Nickel-Catalyzed Cyanation of Aryl Thioethers

Originally published in:
Organic Letters 23(18), https://doi.org/10.1021/acs.orglett.1c02285

Funding acknowledgement:
184658 - Catalytic synthesis of unprotected amines and heterocycles (SNF)

OL Organic Letters

pubs.acs.org/OrgLett Letter

Nickel-Catalyzed Cyanation of Aryl Thioethers

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Cite This: *Org. Lett.* 2021, 23, 7018–7022 Read Online

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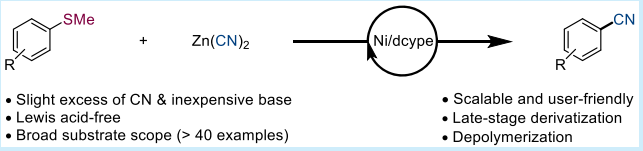
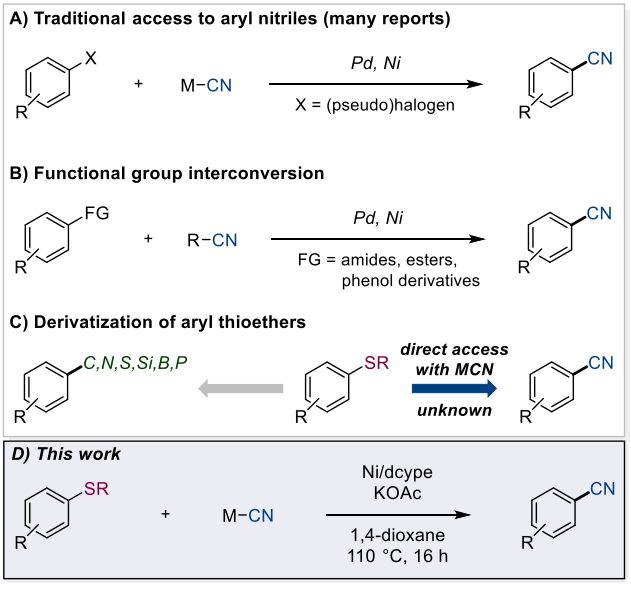
ABSTRACT: A nickel-catalyzed cyanation of aryl thioethers using $Zn(CN)_2$ as a cyanide source has been developed to access functionalized aryl nitriles. The ligand dcype (1,2-bis(dicyclohexylphosphino)ethane) in combination with the base KOAc (potassium acetate) is essential for achieving this transformation efficiently. This reaction involves both a C−S bond activation and a C−C bond formation. The scalability, low catalyst and reagents loadings, and high functional group tolerance have enabled both late-stage derivatization and polymer recycling, demonstrating the reaction's utility across organic chemistry.



Aryl nitriles are important compounds due to their occurrence in natural products, pharmaceuticals, agrochemicals, materials, and dyes.[1,2] They are also versatile building blocks for accessing a wide range of other functional groups such as benzoic acid, ketone, aldehyde, and amine.[3−5] Aryl nitriles were historically obtained via a Rosenmund−von Braun[6] or a Sandmeyer reaction.[7] Lately, with the advent of metal-catalyzed reactions, aryl nitriles have been synthesized through the cross-coupling between an aryl (pseudo)halide and an inorganic or organic cyanide species (Scheme 1).[8−10] Recently, chemists have dedicated their efforts to using other electrophiles such as phenol derivatives,[11,12] esters,[13] or amides.[14] Moreover, thioethers have been investigated as electrophiles in the past decade.[15−18] Several reports have employed aryl thioethers or thioesters to introduce a wide range of functional groups, such as alkyl and aryl groups,[19,20] amines,[21,22] functionalized thioethers,[23] boryl and silyl groups,[24,25] phosphonates,[26] and hydrides.[27−29] However, despite the occurrence of thioethers and the synthetic potential of nitriles, direct methods to convert aryl sulfides to the corresponding aryl nitriles using a metal cyanide reagent are unknown. To date, only a functional group metathesis between aryl nitriles and aryl thioethers has been reported to access valuable aryl nitriles from the corresponding aryl thioethers.[30]

Scheme 1. Context of This Work



We started our investigation using thioanisole as a benchmark substrate and $Zn(CN)_2$ as cyanide source. Guided by recent reports on the activation of C−S bonds and the formation of C−CN bonds[11−13,22,30] as well as the high abundance and low price of nickel, we decided to use $Ni(COD)_2$ as a precatalyst and KOAc as a base. Several bidentate ligands were tested such as XantPhos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene), DPEPhos ((oxydi-2,1-phenylene)bis(diphenylphosphine)), dppm (bis(diphenylphosphino)methane), and dppe (1,2-bis(diphenylphosphino)ethane), but no formation of the desired product was observed.

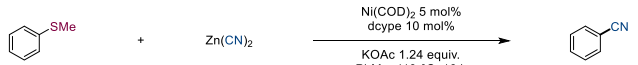
We next tested dcypm (bis(dicyclohexylphosphino)methane), which has previously shown its ability to break C−S bonds;[22] however, no conversion of thioanisole was observed. When using dcype instead of dcypm, a promising 41% yield of benzonitrile could be observed by gas chromatography analysis of the reaction mixture. This result is in accordance with recent reports in this field, as this ligand, in combination with a nickel precatalyst, has been used to activate C−S bonds and to form C−CN bonds.[11,12,22,30]

Received: July 8, 2021
Published: August 26, 2021

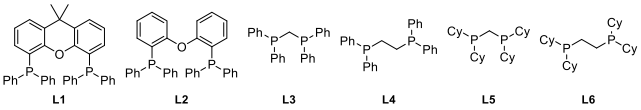
https://doi.org/10.1021/acs.orglett.1c02285
Org. Lett. 2021, 23, 7018−7022

Unlike Szostak and coworkers, who showed no need for the external base in their decarbonylative cyanation of amides,[14] in our case, the absence of a base resulted in no conversion of thioanisole. An extensive screening of different bases did not lead to any yield improvement. (See the SI and Table 1.)

Table 1. Optimization of the Ni-Catalyzed Cyanation of Aryl Thioethers[a]



entry	deviation from standard conditions	yield (%)[b]
1	none	41
2	**L1** instead of **L6**	0
3	**L2** instead of **L6**	0
4	**L3** instead of **L6**	0
5	**L4** instead of **L6**	0
6	**L5** instead of **L6**	0
7	no base	0
8	K_2CO_3 instead of KOAc	20
9	1,4-dioxane instead of PhMe	70
10	0.5 mL of 1,4-dioxane instead of 1.5 mL of toluene	89

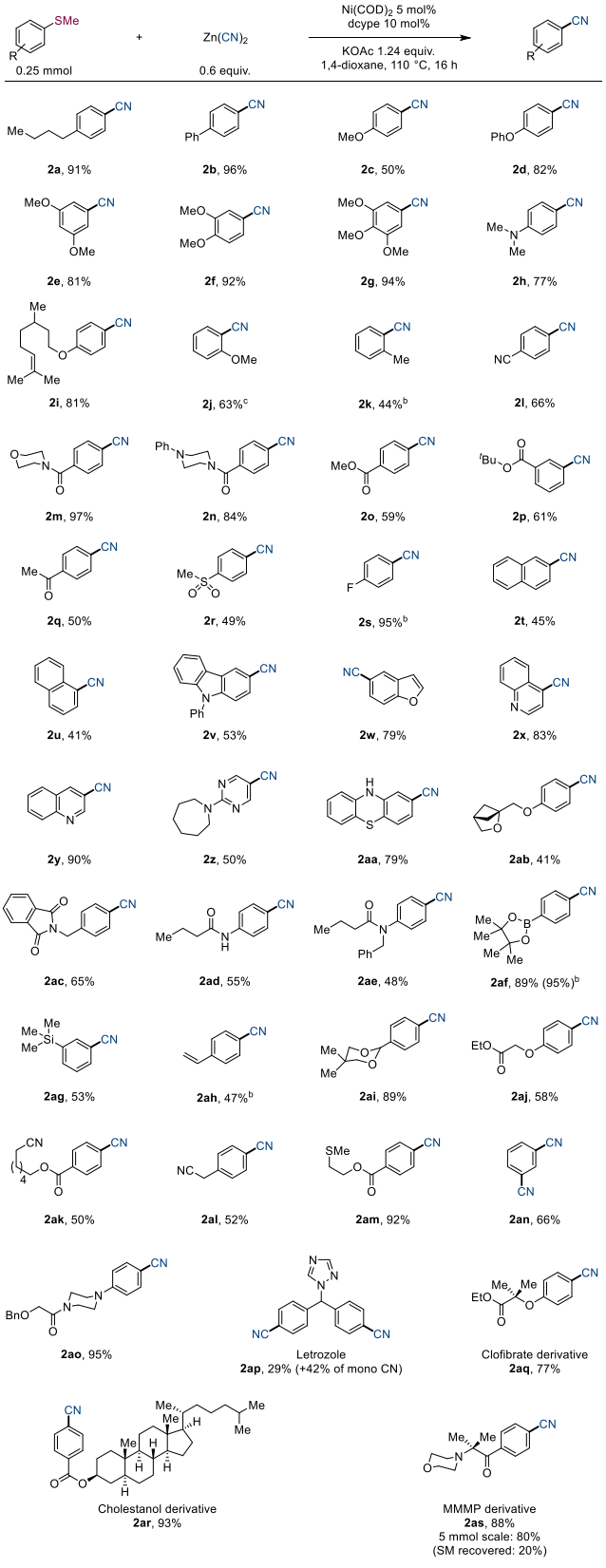


[a]PhSMe (0.25 mmol), $Zn(CN)_2$ (0.6 equiv), $Ni(COD)_2$ (5 mol %), dcype (10 mol %), PhMe (1.5 mL), 110 °C, 16 h. [b]GC yield using *n*-dodecane as an internal standard.

However, switching the solvent to 1,4-dioxane drastically improved the outcome of the reaction, affording benzonitrile in 70% yield. A further examination of the molarity of the reaction led to product formation in 89% yield using a concentration of 0.5 mol/L.

With the best conditions in hand, we explored the substrate scope of this synthetic transformation (Scheme 2). We started the investigation by subjecting several electron-neutral (**2a**, **2b**) and electron-rich thioanisoles (**2c**−**2h**) to the reaction conditions. Gratifyingly, all of them gave the corresponding product in good to excellent yield. An aryl thioether bearing an alkene, which could have deactivated the catalyst via chelation,[31] was also tolerated (**2i**). Sterically hindered substrates worked well under the reaction conditions (**2j**, **2k**). Furthermore, aryl sulfides bearing electron-withdrawing functional groups, such as nitrile (**2l**), morpholine, and piperazine amides (**2m**, **2n**), methyl and *tert*-butyl esters (**2o**, **2p**), ketone (**2q**), and a sulfone (**2r**), worked smoothly under the reaction conditions (49−97%). Importantly, fluoro-containing thioanisole was also a competent partner in this reaction (**2s**). We next tested the ability of this transformation toward naphthalene units (**2t**, **2u**), which worked in moderate yields (41−45%). Several aromatic heterocycles, such as carbazole (**2v**), which is an important class of compounds in organic electronics,[32] benzofuran (**2w**), quinoline (**2x**, **2y**), a pyrimidine bearing an azepane moiety (**2z**), and a phenothiazine possessing a free aniline group (**2aa**), were readily accommodated. Furthermore, nonaromatic heterocycles such as a thioanisole bearing a 2-oxabicyclo[2.1.1]-hexane moiety (**2ab**), a water-soluble bioisostere of benzene,[33] gave the desired product in good yield. To further demonstrate the synthetic potential of this transformation, we subjected aryl

Scheme 2. Scope of Aryl Thioethers[a]



[a]Yield of isolated product. ArSMe (0.25 mmol), $Zn(CN)_2$ (0.6 equiv), KOAc (1.24 equiv), $Ni(COD)_2$ (5 mol %), dcype (10 mol %), 1,4-dioxane (0.5 M), 110 °C, 16 h. [b]NMR yield. [c]150 °C.

https://doi.org/10.1021/acs.orglett.1c02285
Org. Lett. 2021, 23, 7018−7022

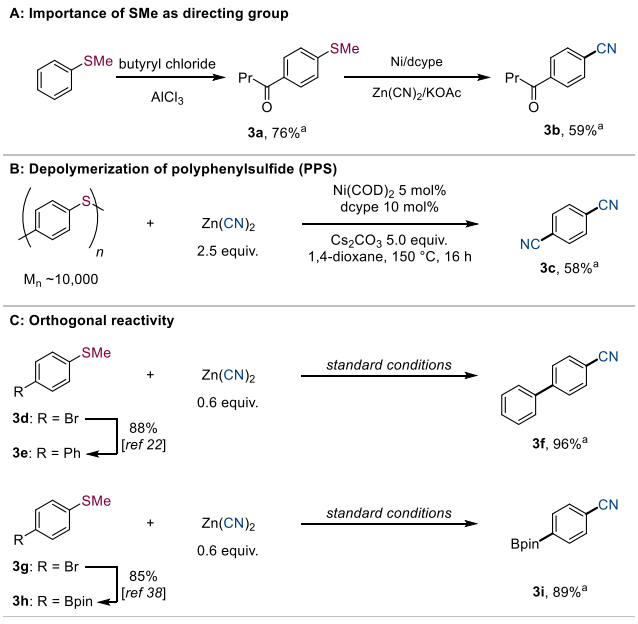
thioethers bearing important functional groups to the reaction conditions. To our delight, aryl sulfides containing a phthalimide (**2ac**), benzyl-protected and unprotected amides (**2ad**, **2ae**), a boronic ester (**2af**), a silyl (**2ag**), a styrene (**2ah**), an acetal-protected aldehyde (**2ai**), and an aliphatic ester (**2aj**) worked efficiently under the reaction conditions (47−89%). We next performed some competition reactions. Aliphatic and benzyl nitriles (**2ak**, **2al**) were not reactive toward the nickel catalyst, confirming the need for a Lewis acid to activate them.[34,35]

Furthermore, an aliphatic thioether (**2am**) was inert to the conditions and led to selective cyanation of the aryl sulfide in excellent yield. Double coupling of an arene bearing two thioether moieties (**2an**) worked smoothly. Finally, we completed this study by performing the late-stage derivatization of commercial molecules. Gratifyingly, the synthesis of the benzyl-protected donitriptan intermediate (**2ao**), an antimigraine drug, worked in excellent yield (95%). Letrozole (**2ap**), a drug used in the treatment of breast cancer, was also successfully transformed to the dicyano compound in 29% yield and the monocyano in 42% yield, showing the ability of this transformation to generate libraries of interesting derivatives. A cholestanol derivative (**2aq**) was obtained in high yield. Furthermore, clofibrate, a drug controlling high cholesterol and triacylglyceride levels in the blood, could also be readily functionalized (**2ar**). The late-stage cyanation of a commercial photoinitiator, MMMP, was also successful, affording the corresponding product (**2as**) in 88% yield. Interestingly, the reaction worked in a lower but good yield on a 5 mmol scale, with 20% of the starting material recovered, demonstrating both the scalability and the excellent mass balance of this otherwise byproduct-free reaction.

We then shifted our focus to synthetic applications. First, we applied our reaction to the two-step synthesis of compound **3b** in 59% yield, which could not be accessed otherwise with this substitution pattern through the direct Friedel−Crafts acylation of benzonitrile (Scheme 3A). We next turned our attention to the depolymerization of a commercial thermoplastic polymer PPS (polyphenylene sulfide).[36,37] After a re-evaluation of the reaction conditions, the polymer was successfully depolymerized in 58% yield to obtain dicyanobenzene (Scheme 3B). These results show the potential of this transformation for upcycling polymer wastes. Moreover, we also demonstrated the utility of our reaction in orthogonal reactions. Under palladium catalysis, the C−Br bond of compound **3d** was selectively functionalized in a Suzuki−Miyaura cross-coupling.[22] Compound **3e** could then be further converted into a nitrile under nickel catalysis (Scheme 3C, top). Furthermore, this selective bond activation was also shown in a Miyaura borylation.[38] Compound **3g**, was indeed selectively borylated at the C−Br bond position using a palladium catalyst. The corresponding boronic ester (**3h**) could then be transformed into the corresponding nitrile under the developed reaction conditions in 89% yield (Scheme 3C, bottom).

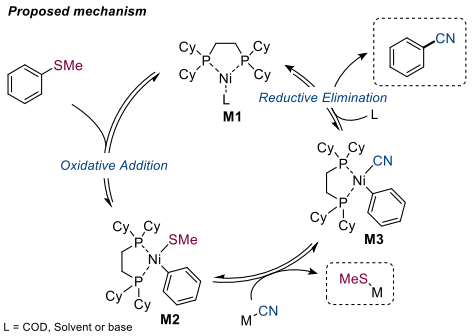
Nickel, in combination with dcype, was previously demonstrated to be competent in the cleavage of C(sp^2)−S bonds.[22,23,30] Furthermore, Rueping and coworkers showed the ability of this nickel catalyst to undergo transmetalation with $Zn(CN)_2$ under basic conditions.[13] The nickel/dcype catalytic manifold has also been reported to enable C−CN bond formation.[11,12,30] Hence, the plausible mechanism of this transformation starts with active catalyst **M1**. Subsequently, the complex is oxidized to Ni(II) in the presence of thioanisole, followed by transmetalation with M−CN leading to complex **M3** and the generation of M−SMe salt. This complex undergoes reductive elimination with the help of an extra ligand to generate back complex **M1** and release the corresponding aryl nitrile (Scheme 4).

Scheme 3. Synthetic Applications



[a]Yield of isolated product (%). For details, see the SI.

Scheme 4. Proposed Mechanism



In summary, we have developed the first nickel-catalyzed direct cyanation of aryl thioethers using a slight excess of zinc cyanide and potassium acetate. This transformation showed great efficiency toward many aryl sulfides as well as high functional group tolerance. The reaction is scalable and user-friendly due to the lower toxicity on $Zn(CN)_2$ compared with other metallic cyanide sources.[39] Furthermore, late-stage derivatizations in combination with synthetic applications showed its potential as a new tool to access densely functionalized aryl nitriles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02285.

https://doi.org/10.1021/acs.orglett.1c02285
Org. Lett. 2021, 23, 7018−7022

Experimental details and nuclear magnetic resonance spectra (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This project received funding from the Swiss National Science Foundation (SNSF 184658). We also thank ETH Zürich. We thank the NMR and MS departments of ETH Zürich for technical assistance as well as our group for critical proofreading of this manuscript. T.D. thanks Philip Boehm (ETH Zürich) for the synthesis of several starting materials.

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