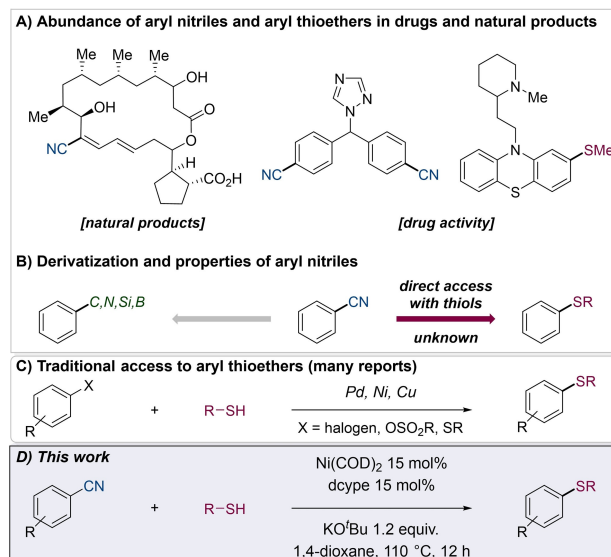


Special Collection
Nickel-Catalyzed Thiolation of Aryl Nitriles
Tristan Delcaillau^[a] and Bill Morandi^{*[a]}

In Memory of Prof. François Diederich

Abstract: A nickel-catalyzed thiolation of aryl nitriles has been developed to access functionalized aryl thioethers. The ligand dcype (1,2-bis(dicyclohexylphosphino)ethane) as well as the base KO^tBu (potassium *tert*-butoxide) are essential to achieve this transformation. This scalable and practical process involves both a C–C bond activation and a C–S bond formation. Furthermore, this reaction shows a high functional-group tolerance and enables the late-stage functionalization of important molecules.

Aryl nitriles are of great interest to the scientific community. Indeed, this moiety is found in many natural products as well as pharmaceuticals (Scheme 1A).^[1,2] Aryl nitriles can be readily transformed into several other functional groups such as carboxylic acids, ketones, aldehydes, or benzylamines derivatives.^[3] The rise of modern cross-coupling reactions has facilitated the access to aryl nitriles. The use of Pd, Ni or Cu as catalysts in combination with a metal cyanide reagent has enabled the efficient access to diversified aryl nitriles from aryl (pseudo)halides.^[4] In contrast, the concept of using the cyano group as an atypical electrophile in cross-coupling has only been developed in the past two decades. For instance, the formation of valuable bi-aryl compounds, aryl amines, aryl boronic esters, aryl organo silicons, aryl phosphines and hydro-aryls using aryl nitriles as electrophiles has expanded the synthetic potential of this functional group (Scheme 1B).^[5] On the other hand, the synthesis of aryl thioethers, which are important compounds in medicinal chemistry^[6] and materials science,^[7] has also taken advantage of modern organic chemistry and the associated generalization of metal-catalyzed reactions. Aryl (pseudo) halides have served as versatile platforms to rapidly generate diversified libraries of aryl thioethers



Scheme 1. Context of the work.

by using either Pd, Ni or Cu catalysts (Scheme 1C).^[8] An interesting feature of thioethers is their facile conversion to other valuable functional groups such as alkyl groups, amines, boryl moieties or sulfoximines.^[9] Despite the synthetic utility of thioethers and the widespread occurrence of aryl nitriles, methods to convert nitriles to the corresponding aryl thioethers are extremely scarce. To date only one method, proceeding through functional group metathesis, has been reported using an aryl thioether as a formal thioether donor.^[10] However, a traditional catalytic approach for the direct conversion of an aryl cyanide to a thioether using an organic thiol has not yet been reported (Scheme 1D).

We started our investigation by using benzonitrile and *n*-dodecanethiol as benchmark substrates. In combination with Ni(COD)₂ (bis(1,5-cyclooctadiene)nickel(0)) as metal catalyst, we evaluated several ligands such as monodentate and bidentate phosphine ligands, as well as *N*-heterocyclic carbenes (NHC). Initial experiments relied on LiHMDS (lithium bis(trimethylsilyl) amide) as a base because it had proven to be efficient in our previously reported aryl thioether metathesis.^[11] First positive results were observed with dppe (1,2-bis(diphenylphosphino)ethane) as ligand, affording the corresponding aryl thioether in 10% yield. Gratifyingly, the use of dcype (1,2-bis(dicyclohexylphosphino)ethane) increased the yield up to 33%. This ligand was previously reported to be effective in the activation of C–CN bonds and the formation of C–S bonds.^[11,12]

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This article belongs to a Joint Special Collection dedicated to François Diederich.

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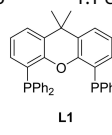
After an extensive screening of different reaction conditions, we found that 1,4-dioxane as solvent in combination with KO^tBu as a base afforded the expected product in 86% yield. To our delight, a slight excess of thiol and base (1.1 equiv. & 1.2 equiv. respectively) was sufficient to obtain the product in high yield (90%).

With the optimized conditions in hand (see Table 1), we started to explore the substrate scope with respect to aryl nitriles (see Table 2). A wide range of benzonitrile derivatives worked efficiently under the reaction conditions. Indeed, electron-neutral and rich arenes (**3a**, **3b**, **3c**, **3d**, **3e**, **3f**, **3g** and **3h**) were compatible, affording the desired products in moderate to excellent yield (50–94%). Moreover, sterically hindered aryl nitriles proved to be competent (**3i**), providing the *ortho*-methyl aryl thioether derivative in 71% yield. We also tested the scalability of this reaction by employing 2.0 mmol of 4-(*tert*-butyl)benzonitrile. For that purpose, we examined the reaction with decreased catalyst loadings (5 and 10 mol% of Ni/dcype), which provided **3d** in synthetically useful yields (66 and 79%).

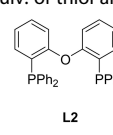
With the optimized amount of catalyst (15 mol%), a similar yield of the product was obtained as for the trials on 0.25 mmol scale, showcasing the potential of this transformation for larger scale reactions. Next, several electron-poor arenes, bearing electron-withdrawing functional groups such as an amide (**3j**) and a ketone (**3k**), were examined. Both led to the formation of product in high yields (91 and 88%). Furthermore, fluorine-containing aryl nitriles also worked smoothly under the reaction conditions (**3l**, 72%). Subsequently, we tested the methodology on heterocyclic compounds (**3m** and **3n**), as well as on a

Table 1. Optimization of the reaction conditions.^[a]

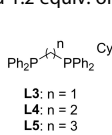
Entry	Deviation from standard conditions	Yield [%] ^[b]
1	None	33
2	L1 instead of L8	0
3	L2 instead of L8	0
4	L3 instead of L8	5
5	L4 instead of L8	10
6	L5 instead of L8	16
7	L6 instead of L8	22
8	L7 instead of L8	0
9	L9 instead of L8	0
10	10 mol% L8 instead of 5 mol%	34
11	10 mol% L8 and Ni(COD) ₂ instead of 5 mol%	52
12	15 mol% L8 and Ni(COD) ₂ instead of 5 mol%	74
13	KO ^t Bu instead of LiHMDS	75
14	KO ^t Bu/1,4-dioxane instead of LiHMDS/ <i>o</i> -xylene	86
15	1.1 equiv. of thiol and 1.2 equiv. of KO ^t Bu	90



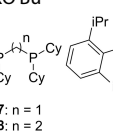
L1



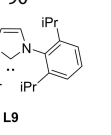
L2



L3: n = 1
L4: n = 2
L5: n = 3
L6: n = 4



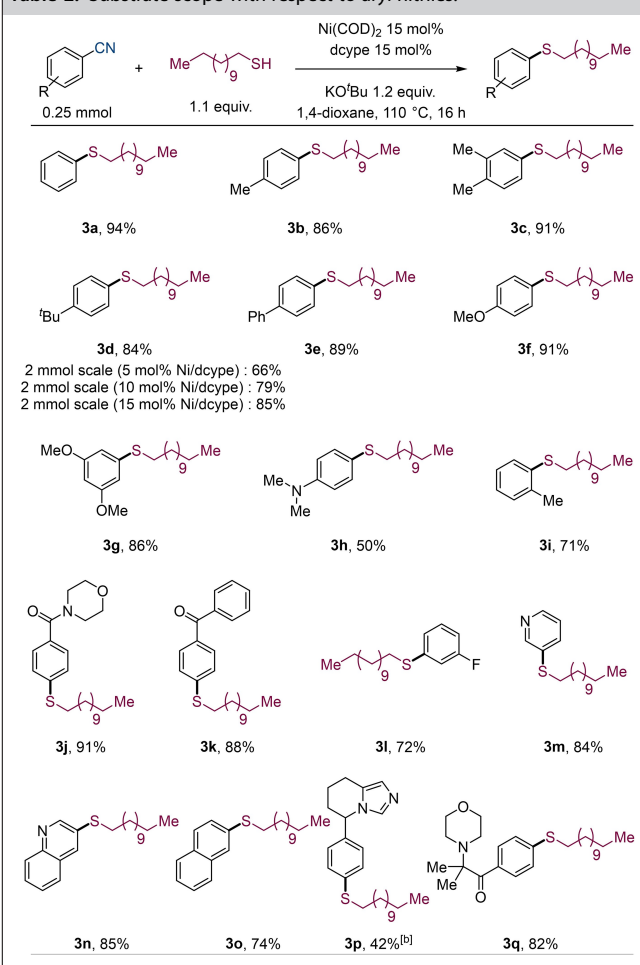
L7: n = 1
L8: n = 2



L9

[a] **1a** (0.25 mmol), **2a** (2.0 equiv.), Ni(COD)₂ (5 mol%), *o*-xylene, 140 °C, 16 h. [b] GC yields using *n*-dodecane as internal standard.

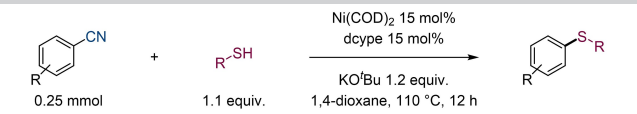
Table 2. Substrate scope with respect to aryl nitriles.^[a]

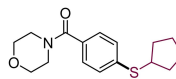
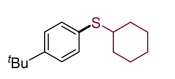
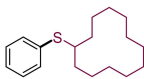
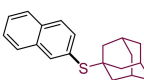
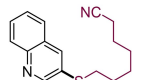
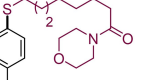
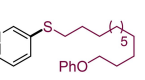
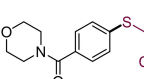
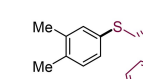
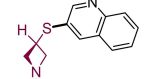
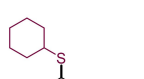



[a] Yield of isolated product. Aryl nitrile (0.25 mmol, 1.0 equiv.), *n*-dodecanethiol (0.275 mmol, 1.1 equiv.), KO^tBu (0.3 mmol, 1.2 equiv.), Ni(COD)₂ (0.0375 mmol, 15 mol%), dcype (0.0375 mmol, 15 mol%), 1,4-dioxane (0.75 mL), 110 °C, 16 h. [b] the HCl salt was used in combination with 2.5 equiv. of KO^tBu.

bicyclic aryl nitrile (**3o**). All of them afforded the expected products in high yields (74–85%). We concluded this exploration of aryl nitriles by performing the late-stage derivatization of the drug Fadzole (**3p**) which is used for the treatment of breast cancer.^[13] Gratifyingly, the corresponding aryl thioether was obtained in 42%. Moreover, the synthesis of a derivative of MMMP (**3q**), a widely used photoinitiator,^[14] could be obtained in 82% yield. Thus, demonstrating the potential of this transformation to derivatize commercial molecules.

We next evaluated the versatility of this reaction with regards to thiols (see Table 3). Readily available aryl nitriles bearing cyclic aliphatic thiols (**4a**, **4b** & **4c**) proved to be competent partners, providing the respective products in high yields (91, 94 and 88%). A sterically hindered thiol also worked efficiently under the reaction conditions affording the desired adamantyl aryl thioether (**4d**) in 91%. We next shifted our focus to densely functionalized thiols. First, we used a thiol bearing an aliphatic nitrile group (**4e**). To our delight, the desired product was obtained in good yield (63%) without any reaction

Table 3. Substrate scope with respect to thiols.^[a]


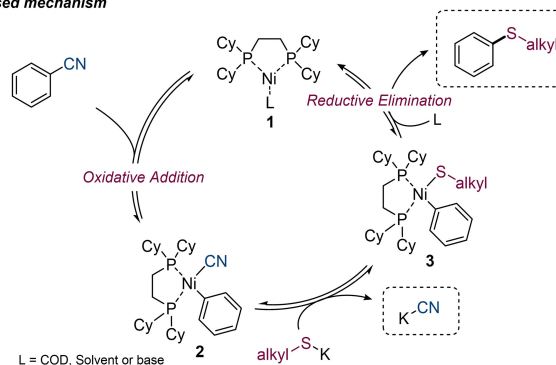
 4a, 94%	 4b, 91%	 4c, 88%	
 4d, 91%	 4e, 63%	 4f, 82%	 4g, 95%
 4h, 83%	 4i, 85%	 4j, 54%	
 4k, 78%	 4l, 84%		

[a] Yield of isolated product. Aryl nitrile (0.25 mmol, 1.0 equiv.), thiol (0.275 mmol, 1.1 equiv.), KOtBu (0.3 mmol, 1.2 equiv.), Ni(COD)₂ (0.0375 mmol, 15 mol%), dcype (0.0375 mmol, 15 mol%), 1,4-dioxane (0.75 mL), 110 °C, 16 h.

on the aliphatic nitrile group occurring, thus demonstrating the selective activation of C(sp²)-CN bonds with this catalytic manifold.^[4e,15] Furthermore, thiols containing an aliphatic amide (4f), ether (4g) and thioether (4h) gave the desired product in good to excellent yield (82–95%). Non-aromatic heterocycles bearing a strongly coordinating amine such as pyrrolidine (4i) and azetidine (4j) were also tolerated under the reaction conditions, affording the expected thioethers in moderate to good yields (85 and 54%). Moreover, performing the double coupling reaction on 1,4-dicyanobenzene (4k) afforded the disulfide product in a satisfactory 78% yield. Finally, we completed this study by using a thiol-derivative of vitamin E (4l). This compound proved to be competent in the here described reaction, delivering the natural product-derivative in 84%, thus showing the potential of this transformation for late-stage diversification.

Although we are currently working to elucidate the mechanism of this transformation, we can already propose a working hypothesis based on previous reports (Scheme 2).^[9b,11] The ability of nickel to oxidatively insert into a C(sp²)-CN bond has been proposed by Nakao and Hiyama.^[16] The subsequent transmetalation at the nickel center, followed by reductive elimination to form a C(sp²)-SR bond and generate back Ni(0), has been formerly reported by our group.^[11a] We hence propose

Proposed mechanism



Scheme 2. Plausible mechanism.

the following mechanism: dissociation of one of the COD of Ni(COD)₂ in the presence of dcype provides the active catalyst 1. Subsequently, the catalyst undergoes oxidative addition by cleaving the C-CN of the aryl nitrile, followed by transmetalation with the potassium thiolate leading to complex 3. The ligand then facilitates the reductive elimination, generating back complex 1 and releasing the aryl thioether.

In summary, we have developed a nickel-catalyzed thiolation of aryl nitriles. Because of the wide occurrence and availability of these compounds, this transformation complements the toolbox of useful methods available for the transformation of the cyano group into other functional groups. The methodology shows a good functional-group tolerance, enabling the late-stage diversification of important molecules. Moreover, we showed that the reaction is a scalable and practical tool to access highly valuable aryl thioethers.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: catalysis · late-stage · nickel · nitrile · thioethers

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