Ni-Catalyzed Aryl Sulfide Synthesis through an Aryl Exchange Reaction

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ABSTRACT: A Ni-catalyzed aryl sulfide synthesis through an aryl exchange reaction between aryl sulfides and a variety of aryl electrophiles was developed. By using 2-pyridyl sulfide as a sulfide donor, this reaction achieved the synthesis of aryl sulfides without using odorous and toxic thiols. The use of a Ni/dcypt catalyst capable of cleaving and forming aryl–S bonds was important for the aryl exchange reaction between 2-pyridyl sulfides and aryl electrophiles, which include aromatic esters, arenol derivatives, and aryl halides. Mechanistic studies revealed that Ni/dcypt can simultaneously undergo oxidative additions of aryl sulfides and aromatic esters, followed by ligand exchange between the generated aryl–Ni–SR and aryl–Ni–OAr species to furnish aryl exchanged compounds.

Aryl sulfide is an important chemical motif that is widely seen in biologically active compounds, as well as in chemical materials.[1] Due to this importance, there has been interest among chemists to expand the methodology toward the synthesis of aryl sulfides. Conventionally, metal-catalyzed C–S bond formations of aryl electrophiles with thiols has been utilized (Figure 1A).[2,3] Contrary to the high reliability of this method, the use of thiols is often shunned because of their odor and toxicity. The reaction of aryl halides with disulfides,[4] and decarbonylation reaction of thioesters have been developed as alternatives.[5] Recently, a reaction using alkyl sulfides as a sulfide source has emerged using palladium catalysis under strongly basic conditions.[6] Despite these progresses in this area, the development of C–S bond formation without thiols is still a topic in its infancy.[7]

Meanwhile, transition metal-catalyzed aryl exchange reactions between two different aryl electrophiles have gained attention in recent years.[8,9] This type of transformation is not only conceptually interesting but also synthetically valuable because it is possible to avoid the use of nucleophilic counterparts which often triggers poor functional group tolerance and catalyst deactivation. As a pioneering work, Morandi and Arndtsen independently reported a Pd-catalyzed aryl exchange reaction between aryl iodides and aroyl chlorides (Figure 1B).[10] Commonly, the development of these reactions requires a high level of design. It is important to choose and/or develop an appropriate metal catalyst enabling both the cleavage and formation of two distinct chemical bonds. Another consideration is the design of a set of substrates to control the equilibrium of the reaction.

In related work, our group developed a Ni-catalyzed aryl exchange reaction between aryl halides and aromatic esters (Figure 1B).[11] The key for this reaction was the high bond-cleaving ability of Ni/dcypt catalyst, which also allowed the reaction of challenging arenol derivatives instead of aryl halides.[12] However, this reaction afforded only aromatic esters as a product, not aryl halides and arenols. We assumed that this is due to the difficulty of reductive elimination of C–X bonds from the Ar–Ni/dcypt–X intermediate (X = halogen and OR). Because it is known that C–S bond reductive elimination is a relatively facile process in metal catalysis,[13] we envisioned that aryl sulfide synthesis by a catalytic aryl exchange reaction would be reasonable and possible. Herein, we report a new aryl sulfide synthesis by means of a Ni/dcypt-catalyzed aryl exchange between aryl sulfides and aromatic esters (Figure 1C). Moreover, this nickel catalysis was revealed to be viable for various aryl electrophiles such as aryl halides and arenols other than aromatic esters. During the preparation of this manuscript, Morandi reported a similar aryl sulfide synthesis using an aryl exchange reaction between aryl sulfides with aryl nitriles.[14]

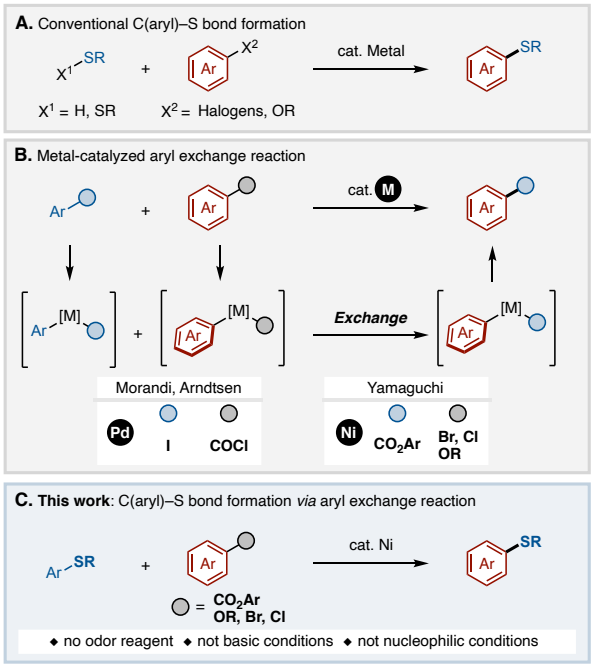
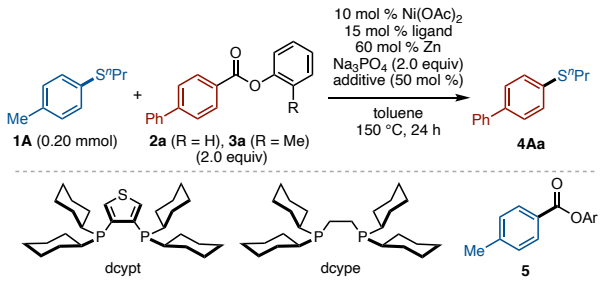


Figure 1. (A) Conventional catalytic C–S bond formations. (B) Catalytic aryl exchange reactions. (C) Ni-Catalyzed aryl sulfide synthesis *via* aryl exchange reaction.

To initiate the study, 4-tolyl sulfide **1A** and 4-phenylbenzoate **2a** were reacted under the conditions for our previous aryl exchange reaction ($Ni(OAc)_2$/dcypt catalyst, Zn, and Na_3PO_4) (Table 1). To our delight, the desired aryl sulfide **4Aa** was obtained in 43% yield along with 16% yield of aromatic ester **5** (Table 1, entry 1). In this case, phenyl propyl sulfide was also generated as a major byproduct, which is derived from the phenol moiety on **2a** through an undesired C(aryl)–O bond cleavage (see the Supporting Information for details).[11,12a–12d] In order to suppress this undesired pathway, we utilized tolyl ester **3a** with the expectation that the *ortho*-methyl group can block the C(aryl)–O bond oxidative addition (Table 1, entry 2). As expected, the yield of **4Aa** was improved to 58%, and significantly decreased the formation of phenyl propyl sulfide. A change from $Ni(OAc)_2$ to $Ni(cod)_2$ decreased the yields of **4Aa** and **5** (Table 1, entry 3). Hypothesizing that the conditions using $Ni(OAc)_2$ and Zn produces $Zn(OAc)_2$ which might promote this reaction, we added a semi-catalytic amount of $Zn(OAc)_2$ into the reaction with $Ni(cod)_2$. As expected, we obtained a comparable result with the conditions using $Ni(OAc)_2$ (Table 1, entries 2 and 4). Moreover, the addition of $Zn(OAc)_2$ to the conditions using $Ni(OAc)_2$ improved the yield of **3Aa** to 80% whereas the yield of **5** remained same (Table 1, entry 5). Removing Na_3PO_4 from these conditions decreased the yields of **4Aa** and **5** (Table 1, entries 6 and 7). It was revealed that Pd/dcypt catalyst can also work without $Zn(OAc)_2$ to give **4Aa** and **5** albeit in lower yields (Table 1, entry 8). Finally, it was found that the choice of ligand was crucial. Our dcypt ligand effectively worked well, yet other diphosphines and monophosphines were totally ineffective (Table 1, entries 9–12). With these studies, $Ni(OAc)_2$/dcypt/Zn/$Zn(OAc)_2$ catalysis was identified as our optimized conditions. Of note, a similar Ni/Zn catalysis was often employed for reductive biaryl coupling of two aryl electrophiles, but such a biaryl formation did not occur in this case.[15]

Table 1. Optimization of reaction conditions



entry	R	ligand	additive	Yield of **4Aa**/%[a]	Yield of **5**/%[a]
1	H	dcypt		43	16
2	Me	dcypt		58	23
3[b]	Me	dcypt		24	17
4[b]	Me	dcypt	$Zn(OAc)_2$	58	24
5	Me	dcypt	$Zn(OAc)_2$	80 (80)[e]	24
6[c]	Me	dcypt		51	19
7[c]	Me	dcypt	$Zn(OAc)_2$	71	16
8[d]	Me	dcypt		33	5
9	Me	dcype	$Zn(OAc)_2$	24	trace
10	Me	dppe	$Zn(OAc)_2$	7	0
11	Me	Xantphos	$Zn(OAc)_2$	0	0
12	Me	P^{n}Bu$_3$	$Zn(OAc)_2$	0	0

Conditions: **1A** (0.20 mmol), **2** (2.0 equiv), $Ni(OAc)_2$ (10 mol %), ligand (bidentate: 15 mol %, monodentate: 30 mol %), Na_3PO_4 (2.0 equiv), toluene (0.80 mL), 150 °C, 24 h. [a] NMR yield. [b] $Ni(cod)_2$ instead of $Ni(OAc)_2$. [c] Without Na_3PO_4. [d] $Pd(OAc)_2$ instead of $Ni(OAc)_2$. [e] Isolated yield.

Although we established the optimized conditions, the two following questions arose. Can two distinct oxidative additions to the same Ni/dcypt catalyst can occur? Can the two generated nickel complexes engage in the exchange reaction? To answer these questions, we next carried out several mechanistic studies. We first confirmed the oxidative addition reaction of aryl sulfide **6A** to Ni(cod)/dcypt complex (Figure 2A).[16] The reaction of equimolar $Ni(cod)_2$, dcypt, and aryl sulfide **6A** (2.0 equiv) in toluene at 80 °C smoothly furnished oxidative addition complex **7** in 83% yield. The structure of **7** was unambiguously confirmed by X-ray crystallographic analysis. Next, we attempted a double oxidative addition of aryl sulfide **6A** and aromatic ester **3b** to $Ni(cod)_2$/dcypt at 80 °C, and the time course plot is shown in Figure 2B (for the details, see the SI). It was observed that **6A** undergoes a much faster oxidative addition than **3b**. Interestingly, during this reaction, the amount of **8** and **9** constantly increased, and that of **7** and Ni(cod)/dcypt decreased, giving yields of **8** and **9** of 49% after 42 h. This result indicates the reversibility of the C–S bond's oxidative addition and reductive elimination. This reversibility was directly confirmed by the reaction between **7** and aromatic ester **3b** in toluene at 90 °C giving nickel complexes **8** and **9** in 11% and 12% yield, respectively (Figure 2C, see the SI for details). With these studies, we concluded that one of the key aspects of these two simultaneous oxidative additions would be the reversible oxidative addition and reductive elimination of C–S bonds. This reversibility would allow for aromatic esters to undergo oxidative additions to the Ni(0) species albeit in a slow reaction rate. Finally, the reaction of **7** and **8** furnished **4Ab** (59% yield) along with **6A**, showing that an exchange reaction between two nickel intermediates is possible (Figure 2D).

Our next interest was to clarify why this reaction provides aryl sulfide **4** as a major product and not aromatic esters. We assumed that the elucidation of the role of Zn/$Zn(OAc)_2$ might give insights on this question. Thus, aryl exchange reaction between **6A** and **3b** in the presence and absence of Zn/$Zn(OAc)_2$ was performed by using three different nickel complexes **7**, **8**, and **9** (30 mol %) in toluene at 150 °C (Figure 2E). Without Zn/$Zn(OAc)_2$, nickel complexes **7** and **9** delivered **4Ab** in 21% and 36%, respectively. However, **8** gave only 8% yield of **4Ab**. By the addition of Zn and $Zn(OAc)_2$ into these reactions, the yield of **4Ab** was improved to over 40% yield in all cases. Judging from these results, we postulated that a Ni–arenoxo complex like **8** would be a resting-state intermediate. To gain further insight on the effect of Zn and $Zn(OAc)_2$ particularly on the aryl–Ni–arenoxo complex, the reaction of aromatic ester **3c** with $Ni(cod)_2$/dcypt catalyst was performed (Figure 2F, entry 1). As a result, we obtained arene **10** in 8% yield, which was thought as a decomposed compound from the aryl–Ni–arenoxo species. Furthermore, the formation of **10** was accelerated only when both Zn and $Zn(OAc)_2$ were used (Figure 2F, entries 2–4). Thus, the main role of Zn and $Zn(OAc)_2$ in this catalysis is the induction of

reductive decomposition of the aryl–Ni–arenoxo complex to regenerate the Ni(0) species. However, the H atom source and detailed action of these zinc reagents were still unclear.

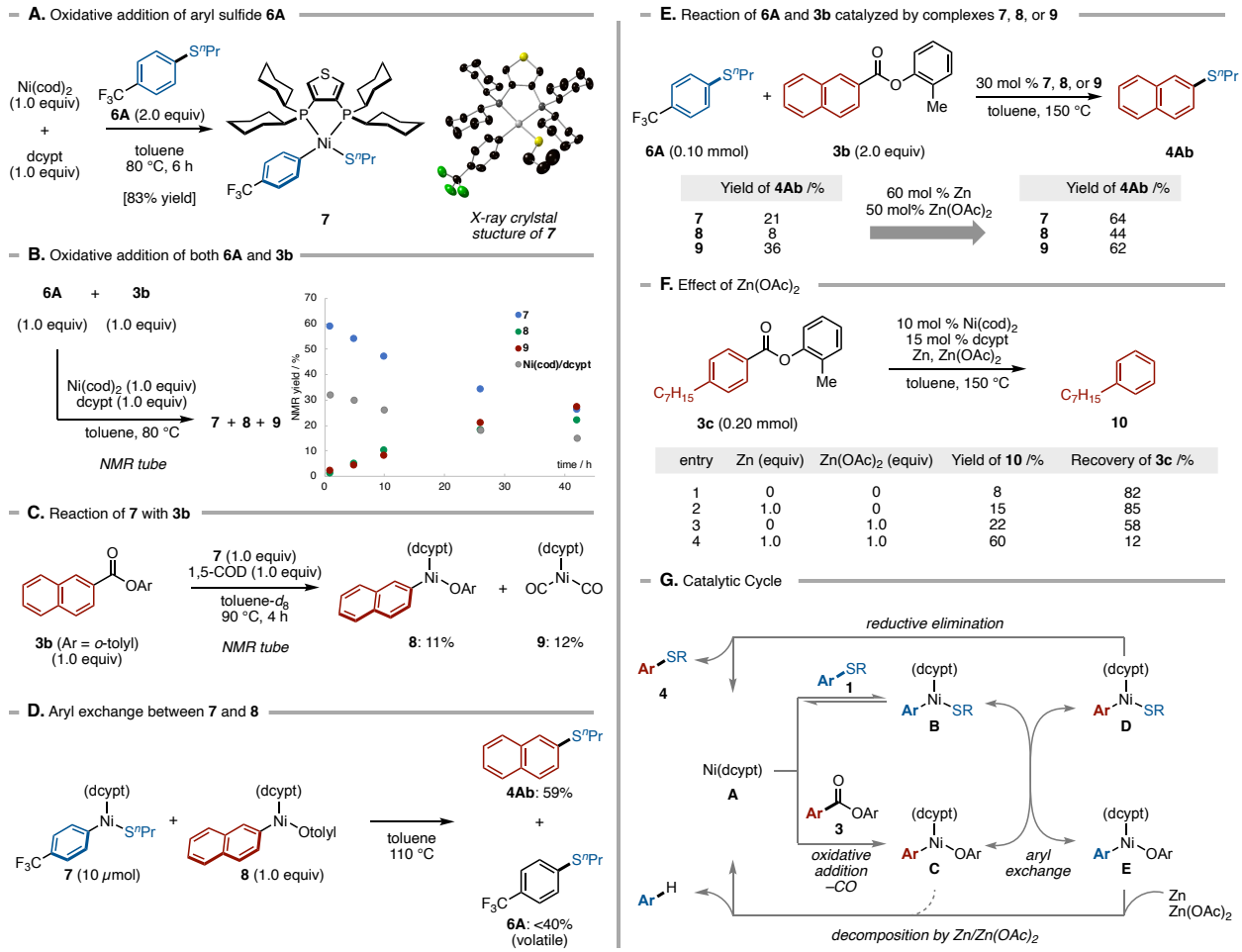
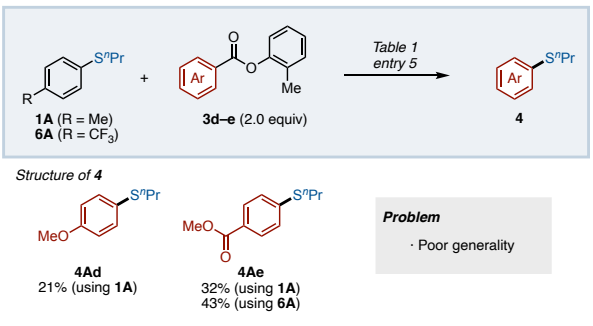


Figure 2. Mechanistic studies. (A) Oxidative addition of **6A**. (B) Double oxidative addition of **6A** and **3b** and its time-course plot. (C) Reversibility of the C–S bond oxidative addition and reductive elimination. (D) Reaction of nickel complexes **7** with **8**. (E and F) Effect of Zn and $Zn(OAc)_2$. (G) A plausible catalytic cycle.

Combining the results from these mechanistic studies, a postulated catalytic cycle is illustrated in Figure 2G. The Ni(0)dcypt complex can undergo two separate oxidative addition pathways, onto aryl sulfide **1** and onto aromatic ester **3**, to generate aryl–Ni–SR species **B** and aryl–Ni–arenoxo species **C**, respectively. These complexes can react with each other, namely an exchange reaction, to give **D** and **E**. The reductive elimination of **D** can furnish aryl-exchanged product **4**. On the other hands, intermediate **E** can be decomposed by Zn and $Zn(OAc)_2$ to afford an arene and regenerate Ni(0) species **A**. In this catalytic cycle, all of the steps except for the decomposition of **E** (and **C**) are thought to be reversible.

These mechanistic studies informed us that the Ni(0) regeneration step from intermediate **E** would be a turnover-limiting step. Although Zn and $Zn(OAc)_2$ enhanced this process, these zinc reagents also effected the undesired decomposition of Ni–arenoxo intermediate **C**. Probably due to this difficulty, the substrate generality of this reaction turned out to be narrow (Scheme 1). For instance, the reactions of electron-rich (**3c**) as well as electron-deficient (**3d**) aromatic esters with **1A** gave the corresponding aryl sulfides **4** in low yields. Even when we changed sulfide donor **1A** to electron-deficient **6A**, the yield of **4Ae** did not improve. In order to solve this issue, we sought an alternative protocol capable of accelerating the turnover-limiting decomposition of **E** selectively.

Scheme 1. Substrate Scope of the Reaction Using 1A and 6A.



Conditions: **1A** or **6A** (0.20 mmol), **3** (2.0 equiv), $Ni(OAc)_2$ (10 mol %), dcypt (15 mol %), Zn (60 mol %), $Zn(OAc)_2$ (50 mol %), Na_3PO_4 (2.0 equiv), toluene (0.80 mL), 150 °C, 24 h.

To this end, we focused on employing 2-pyridyl sulfide as a sulfide donor (Figure 3A). We previously developed a decarbonylative synthesis of diarylethers, where we found that only the reductive elimination of 2-azinyl–O bonds from a Ni/dcypt complex was facile, but that of other aryl–O bonds is difficult.[17,18] Accordingly, the use of 2-pyridyl sulfide can "funnel" this reversible catalytic cycle into desired products **4** by the selective enhancement of the reductive elimination of intermediate **E**. To support this funneling strategy, we first subjected 2-pyridyl sulfide **11A** with aromatic ester **3b** to the aryl exchange reaction by using $Ni(cod)_2$/dcypt in toluene at 150 °C (Figure 3B). Delightfully, the reaction furnished aryl sulfide **4Ab** in 48% yield together with decarbonylative etherification product **12** in 53% yield. The reverse reaction was also conducted, generating only a tiny amount of **11A**. This suggested that the reaction is no longer reversible with **11A**. In contrast, when **1A** was subjected to these conditions instead of **11A**, we confirmed that the reaction was completely reversible (See the SI for detail).

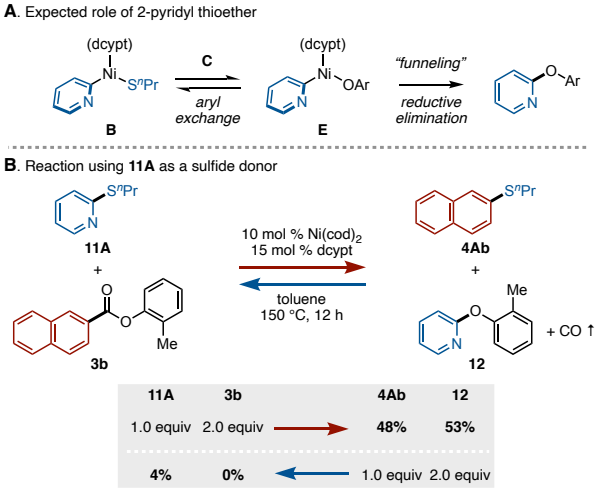
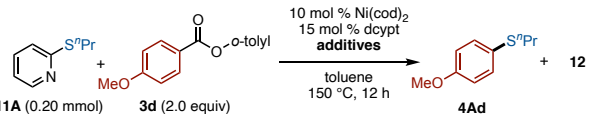


Figure 3. (A) 2-Pyridyl sulfide for a funneling strategy. (B) Forward reaction and reverse reaction of **11A**.

Encouraged by this result, we optimized the reaction conditions by using **11A** and **3d** (Table 2). The use of $Ni(cod)_2$/dcypt afforded **4Ad** in 23% yield and **12** in 20% yield (Table 2, entry 1). When **11A** was used as a sulfide donor, the addition of $Zn(OAc)_2$ and Na_3PO_4 was not effective, but the addition of only Zn improved the yields of **4Ad** and **12** (Table 2, entries 2–4). Increasing the amount of Zn slightly improved the yield (Table 2, entry 5). Finally, a longer reaction time gave the best result (Table 2, entry 6).

Table 2. Optimization of Reaction Conditions Using 11A.

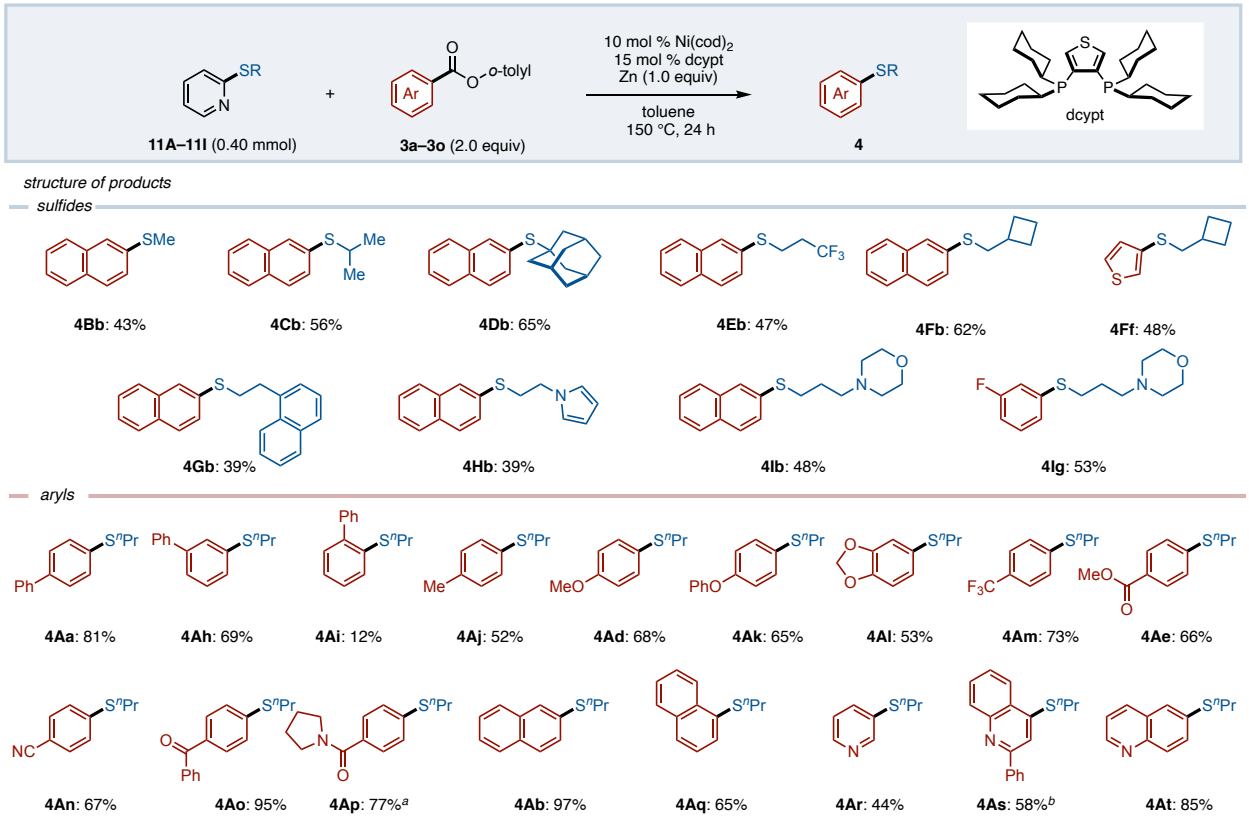


entry	Zn 60 mol %	$Zn(OAc)_2$ 50 mol %	Na_3PO_4 2.0 equiv	Yield of **4Ad**/%[a]	Yield of **12**/%[a]
1	–	–	–	23	20
2	○	○	○	26	4
3	○	–	○	30	33
4	○	–	–	46	54
5	○[b]	–	–	49	54
6[c]	○[b]	–	–	66	81

Conditions: **11A** (0.20 mmol), **3d** (2.0 equiv), $Ni(cod)_2$ (10 mol %), dcypt (15 mol %), toluene (0.80 mL), 150 °C, 12 h. [a] Determined by ^1H NMR analysis. [b] Zn (1.0 equiv). [c] 24 h.

Scheme 2. Substrate Scope of the Reaction Using 11. [a]

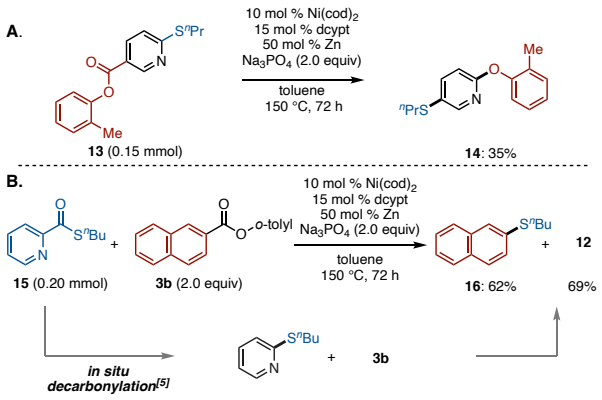
With the optimized conditions in hand, we then evaluated the substrate scope of the present reaction (Scheme 2). First, we examined the scope of sulfide groups. This reaction successfully transferred primary, secondary, and tertiary alkyl sulfide groups to give the corresponding aryl sulfides in moderate yields (**4Bb**, **4Cb**, **4Db**). Of note, for the methyl sulfide **4Bb** synthesis, the present method is more advantageous than typical cross-coupling methods using methane thiol, because methane thiol is a gaseous (b.p. = 6 °C) and strongly odorous reagent, often associated with cumbersome handling. Other alkyl sulfides bearing CF_3 (**4Eb**), cyclobutyl (**4Fb**, **4Ff**), and arenes (**4Gb**) were synthesized in acceptable yields. Nitrogen substituents on sulfide groups were compatible with the present reaction (**4Hb**, **4Ib**, **4Ig**). The scope of arenes was next investigated. It was revealed that *para*- and *meta*-substituents did not affect on this reaction significantly (**4Aa**, **4Ah**), however, *ortho*-substituents inhibited the reaction due to steric repulsions with the catalyst (**4Ai**). With respect to the electronic nature of substituents, both electron-donating and electron-withdrawing groups at the *para*-position were applicable to the present reaction. Aryl sulfides bearing methyl (**4Aj**), methoxy (**4Ad**), phenoxy (**4Ak**) and dioxole (**4Al**) were obtained in moderate yields. Compared to Morandi's recent method that was mainly effective for the synthesis of aryl sulfides with electron-withdrawing groups,[14] it is noteworthy that our present reaction can also synthesize highly electron-rich arenes such as methoxy and phenoxy aryl sulfides (**4Ad**, **4Ak**). Several electron-withdrawing groups including highly reactive functional groups such as alkyl ester (**4Ae**), cyano (**4An**), ketone (**4Ao**), and amide (**4Ap**) were tolerated. Naphthyl sulfides (**4Ab**, **4Aq**) were obtained in good to moderate yields. The exchange reaction of heteroaromatic esters was also viable to this reaction, furnishing the corresponding heteroaryl sulfides in moderate yields (**4Ff**, **4Ar**, **4As**, **4At**).



Conditions: **11** (0.40 mmol), **3** (2.0 equiv), $Ni(cod)_2$ (10 mol %), dcypt (15 mol %), Zn (1.0 equiv), toluene (1.6 mL), 150 °C, 24 h. Yields of isolated products are shown. [a] Obtained as a sulfone after oxidation by *m*CPBA. [b] Obtained as a sulfoxide after oxidation by Oxone®.

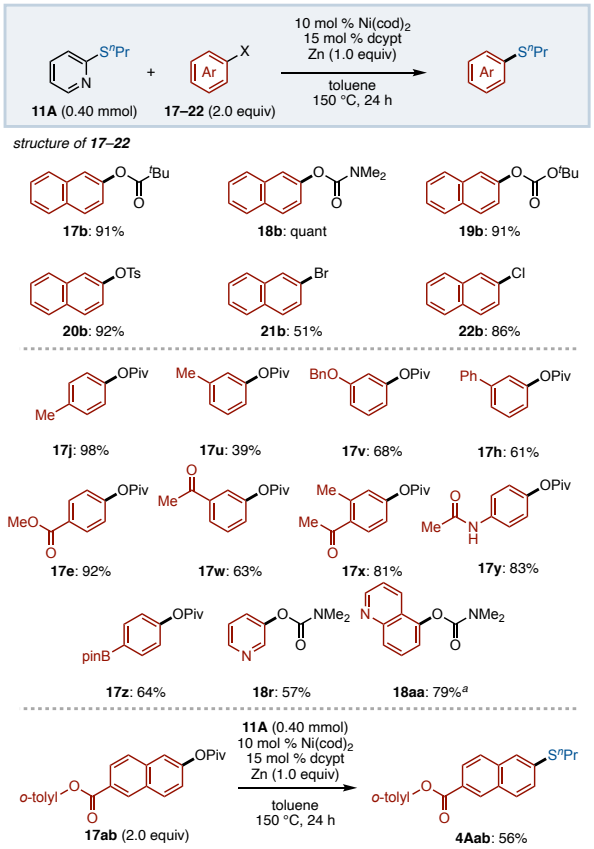
We then performed this reaction in an intramolecular setting. Pyridine **13** bearing both a sulfide and a tolylester was treated under the optimized conditions (Scheme 3A). As a result, we obtained 2-arenoxylated 3-pyridyl sulfide **14** in 35% yield. This transformation proceeds through a double exchange reaction on the pyridine ring, which is rare in other exchange reactions.[10] Next, we expected that thioester **15** can be used as a sulfide donor through our previously developed Ni-catalyzed decarbonylation[5e] to form 2-pyridyl sulfide *in-situ* (Scheme 3B). Delightfully, under the Ni/dcypt catalysis, we obtained aryl sulfide product **16** in 62% yield along with 2-arenoxypyridine **12** in 69% yield.

Scheme 3. (A) An Intramolecular Reaction of 13 (B) A Reaction Using Thioester 15.



Because Ni/dcypt catalyst is known to be effective for the oxidative addition of aryl halides as well as arenol derivatives, we thought that it is possible to utilize other aryl electrophiles than aromatic esters (Scheme 4).[12] Delightfully, Ni/dcypt/Zn catalysis was found to be applicable to aryl pivalate, carbamate, carbonate, sulfonate, bromide, and chlorides, giving a desired aryl sulfide **4Ab** in generally good yields. We evaluated the substrate generality of the reaction using aryl pivalates **17** and aryl carbamates **18**. Pivalates **17** bearing both electron-donating groups (**17j**, **17u**, **17v**) and phenyl (**17h**) engaged in this reaction to give the corresponding aryl sulfides. Sensitive functional groups such as esters (**17e**), ketones (**17w** and **17x**), secondary amides (**17y**), and boronic esters (**17z**) were tolerated. Pyridyl (**18r**) and quinolinyl (**18aa**) carbamates were also suitable substrates, being converted to the corresponding aryl sulfides in good yields. Furthermore, naphthalene with both pivalate and aryl ester (**17ab**) was tested to examine which group reacts faster. As a result, aromatic ester **4Aab** was obtained as a major product in 56% yield (see the SI for details).

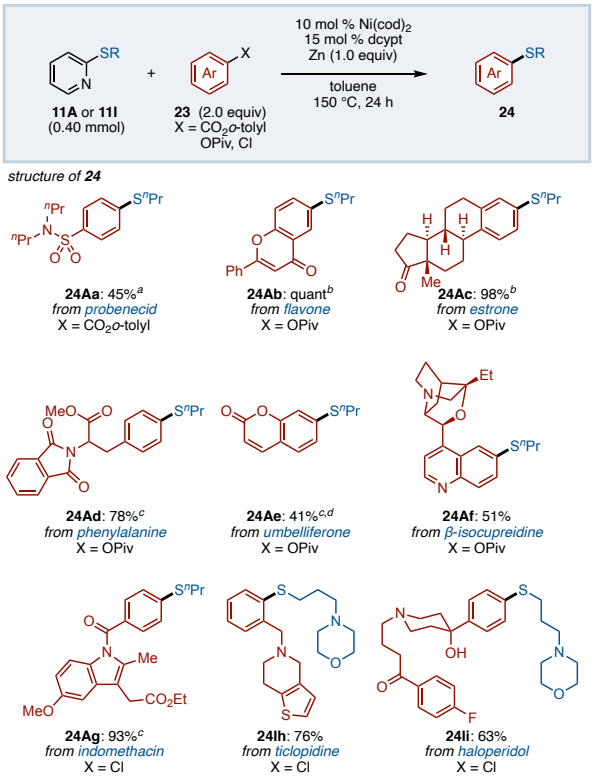
Scheme 4. Scope of Sulfide Acceptors



Conditions: **11A** (0.40 mmol), **17**–**22** (2.0 equiv), $Ni(cod)_2$ (10 mol %), dcypt (15 mol %), Zn (1.0 equiv), toluene (1.6 mL), 150 °C, 24 h. Yields of isolated products are shown. [a] Obtained as a sulfone after oxidation by *m*CPBA.

Aromatic esters, arenols, and aryl halides are frequently seen in natural products and pharmaceuticals. Expecting that the present method can be applied to a late-stage C–S bond formation *via* functional group interconversion, we performed reactions on known substrates with many functional groups.[19] As a result, we succeeded in derivatizing biologically active molecules such as probenecid aryl ester, flavone, estrone, phenylalanine, umbelliferone, and β-isocupreidine pivalates in good yields (Scheme 5). Drug molecules containing an aryl chloride moiety were also transformed into the corresponding aryl sulfides in good yields. Of note, in these demonstrations, it was shown that the present method was compatible with reactive functional groups such as ketones, imides, esters, tertiary amines, and tertiary alcohol groups.

Scheme 5. Late-Stage C–S Bond Formation via Functional Group Interconversion.



Conditions: **11** (0.40 mmol), **23** (2.0 equiv), $Ni(cod)_2$ (10 mol %), dcypt (15 mol %), Zn (1.0 equiv), toluene (1.6 mL), 150 °C, 24 h. Yields of isolated products are shown. [a] Obtained as a sulfone after oxidation by Oxone®. [b] Obtained as a sulfoxide after oxidation by *m*CPBA. [c] Obtained as a sulfone after oxidation by *m*CPBA. [d] $Ni(OAc)_2$ (10 mol %), dcypt (15 mol %), Na_3PO_4 (2.0 equiv), Zn (60 mol %), $Zn(OAc)_2$ (50 mol %).

In summary, we have developed a Ni-catalyzed aryl sulfide synthesis through an aryl exchange. By using 2-pyridyl sulfide as a sulfide donor, not only aromatic esters, but also arenols and haloarenes can be used as a sulfide acceptor. This method presents a new aryl sulfide synthesis without using highly nucleophilic and odorous thiols. Mechanistic studies confirmed that this reaction proceeded through two oxidative additions of aryl sulfides and aromatic esters at the same time, followed by exchange reaction between the resulting nickel complexes. Further studies to develop other aryl exchange reactions and detailed mechanistic studies in detail are ongoing in our laboratory.[20]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge.

Experimental procedures and spectroscopic data for compounds including ^{1}H-, ^{13}C-, ^{19}F-, and ^{31}P NMR spectra and crystallographic data (PDF). CCDC 2074846 contains the supplementary crystallographic data for this paper.

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Notes

The authors declare no competing financial interest.

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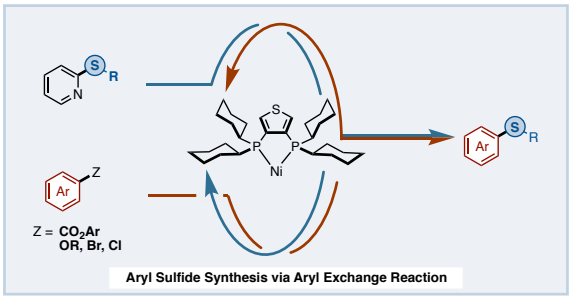

Aryl Sulfide Synthesis via Aryl Exchange Reaction