

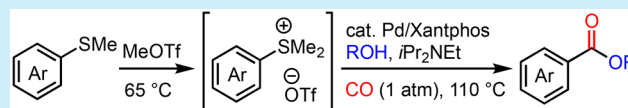
Palladium-Catalyzed Alkoxy carbonylation of Arylsulfoniums

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S Supporting Information

ABSTRACT: Alkoxy carbonylation of arylsulfoniums has been developed with the aid of a catalytic amount of a palladium-Xantphos complex under an atmospheric pressure of CO gas. Various functional groups such as carbonyl, cyano, halo, and sulfonyl groups were well tolerated under the present catalysis. Since aryl dimethylsulfoniums were readily prepared from the corresponding aryl methyl sulfides and methyl triflate, one-pot alkoxy carbonylation of aryl methyl sulfides could be accomplished.



Arenecarboxylate esters are ubiquitous constituents of numerous natural products, pharmaceuticals, and agrochemicals, and hence various methods for the synthesis of aromatic esters have been developed. Among them, transition-metal-catalyzed alkoxy carbonylation of aryl electrophiles with carbon monoxide (CO) and alcohols is a useful synthetic route and has been intensively investigated.^{1,2}

Organosulfur compounds occupy a unique position in organic synthesis because of their accessibility and intriguing reactivity. As a valuable transformation of organosulfur compounds, transition-metal-catalyzed C–S bond cleavage has attracted much attention.³ However, alkoxy carbonylation of aromatic organosulfur compounds via C–S bond cleavage is strictly limited to highly reactive sulfonyl compounds such as arenensulfonyl chlorides⁴ and diazenes⁵ (Scheme 1a). Although cobalt-catalyzed alkoxy carbonylation of arenethiols was reported,⁶ harsh reaction conditions (60 atm of CO, 190 °C) were necessary (Scheme 1b).

During the carbonylation process, carbon monoxide strongly coordinates to transition metal catalysts due to its σ -donating and π -accepting ability.⁷ The π -accepting character reduces the electron density of the metal center resulting in suppression of

the oxidative addition process. Generally, C–S bonds of organosulfur compounds are difficult to cleave unless electron-rich transition metals are used. We thus assumed that the necessity of reactive substrates and/or harsh reaction conditions would be attributed to the dilemma: cleavage of C–S bonds with electron-poor CO-coordinated transition metals.

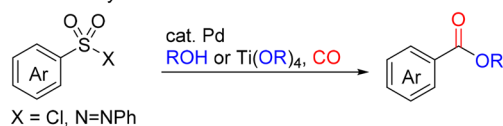
To address this dilemma, we focused on arylsulfoniums that are reasonably reactive, readily preparable, and easy-to-handle organosulfur compounds. Owing to the electron deficiency of arylsulfoniums, their C–S bonds can be cleaved more easily than those of aryl sulfides. Moreover, the departing sulfides as leaving groups would be less catalyst poisoning than thiolate anions derived from aryl sulfides. As a seminal work, Liebeskind reported cross-coupling of arylsulfoniums with various organometallic reagents such as organozinc, -boron, and -tin reagents.⁸ Because of the good reactivity of arylsulfoniums, the reactions proceeded under mild reaction conditions. Recently, catalytic transformations of arylsulfoniums have gained much attention,^{3,9} and arylation,¹⁰ alkenylation,¹¹ alkynylation,¹² and borylation¹³ have been developed.

Here, we report palladium-catalyzed alkoxy carbonylation of arylsulfoniums with alcohols under an atmospheric pressure of CO (Scheme 1c). Since arylsulfoniums can be readily prepared from the corresponding aryl sulfides, formal C–S alkoxy carbonylation of aryl sulfides was executed in a one-pot manner.

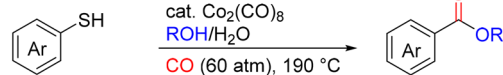
The reaction of arylsulfonium **1a** with 10 equiv of 1-butanol (**2a**) was chosen as a model reaction. We started the investigation with catalytic amounts of Pd(OAc)₂ and dppf, inspired by the success in the carbonylation of chloroarenes with a bidentate ligand by Milstein and Beller.¹⁴ First, we screened bases (Table 1). We employed inorganic bases such as K₂CO₃ and K₃PO₄ which were optimal for our previous borylation.¹³ Although desired product **3aa** was formed, the yields were less than 50% (entries 1 and 2). Next, we attempted to use amine bases. We previously found that

Scheme 1. Alkoxy carbonylation of Aromatic Organosulfur Compounds via C–S Bond Cleavage

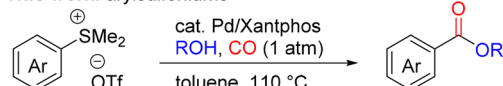
(a) arenensulfonyl chlorides and diazenes



(b) arenethiols



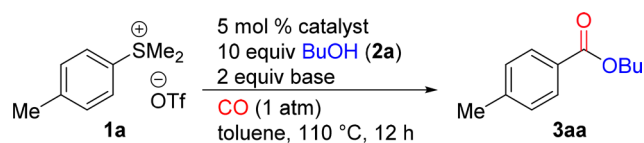
(c) **This work:** arylsulfoniums



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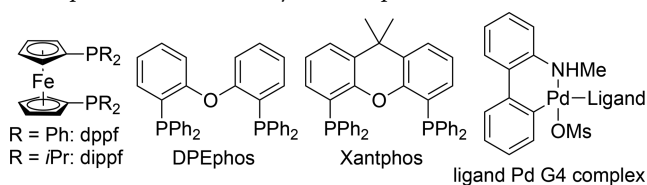
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Table 1. Optimization of Reaction Conditions



entry	catalyst	base	NMR yield (%)
1	Pd(OAc) ₂ /10 mol % dppf	K ₂ CO ₃ ^a	42
2	Pd(OAc) ₂ /10 mol % dppf	K ₃ PO ₄ ^a	18
3	Pd(OAc) ₂ /10 mol % dppf	<i>i</i> Pr ₂ NEt ^a	69
4	Pd(OAc) ₂ /10 mol % dppf	<i>i</i> Pr ₂ NEt ^a	29
5	Pd(OAc) ₂ /10 mol % dppf	<i>i</i> Pr ₂ NEt ^a	32
6	Pd(OAc) ₂ /10 mol % DPEphos	<i>i</i> Pr ₂ NEt ^a	9
7	Pd(OAc) ₂ /10 mol % Xantphos	<i>i</i> Pr ₂ NEt ^a	66
8	Pd(OAc) ₂ /10 mol % Xantphos	<i>i</i> Pr ₂ NEt	69
9	Pd(Xantphos)Cl ₂	<i>i</i> Pr ₂ NEt	78
10	Xantphos Pd G4 (Pd-1)	<i>i</i> Pr ₂ NEt	86 (84) ^b
11	Xantphos Pd G4 (Pd-1)	<i>i</i> Pr ₂ NEt	74 ^c
12	dppf Pd G4	<i>i</i> Pr ₂ NEt	77

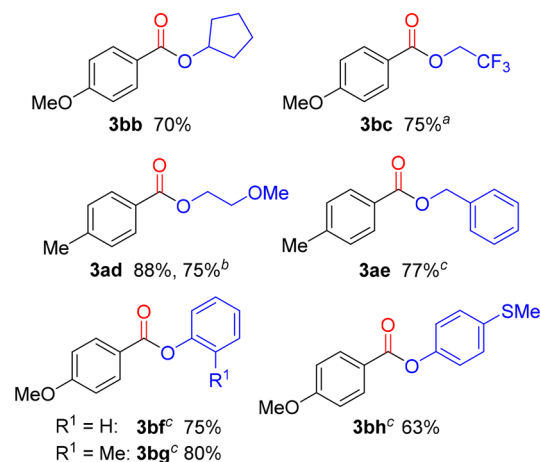
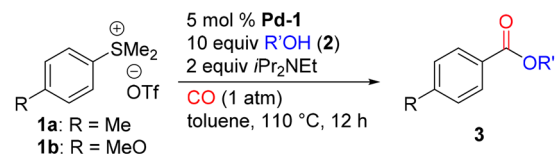
^a1.3 equiv of base. ^bIsolated yield. ^c3 equiv of 2a.



aryldimethylsulfoniums were easily demethylated by less hindered amines such as NEt₃. Therefore, we conducted the reaction with sterically congested *i*Pr₂NEt. As a result, the yield of 3aa was increased to 69% (entry 3). We then checked the effect of ligands. In place of dppf, other bidentate phosphine ligands such as dppf, dppp, and DPEphos afforded 3aa in lower yields (entries 4–6). On the other hand, Xantphos showed good catalytic activity comparable to that of dppf (entry 7). The use of 3 equiv of *i*Pr₂NEt slightly increased the yield of 3aa (entry 8). Product 3aa was obtained in 78% yield when Pd(Xantphos)Cl₂ was employed as the catalyst (entry 9). In this case, a 13% yield of methyl *p*-tolyl sulfide was formed as a byproduct (see Figure S1 for details). We inferred that the 10 mol % of chloride anion derived from Pd(Xantphos)Cl₂ would induce the demethylation. To circumvent this side reaction, we focused on the use of Pd G4 complexes¹⁵ which depart less nucleophilic mesylate anion ([−]OMs) and 9-methylcarbazole during the generation of palladium(0). As we expected, the employment of Xantphos Pd G4 (Pd-1) improved the yield of 3aa to 86% (entry 10). Reducing the amount of 2a to 3.0 equiv slightly decreased the yield of 3aa (entry 11). Compared to Pd-1, dppf Pd G4 was less effective as the catalyst (entry 12).

With the optimized reaction conditions in hand, we then explored the reaction scope with respect to alcohols (Scheme 2). Instead of 1-butanol, cyclopentanol (2b) also underwent the reaction with *p*-anisyl dimethylsulfonium 1b to furnish 3bb in 70% yield. The reaction with 2,2,2-trifluoroethanol (2c) provided 2,2,2-trifluoroethyl 4-methoxybenzoate (3bc) in 75% yield. Simultaneously, 2,2,2-trifluoroethyl benzoate was formed in 13% NMR yield (see Figure S2 for details). The benzene ring would be transferred from Xantphos via the interchange between the palladium- and phosphine-bound aryl rings.¹⁶ The lower reactivity of 2,2,2-trifluoroethanol than 1-butanol (2a) is consistent with alcoholysis of cationic acylpalladium species.¹⁷

Scheme 2. Scope of Alcohols 2

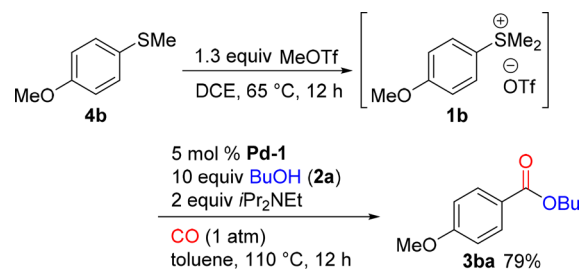


^a2,2,2-Trifluoroethyl benzoate was formed in 13% NMR yield. ^b7 mmol of 1a. ^c3 equiv of alcohol.

On the other hand, the reaction with 2-methoxyethanol provided 3ad in 88% yield with a trace amount of the byproduct derived from the aryl–phenyl interchange. This reaction was applicable to large-scale synthesis, and a 75% yield of 3ad was obtained from 7 mmol of 1a. The present reaction accommodated benzyl alcohol (2e) as well as phenols 2f–h to afford the corresponding alkoxycarbonylation products in moderate to good yields. In these cases, to avoid difficulties in separation of the products from the remaining alcohols, the amounts of the alcohols were reduced to 3 equiv. Of note, because the reaction selectively took place at the C–S bond of sulfonium, the methylsulfanyl moiety of 4-(methylsulfanyl)phenol (2h) remained untouched. We also attempted the aminocarbonylation of sulfonium 1b by using aniline instead of alcohols. However, demethylation by aniline exclusively proceeded and no amide product was obtained.

From the viewpoint of organic synthesis, avoidance of preparation and purification of aryl dimethylsulfoniums 1 is desirable. In this context, we attempted one-pot carbonylation of aryl methyl sulfide 4b via in situ methylation with MeOTf (Scheme 3).^{11b,13} By treating 4b with 1.3 equiv of MeOTf in 1,2-dichloroethane (DCE), 1b was generated quantitatively. After removal of all volatiles including MeOTf under a reduced pressure (ca. 1 Torr), the carbonylation was subsequently

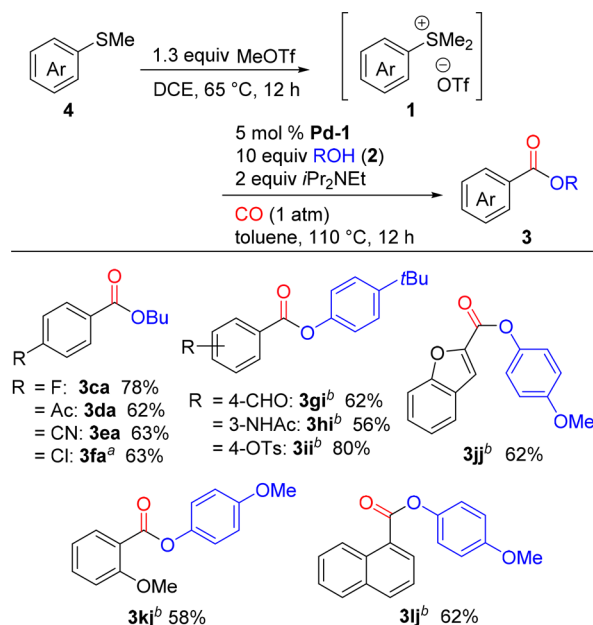
Scheme 3. One-Pot Alkoxycarbonylation of Aryl Sulfide



conducted by adding Pd-1 and the other reaction components. As a result, desired product **3ba** was obtained in 79% yield over two steps.

By means of this one-pot procedure, we next investigated the scope of aryl sulfides (Scheme 4). Due to the mild reaction

Scheme 4. Scope of Aryl Sulfides 4

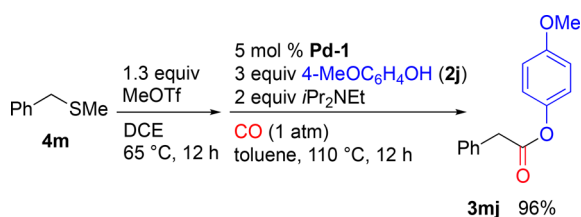


^aThe second step was conducted at 90 °C for 2 h. ^b3 equiv of phenol.

conditions, various functional groups such as acetyl, formyl, and cyano groups were well tolerated. When electron-deficient arylsulfoniums **1c–1g** were employed, 10–15% yields of aryl sulfides **4c–4g** were formed via demethylation of **1c–1g** as the byproduct. Owing to the electron deficiency of the aryl rings, the departing sulfides **4c–4g** would be better leaving groups, thus allowing demethylation to be enhanced. When 4-chlorophenyl sulfide **4f** reacted under the standard conditions, the alkoxy carbonylation took place at both of the C–S and C–Cl bonds. Fortunately, a lower reaction temperature (90 °C) and a shorter reaction time (2 h) improved the chemoselectivity, and **3fa** was isolated in 63% yield. Of note, the tosyloxy group of **4i** was intact under the reaction conditions despite its intrinsic reactivity toward carbonylation reactions.¹⁸ The present alkoxy carbonylation was also applicable to π -extended aryl sulfides **4j** and **4l** to yield **3jj** and **3lj**, respectively.

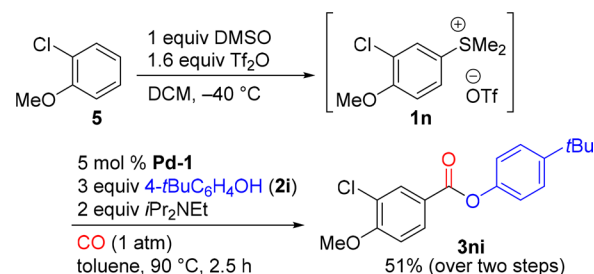
Not only aryl sulfides but also benzyl sulfide **4m** was involved in this alkoxy carbonylation, and the corresponding carbonylation product **3mj** was obtained in 96% yield (Scheme 5).

Scheme 5. Alkoxy carbonylation of Benzyl Sulfide 4m



To demonstrate the synthetic utility of the present reaction, we performed the alkoxy carbonylation in combination with S_EAr sulfonium synthesis. In the presence of DMSO and Tf₂O, electron-rich arene **5** was converted to the corresponding aryl dimethylsulfonium **1n** in a regioselective manner (Scheme 6).¹⁹ After aqueous workup, the alkoxy carbonylation with phenol **2i** was then applied to the crude mixture of **1n**. Over two steps, desired ester **3ni** was obtained in 51% yield.

Scheme 6. Sequential S_EAr and Alkoxy carbonylation



A plausible reaction mechanism is depicted in Figure 1a. First, palladium(0) species **A** would be generated from Pd-1

a) Plausible catalytic cycle

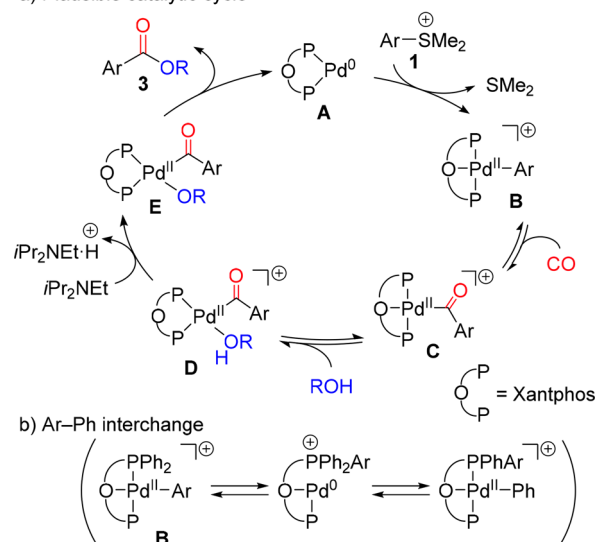
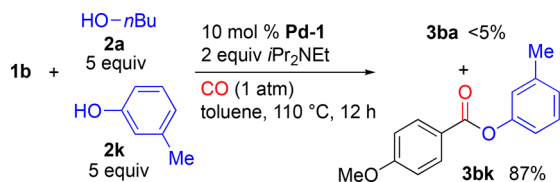


Figure 1. Plausible reaction mechanism.

with the aid of *i*Pr₂NEt. Arylsulfonium **1** would undergo oxidative addition with **A** to form cationic arylpalladium(II) **B** on which Xantphos acts as η^3 -tridentate P₃O,P ligand.²⁰ Insertion of CO into the C–Pd bond of **B** would provide arylpalladium(II) **C**. It is known that the CO insertion into cationic arylpalladium is faster than that into a neutral one.²¹ After the coordination of alcohol to intermediate **C**,¹⁷ deprotonation from the resulting **D** by *i*Pr₂NEt would form alkoxy palladium **E**. Finally, reductive elimination would provide alkoxy carbonylation product **3** and regenerate palladium(0) **A**. It was suggested that the coordination of alcohol to cationic palladium species (**C** to **D** in Figure 1) would be the turnover-limiting step in alcoholysis of cationic acylpalladiums.¹⁷ Electron-deficient 2,2,2-trifluoroethanol (**2c**) would be reluctant to coordinate to acylpalladium **C**; thus, the aryl-phenyl interchange from **B** would compete with the alkoxy carbonylation (Figure 1b).¹⁶ In contrast, coordination of

2-methoxyethanol or phenols to **C** would be enhanced with the aid of their methoxy group or π -systems as additional coordination sites. Indeed, competition reaction revealed that *m*-cresol (**2k**) reacted much faster than 1-butanol (**2a**) to provide **3bk** in 87% yield (Scheme 7).

Scheme 7. Competition Reaction between **2a** and **2k**



In conclusion, we have developed palladium-catalyzed alkoxylation of aryldimethylsulfoniums under an atmospheric pressure of CO. With characteristic reactivity of organosulfur compounds, the present alkoxylation will open up a new way of utilizing carbonylative transformations of organosulfur compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00067.

Detailed experimental procedures, and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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