Nickel-Catalyzed Reversible Functional Group Metathesis between Aryl Nitriles and Aryl Thioethers

Journal Article

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ABSTRACT: We describe a new functional group metathesis between aryl nitriles and aryl thioethers. The catalytic system nickel/dcype is essential to achieve this fully reversible transformation in good to excellent yields. Furthermore, the cyanide- and thiol-free reaction shows high functional group tolerance and great efficiency for the late-stage derivatization of commercial molecules. Finally, synthetic applications demonstrate its versatility and utility in multistep synthesis.

Aryl nitriles and aryl thioethers are often found in biologically active molecules such as natural products, pharmaceuticals, fragrances, and agrochemicals.[1−4] Notably, these two functional groups are complementary in terms of their reactivity and directing ability for aromatic functionalization chemistry. The CN group is a traditional electron-withdrawing group that deactivates an aromatic ring and directs electrophilic aromatic substitution to the *meta* position.[5,6] In contrast, aryl thioethers are relatively electron-neutral substituents which facilitate these reactions at the *para* position.[7−9] Moreover, while cyanides are common precursors to carboxylic acids, ketones and amines, aryl thioethers are precursors to a wide range of important sulfur-containing products and can be used as handles for directed metalation reactions.[10−12] Many efforts have been realized to further transform aryl nitriles and aryl thioethers into other functional groups.[13−20] In light of the inherent orthogonality and complementarity of these two important functional groups, the development of efficient methods to interconvert them is an important goal in target-oriented synthesis (Scheme 1A).

Traditionally, these two classes of important products have been accessed from conventional aryl halide electrophiles using cyanide salts or thiols (Scheme 1B).[21−27] Because of the inconvenient nature of these reagents, such as high toxicity in the case of cyanide salts and low-molecular-weight thiols, researchers have tried to develop suitable alternatives. Recently, to avoid traditional metal cyanide reagents and classical toxic sources such as TMSCN and acetone cyanohydrin,[28−30] the development of less-toxic organic nitriles has emerged as an attractive alternative. Selected examples include the use of MeCN, butyronitrile and 2-methyl-2-phenylmalononitrile.[31−34] With regard to thiols, Walsh and co-workers have described an elegant access to functionalized diaryl thioethers via a debenzylative pathway between aryl benzyl sulfides and aryl bromides.[35] More recently, an example of aryl thioether formation using an aliphatic thioether as a formal thiol donor has been reported by Wu and co-workers.[36] Overall, while these methods provide useful and safer alternatives to the common cyanide and thiol reagents, they do follow a classical cross-coupling paradigm
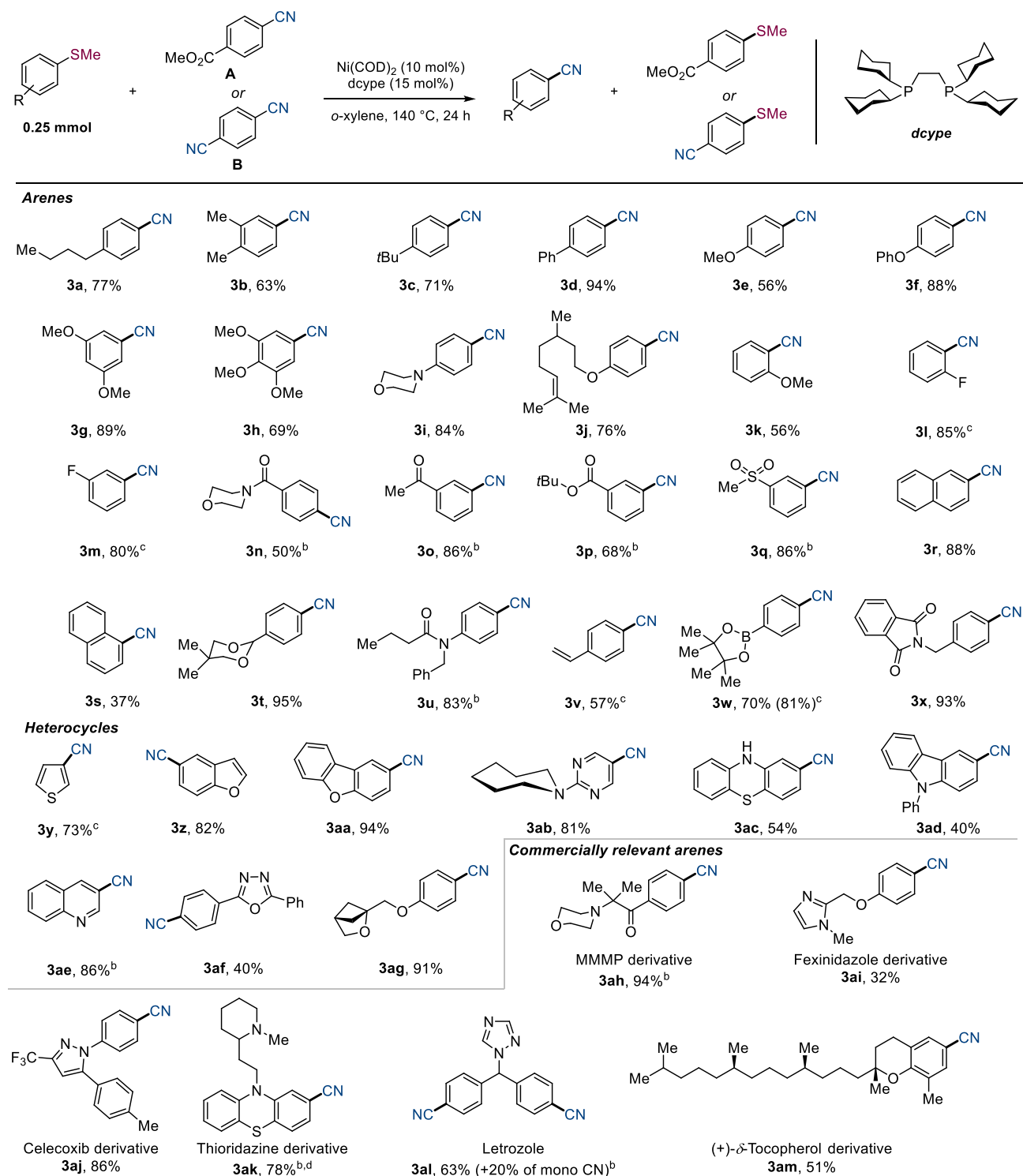
Scheme 1. Context of the Work
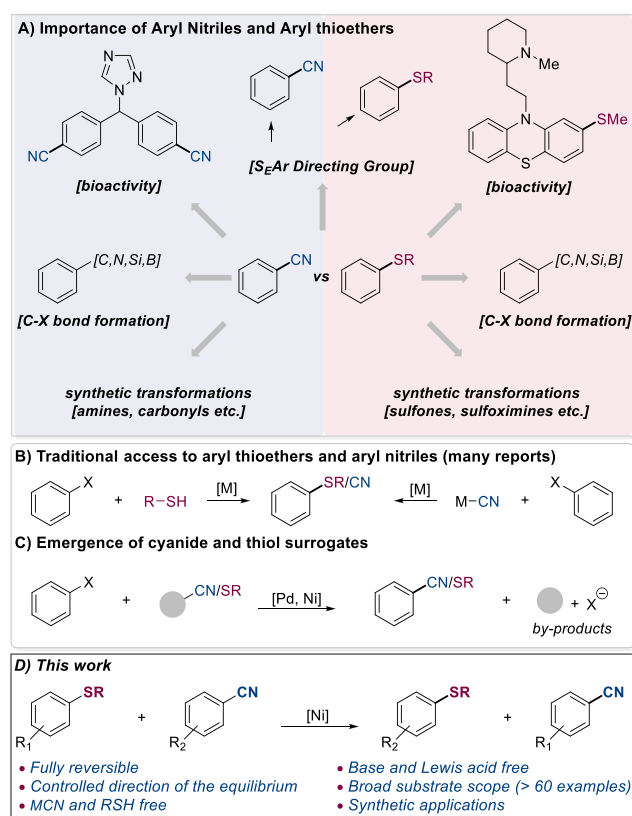
proceeding through the irreversible coupling of aryl halide electrophiles. (Scheme 1C).

Table 1. Scope with Respect to Aryl Thioethers[a]

Arenes

3a, 77% **3b**, 63% **3c**, 71% **3d**, 94% **3e**, 56% **3f**, 88%

3g, 89% **3h**, 69% **3i**, 84% **3j**, 76% **3k**, 56% **3l**, 85%[c]

3m, 80%[c] **3n**, 50%[b] **3o**, 86%[b] **3p**, 68%[b] **3q**, 86%[b] **3r**, 88%

3s, 37% **3t**, 95% **3u**, 83%[b] **3v**, 57%[c] **3w**, 70% (81%)[c] **3x**, 93%

Heterocycles

3y, 73%[c] **3z**, 82% **3aa**, 94% **3ab**, 81% **3ac**, 54% **3ad**, 40%

3ae, 86%[b] **3af**, 40% **3ag**, 91%

Commercially relevant arenes

MMMP derivative
3ah, 94%[b]

Fexinidazole derivative
3ai, 32%

Celecoxib derivative
3aj, 86%

Thioridazine derivative
3ak, 78%[b,d]

Letrozole
3al, 63% (+20% of mono CN)[b]

(+)-δ-Tocopherol derivative
3am, 51%

[a]Yield of isolated product. ArSMe (0.25 mmol), donor **A** (2.0 equiv), Ni(COD)₂ (10 mol %), dcype (15 mol %), *o*-xylene (0.25 M), 140 °C, 24 h. [b]Donor **B** (2.0 equiv) was used. [c]NMR yield. [d]The HCl salt was used with LiHMDS (1.1 equiv).

In 2018, Arndtsen's group and our group independently reported a distinct approach to cross-coupling reactions proceeding through the reversible metathesis of two electrophiles, acid chlorides and aryl iodides.[37−39] This new class of reactions effectively provides a means to interconvert, at will, these functional groups using a single catalytic system. Subsequently, Yamaguchi and co-workers elegantly used this concept to transfer an ester moiety to several aryl (pseudo)-halides.[40] We wondered whether a functional group metathesis approach could be applied to completely different classes of functional groups, such as aryl cyanides and thioethers. If such a transformation could be realized, then it would not only provide a unique way to interconvert these two orthogonal functional groups in a cyanide and thiol-free manner, but

would also considerably expand the scope of the emerging class of single-bond metathesis reactions (Scheme 1D).

On the basis of the recent success in activating both C−CN and C−SR bonds under nickel catalysis,[41−47] we reasoned that a Ni-based catalytic manifold could provide an appropriate platform to develop this reaction. However, two main challenges were identified: (1) a single catalyst and set of reaction conditions need to be competent for two distinct and reversible oxidative additions; (2) a suitable transfer mechanism, such as a direct crossover between two oxidative addition complexes, needs to be kinetically accessible. We initially explored this process by evaluating a range of ligands, in combination with a Ni(COD)$_2$ precatalyst, for the metathesis between thioanisole and 4-methylbenzonitrile. Traces of 4-methylthioanisole and benzonitrile were observed by employing 1,2-bis(dicyclohexylphosphino)ethane (dcype) as a ligand (details in the SI), which has been shown previously to enable the activation and the formation of C−SR and C−CN bonds.[45,48−50] After an extensive study (details in the SI), Ni(COD)$_2$ (10 mol %) and a slight excess of dcype (15 mol %) in o-xylene at 140 °C for 24 h were found to be most effective at reaching the equilibrium of the reaction, namely, to get the same product distribution in the forward and reverse reactions.

We next investigated different nitrile donors to find suitable conditions to shift the equilibrium of this reversible and thermodynamically controlled reaction toward the product (Ar−CN) side. We reasoned that an electronic mismatch could serve as a potent driving force for the reaction.[39] For electron-neutral and -rich aryl thioether acceptors, 2.0 equiv of methyl 4-cyanobenzoate (donor **A**) were competent to achieve the transformation in high yield, whereas for electron-poor aryl thioethers, 2.0 equiv of 1,4-dicyanobenzene (donor **B**) were employed. We next explored the scope of the reaction (Table 1). To our delight, a wide range of thioanisole derivatives worked efficiently under the reaction conditions. Indeed, both electron-neutral and electron-rich substrates (**3a−3i**) worked well, affording the corresponding products in good to excellent yield (56−94%). A citronellol-based ether, bearing an alkene that could possibly deactivate the catalyst through coordination, afforded the expected product (**3j**) in 76% yield.[51] Sterically hindered aryl thioethers bearing an ortho substituent (**3k** and **3l**) also proved to be competent partners in affording the desired product in 56 and 85% yields, respectively. We then applied the optimal conditions by using the other donor, 1,4-dicyanobenzene (donor **B**), to different electron-poor thioanisoles. Gratifyingly, many electron-withdrawing functional groups, such as fluoride (**3m**), amide (**3n**), ketone (**3o**), ester (**3p**), and sulfone (**3q**), were tolerated. In all cases, the desired product was obtained in moderate to excellent yield (50−87%). Bicyclic compounds such as 2- and 1-naphthyl derivatives (**3r** and **3s**) reacted smoothly under the reaction conditions (88 and 37%). We then successfully subjected several arenes bearing common functional groups, including acetal (**3t**,), benzyl-protected amide (**3u**), vinyl (**3v**), pinacol boronic ester (**3w**), and phthalimide-protected amine (**3x**), to our reaction. Furthermore, several heterocycles, such as a thiophene (**3y**), a benzofuran (**3z**), a dibenzofuran (**3aa**), a pyrimidine bearing an azepane moiety (**3ab**), a phenothiazine possessing a free aniline (**3ac**), a carbazole (**3ad**), which is an important class of compounds in organic electronics,[52] a quinolone (**3ae**), and a 1,3,4-oxadiazole (**3af**), all afforded the metathesis product in moderate to excellent yield (40−94%).
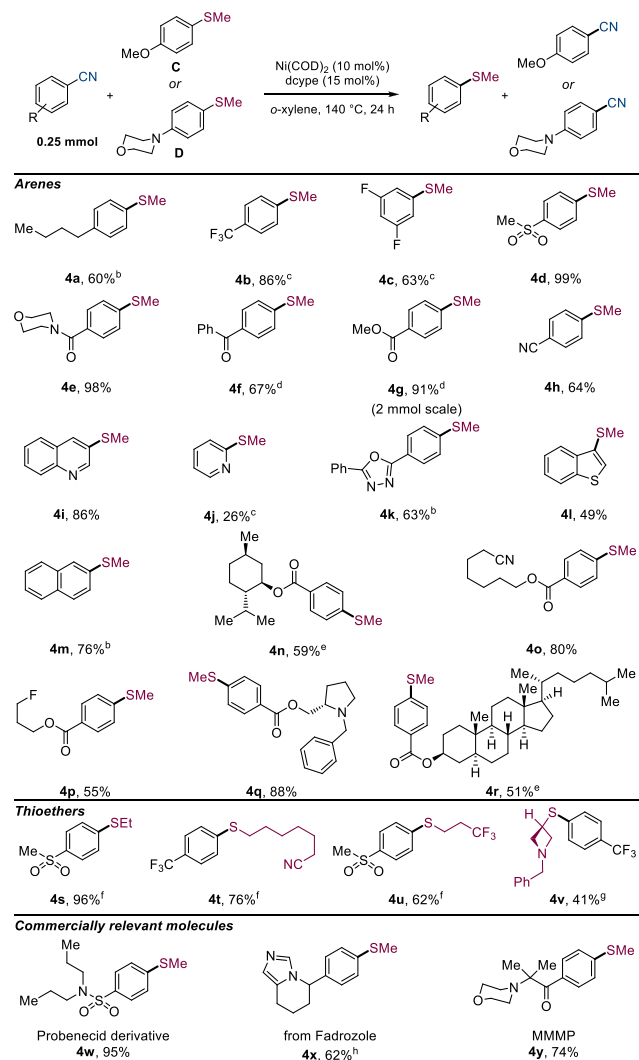
We also applied this methodology to a thioanisole bearing a 2-oxabicyclo[2.1.1]hexane moiety (**3ag**), which was recently shown to be a water-soluble bioisostere of benzene.[53] Gratifyingly, the expected nitrile product was obtained in excellent yield (91%).

Finally, we subjected several commercially relevant molecules to the reaction conditions. To our delight, the late-stage derivatization of photoinitiator MMMP (**3ah**)[54] and fexinidazole (**3ai**), a drug used to treat sleeping sickness,[55] proceeded smoothly. Furthermore, the synthesis of the nitrile derivative of celecoxib (**3aj**), a COX-2 inhibitor,[56] and the late-stage derivatization of thioridazine (**3ak**) were successfully achieved. We could also access a drug used in the treatment of breast cancer, letrozole (**3al**),[57] in an efficient way (63% yield), showing the possibility to transfer two cyanides in a single-step protocol. We finally synthesized a derivative of δ-tocopherol (**3am**) with this catalytic manifold in a synthetically useful yield of 51%.

The reverse reaction (i.e., the conversion of an aryl nitrile to an aryl thioether) was next explored (Table 2). We found that both 4-methoxythioanisole (donor **C**) and 4-morpholinethioanisole (donor **D**) were suitable donors for this reaction due to their electron-donating properties that thermodynamically favor the donation of the SMe group. Similar to the forward reaction, the functional group tolerance proved to be high. Indeed, thioanisoles bearing an alkyl (**4a**), trifluoromethyl (**4b**), difluoro (**4c**), sulfone (**4d**), amide (**4e**), ketone (**4f**), ester (**4g**), or cyano (**4h**) group were obtained in good to quantitative yield (60−99%). Several heterocycles and bicycles, such as quinoline (**4i**), pyridine (**4j**), 1,3,4-oxadiazole (**4k**), benzothiophene (**4l**), and 2-naphtalene (**4m**), worked in modest to excellent yield (26−86%). Furthermore, menthol (**4n**), a fluorine-containing substrate (**4p**), proline (**4q**), and cholesterol derivatives (**4r**) were all found to be competent partners. Notably, an aryl nitrile bearing an alkyl nitrile (**4o**) worked smoothly under the reaction conditions, confirming that aliphatic carbon−cyanide bonds do not react with nickel in the absence of Lewis acids.[58] We next explored the substrate scope of alkyl thioethers. To our delight, thioethers bearing either an ethyl (**4s**), an alkyl nitrile (**4t**), an alkyl CF$_3$ (**4u**), or an azetidine (**4v**) group were efficiently transferred to the metathesis products in moderate to excellent yield (41−96%). A derivative of probenecid (**4w**) was successfully obtained in 95% yield, as well as the late-stage derivatized fadrozole (**4x**, 62%). Finally, the synthesis of widely used photoinitiator MMMP (**4y**) was performed, affording the desired product in good yield (74%).[52]

Inspired by Yamaguchi and co-workers' recent work, the ester dance on an aromatic ring,[59] we explored the possibility of scrambling the cyano and thioether groups located on a single substrate (Scheme 2A). We thus subjected starting material **5a**, bearing one electron-rich and one electron-poor aromatic ring, to the optimized conditions to obtain the clean formation of three new products in addition to the starting material. Gratifyingly, we were able to separate the four different compounds which were further characterized. This result shows the potential of this methodology to generate a library of derivatives through late-stage nitrile/thioether metathesis diversification.
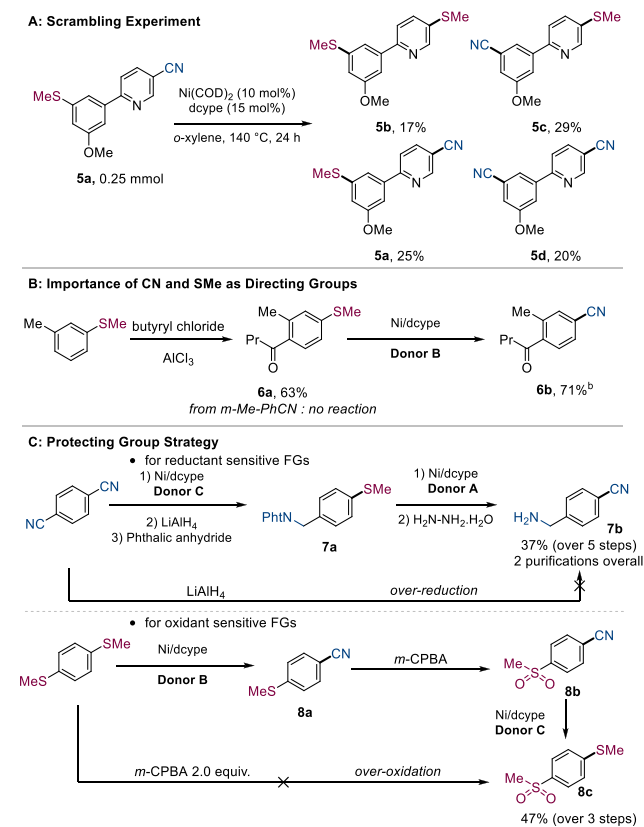
We next turned our attention to the intrinsic electronic properties of both functional groups and their influence on Friedel−Crafts acylation (Scheme 2B). The thioether group usually directs the reaction to the *para* position,[7−9] while the

Table 2. Scope with Respect to Aryl Nitriles[a]

Scheme 2. Synthetic Applications[a]

A: Scrambling Experiment

B: Importance of CN and SMe as Directing Groups

C: Protecting Group Strategy

[a]Yield of isolated product (%). [b]Isolated as an alcohol after reduction. For details, see the SI.

[a]Yield of isolated product. ArCN (0.25 mmol), donor **C** (3.0 equiv), Ni(COD)$_2$ (10 mol %), dcype (15 mol %), o-xylene (0.25 M), 140 °C, 24 h. [b]Donor **D** (3.0 equiv) was used. [c]NMR yield. [d]Isolated as an alcohol after reduction. [e]Isolated as sulfone after oxidation. [f]2.0 equiv of the respective MeO−Ph−SR donor. [g]1.0 equiv of the respective MeO−Ph−SR donor. [h]The HCl salt was used with LiHMDS (1.1 equiv). For details, see the SI.

deactivating electron-withdrawing nitrile directs the reaction to the *meta* position.[5,6] By subjecting 3-methylthioanisole to a mixture of butyryl chloride and aluminum chloride, 63% of the desired ketone product (**6a**) was isolated. Interestingly, the same set of conditions did not lead to any conversion using 3-methylbenzonitrile, and no product was observed even under more forcing conditions, confirming the strong deactivating effect of this group (details in the SI). We could then successfully transform the thioanisole derivative to aryl nitrile **6b** in 71% yield, thus highlighting the possibility to synthesize densely substituted aromatic products with challenging substitution patterns.

Nitrile and thioether groups have orthogonal chemical reactivity. The former is tolerant to oxidative conditions but nontolerant to reductive ones, which is the exact opposite for thioethers. This complementary behavior offers strategic opportunities for target-oriented synthesis. In this context,

the reversibility of our metathesis reaction can be harnessed as a useful protecting group strategy for cyanides and thioethers. Our initial idea was to protect a nitrile group as a thioether to perform a selective reduction (Scheme 2C). The selectively monoreduced product (**7b**) was obtained in a synthetically useful yield of 37% over five steps, with only two purifications. We next transiently protected a thioether group as a nitrile to perform an oxidation process (Scheme 2C). Using this strategy, the mono-oxidized product was obtained in 47% yield over three steps. These results clearly show the potential of this new metathesis reaction to overcome conventional synthetic challenges through a new kind of protecting group strategy.

In conclusion, we have developed a functional group metathesis between aryl nitriles and aryl thioethers under nickel catalysis. This transformation does not require any cyanide or thiol reagents, making it a convenient alternative to traditional cross-coupling reactions. Late-stage derivatization of commercial molecules further demonstrated the synthetic potential of the transformation. In a broader context, this new example of functional group metathesis significantly expands the scope of this emerging class of reactions.

■ ASSOCIATED CONTENT

ⓈSupportingInformation

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00529.

Experimental details for all reactions and analytic details for all products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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