

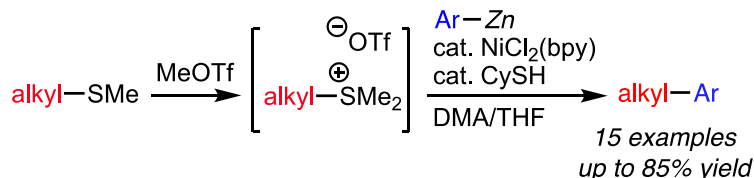
Nickel-Catalyzed Negishi-type Arylation of Trialkylsulfonium Salts

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Abstract Negishi-type arylation of trialkylsulfonium salts with arylzinc reagents has been accomplished under nickel catalysis. The use of cyclohexanethiol as an additional ligand was found to be particularly important to promote C–S cleavage. The present reaction accommodates one-pot arylation of dialkyl sulfides by combining with *S*-methylation with MeOTf. Mechanistic experiments suggest that C–S cleavage would proceed via single-electron transfer (SET) to generate the most stable carbon-centered radical and that the thiolate ligand would promote the C–S cleavage and radical recombination step.

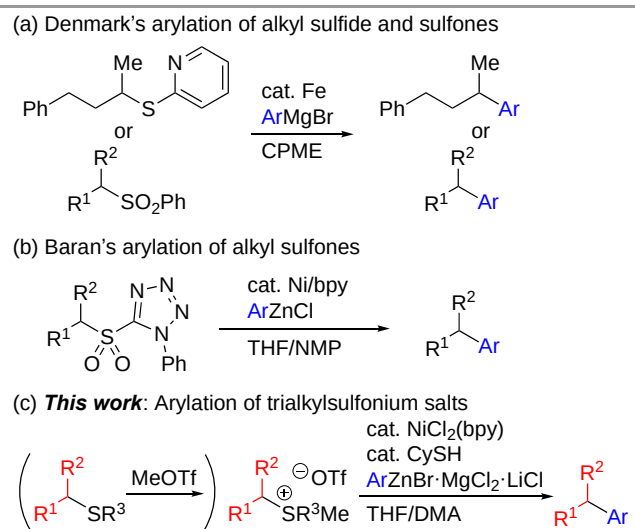
Key words Negishi coupling, trialkylsulfonium salt, nickel catalysis, thiolate ligand, radical

Transition-metal-catalyzed cross-coupling represents a privileged class of molecular transformations for the construction of C–C bonds, and is regarded as an indispensable tool in many scientific disciplines that employ organic molecules.¹ Conventionally, aryl and alkenyl (pseudo)halides having C(*sp*²)-halogen bonds have been used as electrophilic coupling partners.

For the last two decades, cross-coupling of *sp*³-hybridized carbon electrophiles with organometallic reagents has been emerging as a powerful strategy for the synthesis of diverse saturated hydrocarbon frameworks.² While alkyl halides are generally employed for such transformations, cross-coupling of aliphatic organosulfur compounds of high accessibility has received far less attention despite continuous reports on C(*sp*²)-S-cleaving transformations of aromatic and vinylic organosulfur compounds.³ Moreover, a limited range of organosulfur compounds including relatively reactive benzylic,⁴ allylic,⁵ difluoromethyl,⁶ and α -carbonyl-activated^{4b,7} C(*sp*³)-S electrophiles are applicable to the reactions.

As a seminal work on C(*sp*³)-S-cleaving cross-coupling, Denmark developed Fe-catalyzed arylation of unactivated alkyl sulfide and sulfones whereas arylmagnesium reagents fairly restrict the reaction scope (Scheme 1a).⁸ In 2018, Baran accomplished

Negishi-type arylation of diverse alkyl sulfones with wider functional group tolerance by means of a tetrazolylsulfonyl leaving group (Scheme 1b).^{9,10}



Scheme 1 Cross-coupling of aliphatic organosulfur compounds.

Recently, we have focused on sulfonium salts as competent electrophiles for catalytic C–S cleaving transformations.^{11–13} We envisioned that trialkylsulfonium salts can participate in C(*sp*³)-S-cleaving cross-coupling, which can expand the repertoire of *sp*³-hybridized carbon electrophiles. Herein we report Negishi-type arylation of trialkylsulfonium triflates with arylzinc reagents under nickel catalysis.¹⁴ The use of cyclohexanethiol as an additional ligand was found to be particularly important for promotion of the C–S cleavage. Our arylation is applicable to one-pot transformation of dialkyl sulfides by combining with *S*-methylation with MeOTf, which showcases the synthetic utility of the present system.

The arylation of dimethyldodecylsulfonium triflate (**1a**) with arylzinc **2a** prepared from the corresponding arylmagnesium bromide, ZnCl₂, and LiCl¹⁵ in THF was chosen as a model reaction

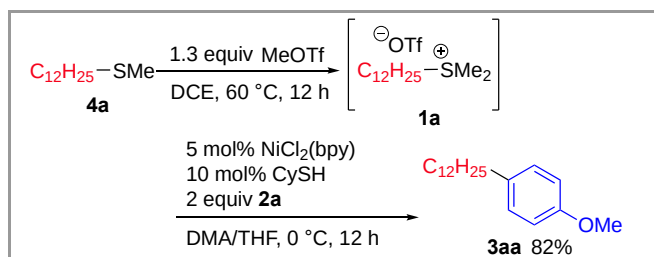
(Table 1).¹⁶ Since nickel catalysts often show good catalytic activity for cross-coupling of alkyl electrophiles,^{2f,h,17} we evaluated several nickel catalysts. Based on brief screening of ligands (See Table S1 in the Supporting Information), the reaction was conducted with 10 mol% of NiCl₂(bpy) (bpy = 2,2'-bipyridyl), and desired product **3aa** was obtained in 26% yield (entry 1). During the initial screening, we suffered from low reproducibility. After careful survey of the reaction system, sulfur impurities proved to provide a positive effect for the reaction. We thus attempted additions of thiols, sulfides, and disulfides to the reaction system. Gratifyingly, the yield of **3aa** dramatically increased to 81% by means of 20 mol% of cyclohexanethiol (CySH) (entry 2). Of note, the C(sp³)-S cleavage selectively proceeded at the C₁₂H₂₅-S bond; 4-methylanisole generated through the cleavage of the Me-S bond was not observed. This selectivity suggests that the reaction would proceed via generation of alkyl radical initiated by single-electron transfer (SET) from low-valent nickel species to the sulfonium salt (See Scheme 7). Other alkane- and arenethiols were less effective compared to CySH (entries 3–5). Although we tested Zn and Mn powders to generate low-valent nickel species, no positive effect was observed (entries 6 and 7). The use of amide cosolvent was crucial for the arylation, and only a 6% yield of the product was obtained without DMA (entry 8). Employment of NMP and DMF instead of DMA slightly lowered the yield of **3aa** (entries 9 and 10). Decreasing the reaction temperature to 0 °C improved the yield to 86% (entry 11). An 86% yield of **3aa** was obtained with lower catalyst loadings, 5 mol% of NiCl₂(bpy) and 10 mol% of CySH, and **3aa** was isolated in 82% yield under the reaction conditions (entry 12).

Table 1 Screening of Conditions

entry	additive	cosolvent	NMR yield (%)
1	none	DMA	26
2	CySH	DMA	81
3	<i>c</i> -C ₅ H ₉ SH	DMA	79
4	BuSH	DMA	69
5	PhSH	DMA	37
6	Zn powder	DMA	26
7	Mn powder	DMA	29
8	CySH	none (THF)	6
9	CySH	NMP	59
10	CySH	DMF	68
11 ^a	CySH	DMA	86
12 ^{a,b}	CySH	DMA	86 (82) ^c

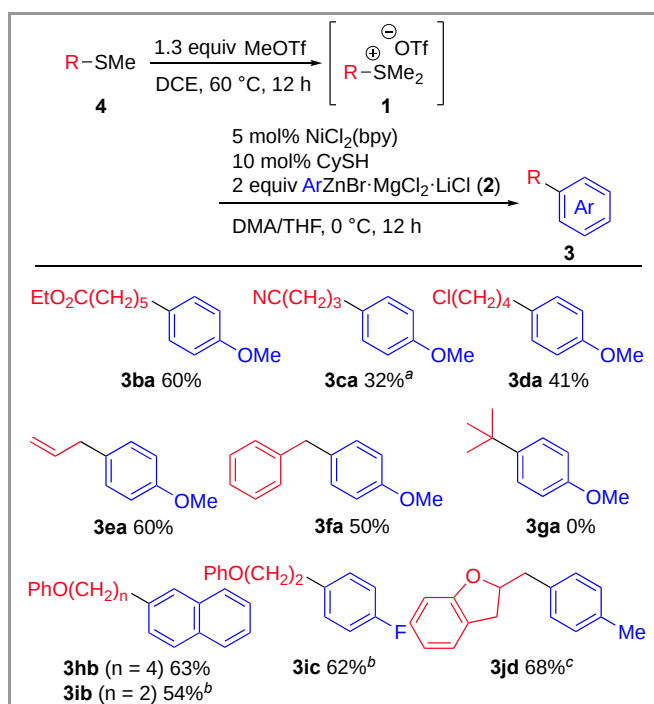
^aAt 0 °C. ^bWith 5 mol% of NiCl₂(bpy) and 10 mol% of CySH. ^cIsolated yield.

The present catalysis is applicable to one-pot arylation of dialkyl sulfides as is the case with our previous one-pot transformations of aryl sulfides.^{11d–f,h,i} After methylation of dodecyl methyl sulfide (**4a**) with MeOTf and removal of all volatiles, sulfonium triflate **1a** generated was arylated with arylzinc **2a** in a one-pot manner to afford **3aa** in 82% yield (Scheme 2).¹⁸



Scheme 2 One-pot arylation of alkyl sulfide **4a**

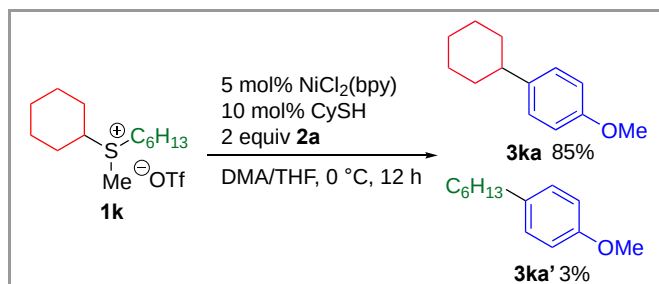
Having the one-pot procedure in hand, we then explored the reaction scope with respect to alkyl methyl sulfides **4** and arylzinc reagents **2** (Scheme 3). Owing to the mild reactivity of arylzinc, sulfide **4b** having an ester functionality could be involved in the reaction to afford **3ba**¹⁹ in 60% yield. Although cyano-substituted **4c** underwent the reaction with **2a**, the yield of **3ca** was not high despite full conversion of the substrate. The present arylation preferentially occurred at the C-SMe₂⁺ bond of sulfonium triflate **1d** over the C-Cl bond to afford **3da** in 41% yield. Allyl and benzyl sulfides **4e** and **4f** took part in the arylation to afford **3ea** and **3fa**. On the other hand, *tert*-butyl methyl sulfide (**4g**) did not undergo the reaction; the desired product was not obtained and only anisole and 4,4'-dimethoxybiphenyl were observed. Instead of 4-methoxyphenylzinc **2a**, 2-naphthylzinc **2b** uneventfully reacted with 4-phenoxybutylsulfonium triflate **1h** to furnish **3hb** in 63% yield. The reactions of 2-phenoxyethylsulfonium **1i** with 2-naphthyl- and 4-fluorophenylzinc reagents afforded arylation products **3ib** and **3ic** in moderate yields. In both cases, phenol was obtained as a byproduct in ca. 20% yield. This byproduct would be generated by β-oxygen elimination from a 2-phenoxyethylnickel intermediate. Alkyl sulfide **4j** having a 2,3-dihydrobenzofuryl moiety underwent the reaction with 4-methylphenylzinc **2d** to provide desired product **3jd** in 68% yield accompanied by a 22% NMR yield of 2-allylphenol formed by the β-oxygen elimination.



Scheme 3 Scope of arylation. ^aWith 10 mol% NiCl₂(bpy) and 20 mol% CySH.

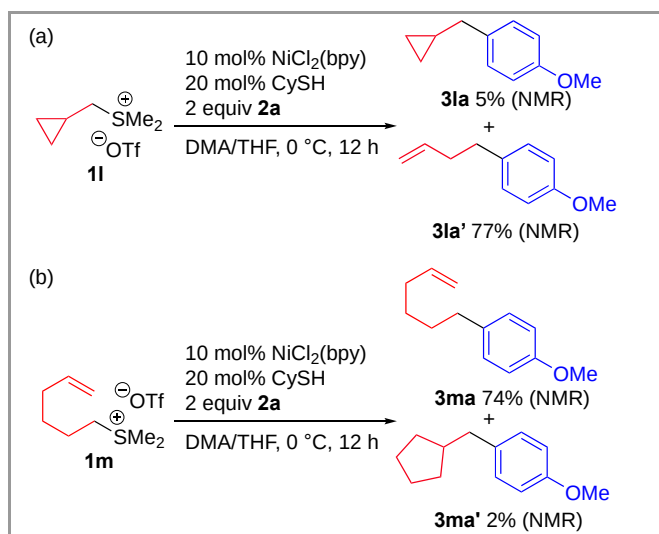
^bPhenol was obtained in ca. 20% yield. ^c2-Allylphenol was obtained in 22% yield.

As shown in Schemes 2 and 3, the arylation of alkyl dimethylsulfonium salts selectively proceeded via cleavage of the C(alkyl)–SMe₂⁺ bonds. To further explore the regioselectivity of the C–S cleavage, we conducted the arylation of trialkylsulfonium triflate **1k** having three different alkyl groups: cyclohexyl, hexyl, and methyl groups (Scheme 4). As a result, 4-cyclohexylanisole (**3ka**) was obtained in 85% yield along with a 3% yield of 4-hexylanisole (**3ka'**), and none of 4-methylanisole was detected. This result indicates that the C–S cleavage would proceed via SET from low-valent nickel species to form the most stable carbon-centered radical preferentially (See Scheme 7).



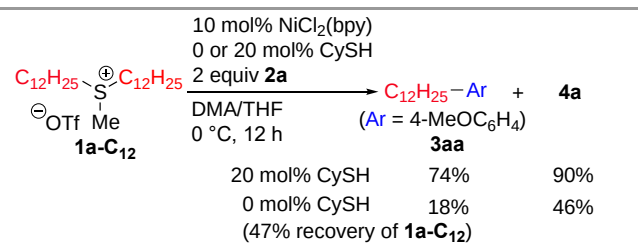
Scheme 4 Regioselective C–S arylation of trialkylsulfonium triflate **1k**.

To verify the intermediacy of radical species, we conducted a radical clock experiment using (cyclopropylmethyl)sulfonium triflate **1l**. The reaction of **1l** with arylzinc **2a** provided ring-opening product **3la'** in 77% yield as the major product, which would be consistent with the intermediacy of radical species (Scheme 5a). We also conducted the arylation with another radical probe, (5-hexen-1-yl)sulfonium triflate **1m**. Although 5-hexenyl radical is known to undergo 5-*exo* cyclization to afford cyclopentylmethyl radical, the reaction of **1m** provided only a 2% yield of the cyclized product **3ma'** (Scheme 5b). Instead, the linear product **3ma** was obtained as the major product in 74% yield. These results indicate that recombination of radical species with nickel (See Scheme 7) would proceed faster than the 5-*exo* cyclization of 5-hexenyl radical (rate constant: $1.0 \times 10^5 \text{ s}^{-1}$),²⁰ but slower than the ring-opening of cyclopropylmethyl radical (rate constant: $1.3 \times 10^8 \text{ s}^{-1}$).²⁰



Scheme 5 Mechanistic experiments with radical probes.

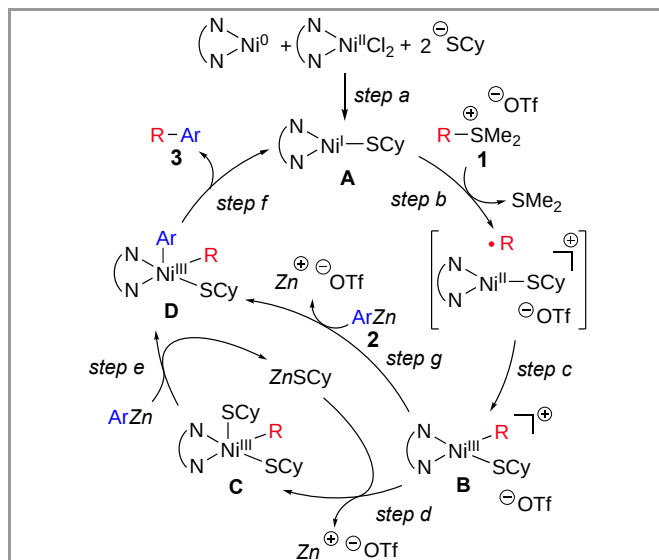
We next carried out the reaction with didodecylmethylsulfonium triflate **1a–C₁₂** to understand the effect of CySH (Scheme 6). Under the standard conditions, **1a–C₁₂** was fully consumed and a 74% yield of 4-dodecylanisole (**3aa**) was obtained along with a 90% yield of departed dodecyl methyl sulfide (**4a**). On the other hand, in the absence of CySH, **1a–C₁₂** was recovered in 47% yield, which suggests that CySH might assist the C–S-cleaving step. Of note, although a 46% yield of **4a** was generated, the yield of arylation product **3aa** was only 18%. This result implies that recombination of radical species after the C–S cleavage might be also assisted by CySH.



Scheme 6 Effect of CySH for arylation.

Although further mechanistic studies should be required for elucidating the reaction mechanism, we suppose the reaction proceeds through a Ni(I)/Ni(III) catalytic cycle involving a SET process (Scheme 7).^{2f,21} Initial reduction of the Ni(II) precatalyst to Ni(0) followed by comproportionation with other Ni(II) species in the presence of CyS[–] anion would generate Ni(I)–SCy **A** (step a). Subsequent SET from **A** to trialkylsulfonium triflate **1** would provide an alkyl radical and a Ni(II) intermediate (step b). The thiolate ligand on **A** might assist the SET process from the nickel center to **1** as an electron-rich donor-type ligand. Subsequently, recombination of the radical and Ni(II) would afford cationic alkylnickel(III) **B** which might be trapped by another CyS[–] anion to generate alkylnickel(III) dithiolate **C** (steps c and d). Finally, transmetalation of **C** with arylzinc **2** (step e) followed by reductive elimination from **D** would provide coupling product **3** with regeneration of Ni(I)–SCy **A** (step f). Instead of the formation of nickel(III) dithiolate **C**, transmetalation of cationic species **B** with arylzinc **2** can also generate alkylarylnickel(III) **D** (step g).

In conclusion, we developed Negishi-type cross-coupling of trialkylsulfonium salts with arylzinc reagents under nickel–thiolate catalysis. The present system was applicable to one-pot arylation of dialkyl sulfides by combining with *S*-methylation with MeOTf. The C–S cleavage would proceed via single-electron transfer (SET) by low-valent nickel species, which leads to regioselective C–S cleavage that provides the most stable carbon-centered radical. Mechanistic experiments revealed that the thiolate ligand would promote the C–S cleavage as well as the radical recombination step, while further mechanistic studies are necessary.



Scheme 7 A possible reaction mechanism.

Acknowledgment

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Supporting Information

Yes

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A 10-mL Schlenk tube was charged with dodecyl methyl sulfide (**4a**, 0.11 g, 0.50 mmol) and DCE (1.0 mL) before an addition of MeOTf (74 μ L, 0.65 mmol). The resulting mixture was stirred for 12 h at 60 °C. After removal of all volatiles under reduced pressure (ca. 1 Torr), NiCl₂(bpy) (7.1 mg, 0.025 mmol), CySH (6 μ L, 0.050 mmol), and DMA (3.0 mL) were subsequently added to the tube. The resulting mixture was cooled to 0 °C, and a solution of 4-methoxyphenylzinc **2a** (0.56 M in THF, 1.8 mL, 1.0 mmol) was then added dropwise. The resulting mixture was stirred for 12 h at 0 °C before an addition of aqueous HCl (2 M). The resulting biphasic solution was extracted with a mixture of hexane and EtOAc (v/v = 10/1, 10 mL $\times$ 3). The combined organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 100/1) to give **3aa** (0.11 g, 0.41 mmol, 82%) as a colorless oil. All the resonances in ¹H and ¹³C NMR spectra were consistent with the reported values in the literature. Komeyama, K.; Ohata, R.; Kiguchi, S.; Osaka, I. *Chem. Commun.* **2017**, *53*, 6401.
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Colorless oil (76 mg, 0.30 mmol, 60%). ¹H NMR (594 MHz): δ 7.08 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.12 (q, *J* = 7.3 Hz, 2H), 3.79 (s, 3H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.68–1.57 (m, 4H), 1.38–1.33 (m, 2H), 1.25 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (149 MHz): δ 174.0, 157.8, 134.8, 129.4, 113.8, 60.3, 55.4, 34.9, 34.4, 31.5, 28.8, 25.0, 14.4. HRMS (APCI-MS, positive): *m/z* = 251.1645. calcd for C₁₅H₂₃O₃: 251.1642 [*M*+*H*]⁺.
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