Cyanation of Phenol Derivatives with Aminoacetonitriles by Nickel Catalysis

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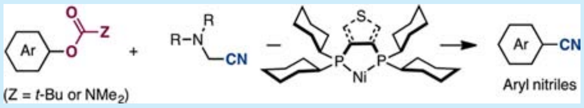
S *Supporting Information*

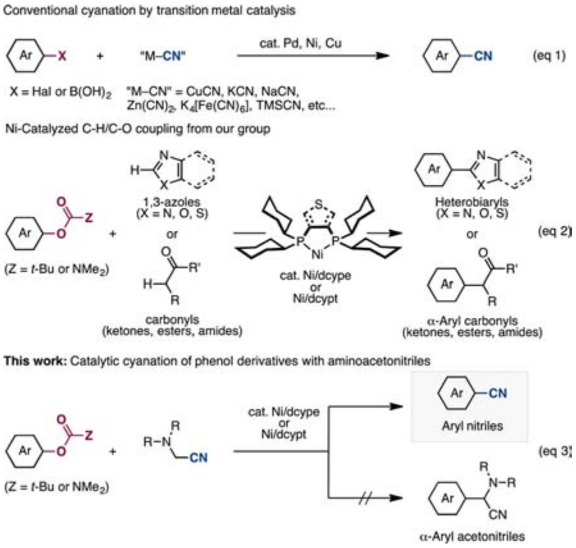
ABSTRACT: Generation of useful arylnitrile structures from simple aromatic feedstock chemicals represents a fundamentally important reaction in chemical synthesis. The first nickel-catalyzed cyanation of phenol derivatives with metal-free cyanating agents, aminoacetonitriles, is described. A nickel-based catalytic system consisting of a unique diphosphine ligand such as dcype or dcypt enables the cyanation of versatile phenol derivatives such as aryl carbamates and aryl pivalates. The use of aminoacetonitriles as a cyanating agent leads to an environmentally and easy-to-use method for arylnitrile synthesis.



Nitriles are recognized as one of the most important functional groups in chemistry. In particular, arylnitriles are omnipresent in pharmaceutically relevant molecules and electronic materials.[1] Moreover, the nitrile moiety can serve as a valuable intermediate that can be readily converted into various functional groups, such as amines, carbonyls, and heterocycles. In the past few decades, transition-metal-catalyzed cyanation reactions of aromatic compounds have greatly progressed.[2] Although these reactions are reliable for the synthesis of arylnitriles, many cyanating agents are metal cyanides, such as CuCN,[3] KCN,[4] NaCN,[5] $Zn(CN)_2$,[6] $K_4[Fe(CN)_6]$,[7] and TMSCN (Scheme 1, eq 1).[8] The risk of utilizing metal cyanides is the generation of hazardous hydrogen cyanide gas and stoichiometric amounts of metal-containing waste after the reaction. Although several practical methods for the synthesis of arylnitriles with nonmetallic cyanating agents have been developed,[9,10] cyanation reactions employing organic cyanating agents remain in their infancy in synthetic chemistry.

Meanwhile, we have developed a range of coupling reactions via inert bond activation using unique nickel catalysts.[11−13] For example, a nickel and 1,2-bis(dicyclohexylphosphino)ethane (dcype) catalytic system enabled the coupling of 1,3-azoles and phenol derivatives through C−H and C−O bond activation (Scheme 1, eq 2).[13] Furthermore, a nickel-catalyzed α-arylation of carbonyl compounds was accomplished with an air-stable thiophene-based phosphine ligand, 3,4-bis(dicyclohexylphosphino)thiophene (dcypt).[14] The use of phenol derivatives instead of aryl halides as the aryl source is beneficial from both synthetic and environmental points of view. Not only are phenol derivatives generally inexpensive and readily available, they also generate non-halogen- and non-sulfur-containing waste. Furthermore, phenol derivatives can be defined as a novel chemical feedstock.[15,16]

Scheme 1. Catalytic Cyanation of Phenol Derivatives with Aminoacetonitriles



Following our successful campaign in nickel-catalyzed C−H/C−O coupling, we set out to investigate the α-arylation of acetonitriles with phenol derivatives in order to synthesize α-aryl acetonitriles. Unfortunately, aminoacetonitriles were not transformed into the desired α-arylated products; however, we serendipitously discovered that this reaction furnished arylnitriles, indicating that aminoacetonitriles function as organic cyanating agents in the catalytic reaction (Scheme 1, eq 3). The use of aminoacetonitriles as cyanating agents in catalytic

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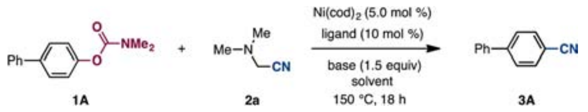
reactions is very rare.[17] Herein, we report the nickel-catalyzed cyanation reaction of phenol derivatives with aminoacetonitriles.

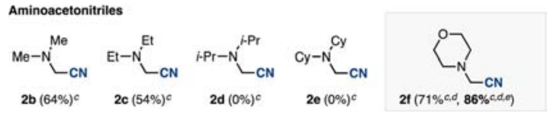
Following the above-mentioned discovery of new aromatic cyanation process, we investigated the effect of reaction parameters in the catalytic cyanation reaction of *p*-biphenyl carbamate **1A** with (dimethylamino)acetonitrile (**2a**) using Ni(cod)$_2$ as a nickel source at 150 °C for 18 h (Table 1).

Table 1. Screening of the Reaction Conditions[a]



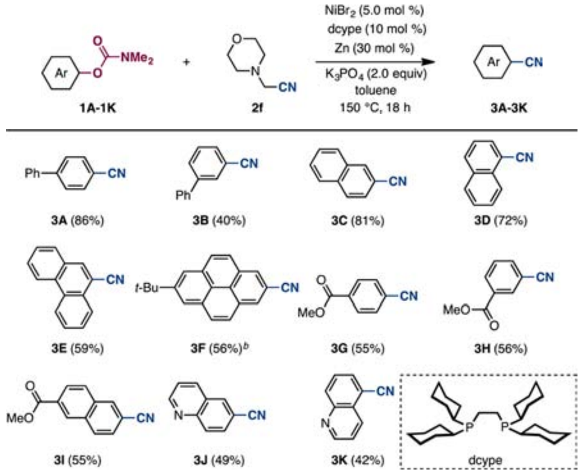
entry	ligand	base	solvent	3A[b] (%)
1	PCy$_3$	K$_3$PO$_4$	toluene	0
2	dppf	K$_3$PO$_4$	toluene	0
3	BINAP	K$_3$PO$_4$	toluene	0
4	IPr·HCl	K$_3$PO$_4$	toluene	0
5	dcype	K$_3$PO$_4$	toluene	52
6	dcypt	K$_3$PO$_4$	toluene	25
7	dcype	Cs$_2$CO$_3$	toluene	10
8	dcype	CsF	toluene	37
9	dcype	K$_2$CO$_3$	toluene	33
10	dcype	KH$_2$PO$_4$	toluene	9
11	dcype		toluene	5
12	dcype	K$_3$PO$_4$	1,4-dioxane	50
13	dcype	K$_3$PO$_4$	THF	29
14	dcype	K$_3$PO$_4$	DMF	1
15	dcype	K$_3$PO$_4$	*t*-amylOH	6

[a] **1A** (0.40 mmol), **2** (2.0 equiv), Ni(cod)$_2$ (5.0 mol %), ligand (bidentate: 10 mol %, monodentate: 20 mol %), base (1.5 equiv), solvent (1.6 mL), 150 °C and 18 h. [b] GC yield. [c] dcype (10 mol %), K$_3$PO$_4$ (2.0 equiv) and toluene (1.6 mL) were used. [d] Isolated yield. [e] NiBr$_2$ (5.0 mol %), Zn (30 mol %), and dcype (10 mol %) were used.



Screening of ligands was conducted in the presence of K$_3$PO$_4$ as a base in toluene. Electron-donating ligands such as PCy$_3$ and IPr did not promote this transformation (Table 1, entries 1 and 4). Although cyanation with diphosphine ligands did not proceed at all (Table 1, entries 2 and 3), electron-rich and bulky ligands such as dcype or dcypt facilitated the cyanation reaction to afford the desired product **3A** in 52% (Table 1, entry 5) and 25% (Table 2, entry 6) yields, respectively. Setting dcype as the optimized ligand, we next investigated the effect of base and solvent. Interestingly, K$_3$PO$_4$ (weaker inorganic base) greatly promoted the reaction compared to Cs$_2$CO$_3$, CsF, K$_2$CO$_3$, and KH$_2$PO$_4$ (Table 1, entries 7−10). The yield was diminished without base (Table 1, entry 11). Toluene and 1,4-dioxane proved to be an appropriate solvent for this reaction; a change to THF led to lower yields of the desired product **3A** (Table 1, entries 12 and 13). Polar solvents shut down the reaction (Table 1, entries 14 and 15). Next, we examined cyanating agents by screening different aminoacetonitriles. Changing the amine substituents from methyl (**2a**) to ethyl (**2b**) gave a slightly lower yield of the product. Aminoacetonitriles bearing more sterically congested alkyl groups, such as diisopropyl (**2c**) and dicyclohexyl (**2d**), did not promote the reaction at all. However, morpholinoacetonitrile **2f** gave access to the cyanated product **3A** in 71% isolated yield. To our delight, the combination of air-stable NiBr$_2$ (5.0 mol %) and Zn (30 mol %) increased the yield of **3A** to 86%.

Table 2. Cyanation of Various Aryl Carbamates with an Aminoacetonitrile by Ni/dcype Catalyst[a]



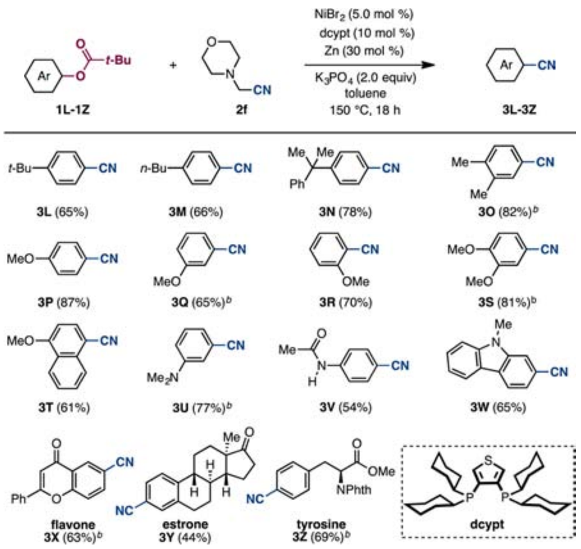
[a] Isolated yield. [b] NiBr$_2$ (10 mol %), Zn (60 mol %), and dcype (20 mol %) were used.

Next, we examined the substrate scope of various aryl carbamates in the nickel-catalyzed cyanation reaction with NiBr$_2$/Zn/dcype/K$_3$PO$_4$ in toluene (Table 2). Biphenyl carbamates **1A** and **1B** were well tolerated, and the corresponding products were obtained in moderate to good yields (**3A** and **3B**). 2-Naphthyl carbamates also reacted well with the cyanating agent to give arylnitriles **3C** and **3D** in good yields. Since polycyclic aromatic hydrocarbons (PAHs) are attractive building blocks in materials science, we employed their carbamates under our reaction conditions. We were delighted to see that the reactions furnished **3E** and **3F** in 59% and 56% yields, respectively. A methyl ester moiety was tolerated, providing the corresponding products **3G−I** in moderate yields. Quinoline carbamates can be converted into **3J** and **3K**, albeit in slightly lower yields.

The scope of aryl pivalates in the nickel-catalyzed cyanation was also examined (Table 3). In this case, we found that dcypt is more effective than dcype. Alkyl *para*-substituted aryl pivalates reacted well with aminoacetonitrile **2f**, providing the desired products **3L−O** in good yields. Aryl pivalates bearing a methoxy group were well tolerated and afforded the target products (**3P−R**) in 87%, 65%, and 70% yields, respectively. Even an electron-rich aromatic compound, dimethoxy benzonitrile **3S**, was obtained in 81% yield (with increased catalyst loading). Furthermore, amine and amide groups were also tolerated and provided the corresponding cyanated products in good yields (**3U** and **3 V**). Both carbazole and flavone derivatives, which are often present in naturally occurring molecules, were applicable under our reaction conditions, affording **3W** and **3X** in good yields. Delightfully, we found that even estrone and tyrosine derivatives underwent the cyanation give the corresponding products (**3Y** and **3Z**) in moderate to good yields.

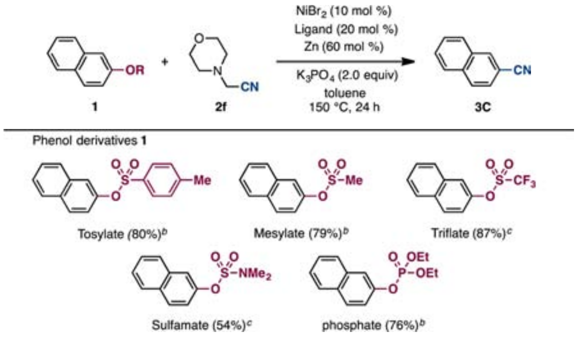
Since our catalytic system allowed the cyanation of aryl carbamates and aryl pivalates, we wondered whether tosylate, mesylate, triflate, sulfamate, and phosphate would also be reacting substrates (Table 4). Gratifyingly, all these phenol derivatives were cyanated in good to excellent yields. To the best of our knowledge, this is the first nickel-catalyzed cyanation reaction of a tosylate, sulfamate, or phosphate.

Table 3. Cyanation of Various Aryl Pivalates with an Aminoacetonitrile by Ni/dcypt Catalysis[a]



[a]Isolated yield. [b]$NiBr_2$ (10 mol %), Zn (60 mol %), and dcypt (20 mol %) were used.

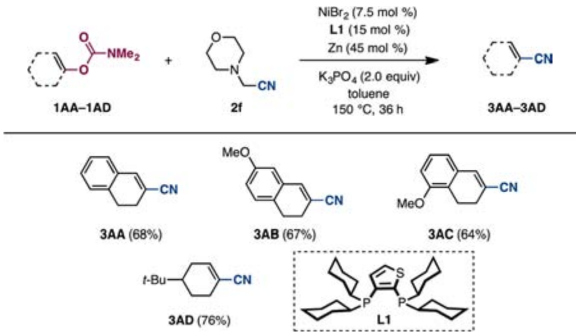
Table 4. Cyanation of Various Phenol Derivatives with an Aminoacetonitrile by Ni Catalysis[a]



[a]NMR yield. [b]dcypt was used. [c]dcype was used.

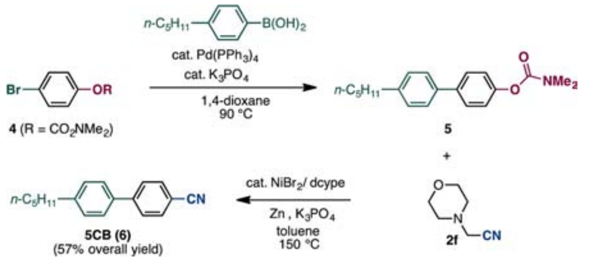
This cyanation can be applicable to the synthesis of alkenyl nitriles from enol derivatives (Table 5). To this end, 2,3-bis(dicyclohexylphosphino)thiophene (**L1**) provided the highest yield of the cyanated product.[18] Under the influence of $NiBr_2$/Zn/**L1** catalyst, enol derivatives **1AA**, **1AB**, and **1AC**, which were readily prepared from α-tetralone derivatives in one step, were smoothly converted to the corresponding alkenyl nitriles **3AA**, **3AB**, and **3AC** in good yields. Even simple cyclohexenyl nitrile derivative **3AD** was also obtained in 76% yield.

Table 5. Cyanation of Various Enol Derivatives with an Aminoacetonitrile by Ni/L1 Catalysis



To demonstrate the synthetic application of this method, we turned our attention to the synthesis of **5CB**,[19] which is one of the best known liquid crystal compounds (Scheme 2). With 4-bromophenyl dimethylcarbamate **4** as the starting material, we first performed a Suzuki–Miyaura coupling, obtaining biaryl compound **5**. Subsequently, **5** was subjected to the nickel-catalyzed cyanation to furnish **5CB** in 57% overall yield over two steps. Thus, the orthogonal reactivity of C–Br (with Pd) and C–O (with Ni) bonds allowed unconventional yet rapid access to important class of arylnitrile materials, highlighting the synthetic utility of the newly discovered cyanation reaction.

Scheme 2. Synthesis of 5CB



Although the detailed reaction mechanism has not been unravelled, a plausible mechanism for this transformation is depicted in Figure 1. We hypothesize that the catalytic cycle of our Ni-catalyzed cyanation reaction is similar to that of transition-metal-catalyzed cyanation reactions of aryl halides with metal cyanides.

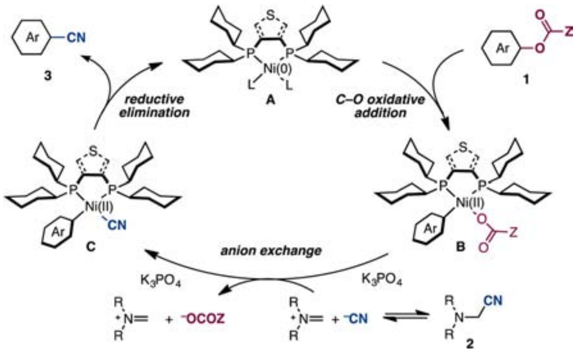


Figure 1. Plausible reaction mechanism.

Initially, C–O oxidative addition of the phenol derivative to Ni(0) catalyst **A** proceeded to afford complex **B**.[13c,14a] Subsequently, anion exchange between $^-$OCOZ (Z = t-Bu, NMe_2) and $^-$CN occurred, providing an aryl-Ni–CN complex **C** and an iminium salt.[20] Finally, the thus generated **C** underwent reductive elimination to provide the arylnitrile product with simultaneous regeneration of Ni(0) species.

In summary, we have discovered the first nickel-catalyzed cyanation of phenol derivatives with metal-free, organic cyanating agents, aminoacetonitriles. Aryl carbamates, pivalates, tosylates, mesylates, triflates, sulfamates, and phosphates as well as enol derivatives are all tolerated and furnished the corresponding cyanated products in good yields. Cyanation of PAHs and naturally occurring complex molecules was also accomplished. Further investigation of the ligand effect and mechanistic studies are currently ongoing in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02265.

Detailed experimental procedures and spectral data for all compounds (PDF)
^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(20) It was assumed that the effect of K_3PO_4 is the acceleration of the anion exchange between complex **B** and **C**.