NiCl_2·6H_2O$	Xantphos	2.0	0.5	DMF	78
17	$NiCl_2·6H_2O$	Xantphos	2.0	0.5	THF	4 (94)
18	$NiCl_2·6H_2O$	Xantphos	2.0	0.5	toluene	– (92)
19		Xantphos	2.0	0.5	CH_3CN	– (96)
20	$NiCl_2·6H_2O$		2.0	0.5	CH_3CN	– (98)

[a]Conditions: **1a** (0.5 mmol), $Zn(CN)_2$ (0.4 mmol), Ni catalyst (0.025 mmol), ligand (0.025 mmol), zinc flakes (0.2 mmol), DMAP (1.0 mmol), *n*-Bu_4NCl (0.25 mmol) in solvent (1 mL) at 100 °C for 8 h. [b]Determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. The yields of recovered **1a** are shown in parentheses. [c]Isolated yield. [d]10 mol % of ligand was used. [e]Mn (0.2 mmol) was used. [f]4-Aminopyridine was used. [g]*n*-Bu_4NBr was used.

peritoneal, LD_{50} = 100 mg kg^{-1},[8a] compared with NaCN, KCN,[8b] intraperitoneal, LD_{50} = 4.72−5.55 mg kg^{-1}) as the cyanating agent without the need for light. It was noted that $Zn(CN)_2$ has not been used as the coupling partner for the cyanation of alkyl halides. The method exhibits a broad substrate scope and can be successfully extended to the efficient cyanation of alkyl bromides. The reaction also represents the first example of thermally driven metal-catalyzed cyanation of unactivated alkyl halides.

Initially, the nickel-catalyzed cyanation of a secondary alkyl chloride 4-chloro-1-tosylpiperidine **1a** was investigated. Inspired by our previous results, $Zn(CN)_2$ was chosen for the alkyl coupling partner due to its low concentration of cyanide ions in organic solvents, which is beneficial for mitigating catalyst poisoning, and facile transmetalation of cyanide to the arylnickel complex/reductive elimination to form Ar−CN in the case of cyanation of aryl halides.[4k] As expected, under the previously developed reaction conditions for the cyanation of aryl halides ($NiCl_2·6H_2O$/dppf/Zn/DMAP/CH_3CN/80 °C),[4k] trace desired nitrile **2a** was observed (the starting material was recovered in 96% yield). A thorough study of the nickel catalyst, ligands, reductants, additives, solvents, and substrate concentration, etc., was then performed, and the detailed results are shown in the Supporting Information. Finally, we found that the additives played important roles for the reaction. The optimization conditions were briefly summarized in Table 1. We were pleased to find that the desired alkyl nitrile **2a** could be formed smoothly in 86% yield at 100 °C in CH_3CN catalyzed by an inexpensive Ni(II) source ($NiCl_2·6H_2O$) and the commonly used ligand of Xantphos with a large bite angle (β = 111°) in the presence of DMAP and *n*-Bu_4NCl as the additives (Table 1, entry 1). Both of DMAP and *n*-Bu_4NCl were found to be the essential additives for the successful transformation (entries 2 and 3), and trace desired products were observed in the absence of the either additive. The amount of *n*-Bu_4NCl was also crucial for this reaction, since decreasing the amount of this additive resulted in significant erosion in yield (entry 5). Both DMAP and *n*-Bu_4NCl (vide infra) may have an effect on the activation of $Zn(CN)_2$ and promote the cyanide anion dissociation. DMAP may also act as a co-ligand during the reaction process.[4k] The catalytic activity of $NiCl_2$(DME) and $Ni(acac)_2$ was also investigated, which resulted in product yields of 77−79% (entries 6 and 7). Other bidentate ligands such as NiXantphos and dppf gave inferior yields, while the use of monodentate phosphine ligands led to no desired product (entries 8−12). Employing 4-aminopyridine or *n*-Bu_4NBr as the additive, the reaction could also take place effectively (entries 14 and 15). Changing the solvent from CH_3CN to DMF afforded **2a** in a lower yield of 78%, while the use of other solvents such as THF and toluene gave either a low yield or led to the recovery of the unreacted alkyl chloride (entries 16−18). It was noted that no desired reaction took place if either the nickel catalyst or a ligand was absent (entries 19 and 20). The results indicated that nickel catalysis is operative in this reaction process.

With the optimized reaction conditions in hand, we next investigated the substrate scope for the cyanation of alkyl halides. As shown in Scheme 2, the reaction proved to be quite general for a wide variety of unactivated secondary alkyl

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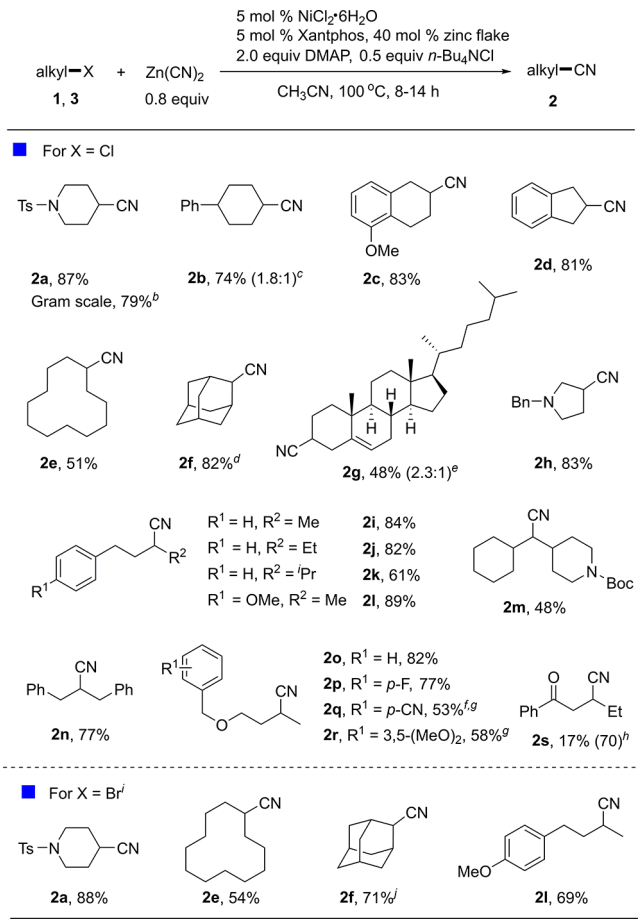
Scheme 2. Nickel-Catalyzed Cyanation of Unactivated Secondary Alkyl Halides[a]



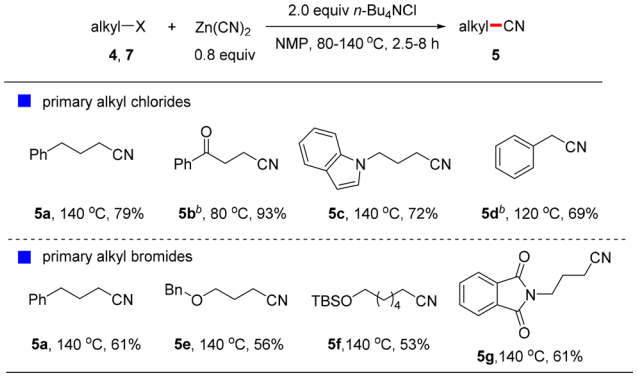
[a]Isolated yields. [Substrate] = 0.5 M. [b]Under refluxing (oil bath temperature: 130 °C). [c]((1S*,4S*)-4-Chlorocyclohexyl)benzene was used. $NiCl_2$(DME) and zinc power (100 mesh) were used instead of $NiCl_2·6H_2O$ and zinc flakes. [d]10 mol % of $Ni(acac)_2$, 10 mol % of Xantphos, 40 mol % of zinc flakes, 2.0 equiv of DMAP, 0.75 equiv of *n*-Bu_4NCl, 120 °C. [e]$NiCl_2$ was used instead of $NiCl_2·6H_2O$. 0.75 equiv of *n*-Bu_4NCl was used instead of 0.5 equiv of *n*-Bu_4NCl. [Substrate] = 0.25 M. [f]$Ni(acac)_2$ was used instead of $NiCl_2·6H_2O$. 90 °C, 12 h. [g][Substrate] = 1 M. [h]5 mol % of [(dppf)NiCl], 2.0 equiv of DMAP, 0.75 equiv of *n*-Bu_4NCl. [i]5 mol % $Ni(acac)_2$, 5 mol % of Xantphos, 2.0 equiv of DMAP, 40 mol % of zinc flakes, 80 °C, 12 h. [j]120 °C, 8 h.

chlorides, leading to the corresponding alkyl nitriles in generally good to high yields within a short reaction time. Cyclic substrates bearing six- or five-membered rings including benzene-fused ones coupled smoothly with $Zn(CN)_2$ (**2b–d**, 74–83% yields). It was noted that **2b** was obtained in only 46% yield under the standard conditions. However, replacing $NiCl_2·6H_2O$ by $NiCl_2$(DME) and using zinc powder as the reductant improved the yield of **2b** significantly. It was also noted that **2b** was obtained as a mixture of two diastereomers from a single diastereomer of **1b**. The results suggested that a radical pathway might be involved in the course of oxidative addition. Alkyl chlorides with a large-sized ring such as chlorocyclododecane worked also well (**2e**). Polycyclic alkyl chlorides such as 2-chloroadamantane gave only trace amounts of the desired nitrile **2f**. However, by switching the nickel catalyst from $NiCl_2·6H_2O$ to $Ni(acac)_2$ and increasing the amounts of both catalyst/ligand and *n*-Bu_4NCl, **2f** could be formed in 82% yield at 120 °C. When alkyl chloride derived from natural products such as **1g** was used as the substrate, the desired product **2g** was not observed, and most of the starting materials remained unchanged. To our delight, increasing the amount of *n*-Bu_4NCl to 0.75 equiv with use of $NiCl_2$ as the catalyst under dilute reaction conditions resulted in the formation of **2g** in 48% yield. Heteroatom-containing substrates such as *N*-benzyl-3-chloropyrrolidine were also compatible, leading to **2h** in 83% yield. Next, the cyanation of a series of acyclic alkyl chlorides was investigated. Linear substrates bearing methyl, ethyl, and even the more sterically demanding isopropyl substituents could also be satisfactorily cyanated, affording **2i–l** in 61–89% yields. Substrate **1m** bearing two-branched cyclic rings provided the desired **2m** in 48% yield, which could not be directly cyanated by TBACN under thermal conditions.[7] Other substrates such as (2-chloropropane-1,3-diyl)dibenzene bearing two aryl rings or ethers bearing various functional groups such as −F, −CN, or −3,5-$(MeO)_2$ on their phenyl rings were also suitable for this reaction (**2n–r**). When alkyl chloride **1s** bearing a ketone functionality was employed as the substrate, only 17% yield was obtained, along with the formation of various byproducts under the standard reaction conditions. After some trails, we were pleased to find that the desired nitrile could be formed in 70% yield catalyzed by a Ni(I) complex of [(dppf)Ni^ICl][9] in the presence of DMAP and *n*-Bu_4NCl.

Encouraged by the above results, we next attempted to examine the possible Ni-catalyzed cyanation of alkyl bromides **3**. During the studies, we found that the reaction proceeded efficiently catalyzed by $Ni(acac)_2$/Xantphos/DMAP/Zn at 80 °C without the need of adding *n*-Bu_4NCl. Under these optimized reaction conditions, various cyclic and acyclic alkyl substrates converted to the desired nitriles smoothly (Scheme 2).

Applying the reaction conditions for secondary alkyl chlorides to the coupling of primary alkyl chlorides such as (3-chloropropyl)benzene **4a** (see Scheme 3) with $Zn(CN)_2$

Scheme 3. Cyanation of Primary Alkyl Halides[a]



[a]Isolated yields. [b]CH_3CN was used as the solvent.

afforded **5a** in only 32% yield. We postulated that a pyridinium salt might be easily formed by the reaction of DMAP with primary alkyl chloride,[10] which may not act as an efficient electrophile in this reaction. Indeed, treatment of **4a** with DMAP at 100 °C for 8 h followed at room temperature for 1 h afforded the pyridinium salt **6** (4-(dimethylamino)-1-(3-phenylpropyl)pyridinium chloride) in 69% yield.[11] The desired nitrile **5a** was not observed by the reaction of **6** with $Zn(CN)_2$

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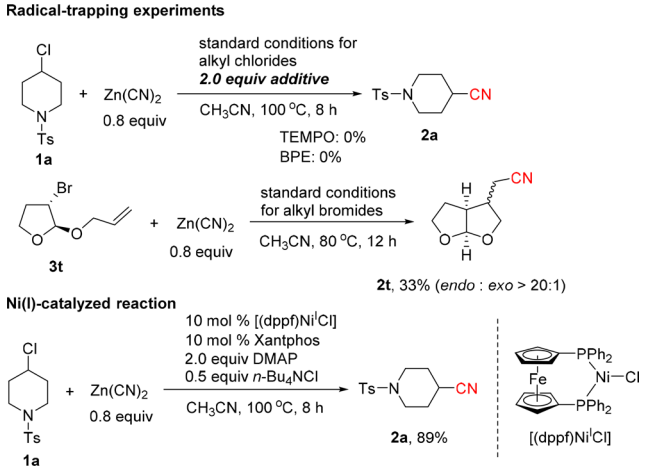
under the standard reaction conditions. By comparison, the reaction of a secondary alkyl chloride **1a** with DMAP was also performed, as we expected, no pyridinium salt was formed in CH_3CN at 100 °C. To our delight, we found that cyanation of primary alkyl chlorides could proceed effectively in the absence of a nickel catalyst. For example, reaction of **4a** with $Zn(CN)_2$ in the presence of 2.0 equiv of *n*-Bu_4NCl at 140 °C afforded the nitrile **5a** in 79% yield (without *n*-Bu_4NCl, no reaction occurred). Substrate **4b** with a ketone functionality could be cyanated at the lower reaction temperature (80 °C). Alkyl chloride with an indole group or benzyl chloride could also be successfully transformed into the corresponding nitriles (**5c**, **5d**). These results also indicated that *n*-Bu_4NCl played a role in activation of $Zn(CN)_2$ in the Ni-catalyzed reaction system. It is considered that a zincate might be formed through the coordination of chloride in *n*-Bu_4NCl to $Zn(CN)_2$, which facilitates the cyanide dissociation.[12] TBACl may also act as a phase-transfer reagent. Similarly, primary alkyl bromides **7** including those bearing aryl, ether, and amide functionalities were all smoothly cyanated (53−61%).

To gain a mechanistic insight into this reaction, various control experiments were performed. As shown in Scheme 4,

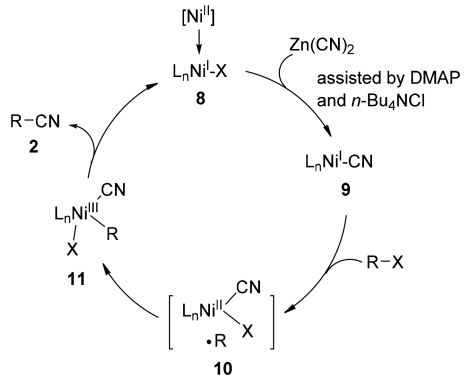
Scheme 4. Mechanistic Studies



addition of a radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) or BPE (1,1-diphenylethylene) inhibited the reaction.[13] Reductive cyclization/coupling of **3t**[14] with $Zn(CN)_2$ under the standard conditions for cyanation of secondary alkyl bromides afforded the cyclized product **2t** through 5-*exo*-*trig* ring closure in 33% yield. The diastereoselectivity observed in this reaction correlates with that observed in radical cyclization of the same substrate.[15] These results implied that radical intermediates might be involved in the nickel-catalyzed cyanation process. By analogy to Ni-catalyzed cross-coupling reactions of unactivated alkyl halides with organometallic reagents such as organoboron and organozinc reported by Fu et al.,[16] we suggest here that an alkyl radical and a Ni^{II} intermediate were generated through the reaction of alkyl halides with a Ni^{I} species, which rapidly combined to give an alkyl−Ni^{III} complex. Then the Ni^{I}/Ni^{III} redox cycle might be a possible reaction pathway. In order to probe the possible Ni^{I}/Ni^{III} redox cycle, cyanation of **1a** catalyzed by $[(dppf)Ni^{I}Cl]$ was investigated. It was found that this Ni^{I} complex showed excellent catalytic activity to give **2a** in 89% yield in the presence of 10 mol % of Xantphos (without Xantphos, **2a** was isolated in 15% yield). The ligand exchange reaction might occur during the process. The above results strongly support the Ni^{I}/Ni^{III} reaction pathway.[17]

On the basis of the above observations, a mechanistic proposal is depicted in Scheme 5. The reaction is initiated

Scheme 5. Possible Reaction Mechanism



through the formation of a L_nNi^{I} complex **8**, which might be generated through the comproportionation of the Ni^{II} species with the in situ formed Ni^{0} intermediate.[18] Complex **8** undergoes transmetalation with $Zn(CN)_2$ leading to $[L_nNi^{I}-CN]$ species **9**. This process is possibly accelerated by DMAP and *n*-Bu_4NCl through the formation of an adduct with enhanced solubility and reactivity. Reduction of alkyl halide by $[L_nNi^{I}-CN]$ complex via a single-electron-transfer pathway generates $[L_nNi^{II}CN(X)]$ intermediate and an alkyl radical **10**. Subsequent recombination of the radical with Ni^{II} complex delivers the Ni^{III} complex **11**. Reductive elimination of **11** provides the nitrile products **2** and regenerates the catalytically active Ni^{I} species. Alternatively, complex **8** may first react with alkyl halide through a radical process followed by transmetalation with $Zn(CN)_2$ and reductive elimination.

In summary, we have developed the first thermally driven nickel-catalyzed cyanation of unactivated secondary alkyl halides with $Zn(CN)_2$. The reaction features the use of air-stable and inexpensive $NiCl_2{\cdot}6H_2O$ or $Ni(acac)_2$ and common ligand of Xantphos as the catalyst components and DMAP and *n*-Bu_4NCl as the additives, providing the alkyl nitriles with a wide functional group tolerance. Preliminary mechanistic studies indicate that a radical species might be generated during the process and nickel(I) complex can also serve as an efficient catalyst for this cyanation reaction. Cyanation of primary alkyl chlorides or bromides was achieved by reaction with $Zn(CN)_2$ in the presence of *n*-Bu_4NCl without the need of nickel catalyst. 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.8b03539.

Experimental details and spectroscopic characterization of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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