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Transition-Metal-Free Aryl−Heteroatom Bond Formation via C−S Bond Cleavage

Jian-Nan Zhao,[†,§] Muzaffar Kayumov,[†,‡] Dong-Yu Wang,*[,†,‡] and Ao Zhang*[,†,‡,§]

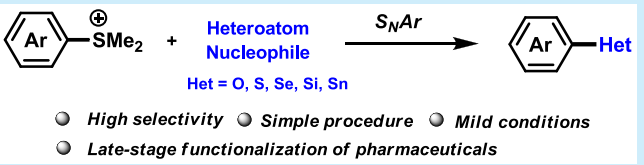
[†]CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica (SIMM), Shanghai 201203, China

[‡]University of Chinese Academy of Sciences, Beijing 100049, China

[§]School of Life Science and Technology, ShanghaiTech University, Shanghai 201210, China

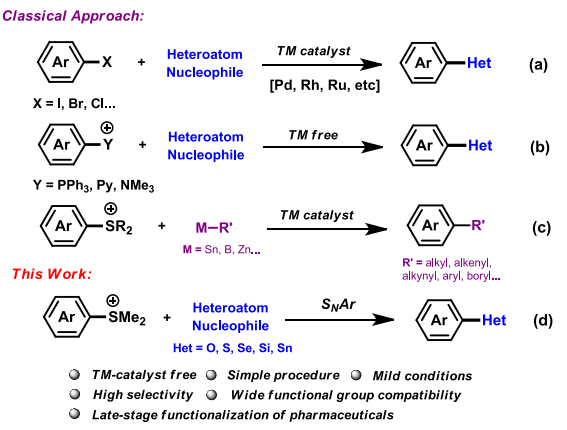
Supporting Information

ABSTRACT: Aryl−heteroatom bonds (C−Het) are almost ubiquitously present in chemical molecules. However, methods for diverse C−Het bond formations from a simple substrate are limited. Herein, we report a convenient and efficient C−S bond transformation of aryl sulfoniums to various C−Het bonds (C−O, C−S, C−Sn, C−Si, C−Se) in the absence of any transition-metal catalyst. These reactions proceeded in mild conditions with a wide substrate scope.



The aryl carbon−heteroatom bond (C−Het) is a common element in organic chemistry. The group 16 element C−Het bonds like C−O,[1] C−S,[2] and C−Se[3] are useful components or building blocks for various important natural products, therapeutic drugs, and organic materials. Meanwhile, the group 14 elements C−Het bonds such as C−Si[4] and C−Sn[5] have also attracted considerable attention due to their widespread applications as high-value synthetic precursors for further functional transformation. Until now, many procedures for C−Het bond construction have been reported.[6−10] Among them, a classical approach relies on the cross-couplings between aryl (pseudo)halides and certain heteroatom nucleophiles initiated by specific transition-metal (TM) catalysts (Scheme 1a). This method generally suffers from air sensitivity and harsh or multifarious reaction conditions. In addition, the transition metals are somewhat expensive, toxic, and difficult to remove completely from the reaction mixture. Therefore, a practical and universal approach for diverse C−Het bond construction without TM catalyst is highly anticipated.

Scheme 1. Strategies for Formation of Aryl−Heteroatom Bonds



Recently, TM-free versions of aryl C−Het bond formations have been successfully realized by McNally,[11a,b] Cornella,[11c] and our[11d,e] groups using aryl phosphonium, pyrylium, or ammonium salts as the electrophilic substrate (Scheme 1b). In addition, cyano-substituted arylmethyl thioethers have been reported to achieve the C−Het bond formation with alcohol or aniline under TM-free conditions, but with very limited thioether examples.[11f] Since arylsulfonium salts are easily available, and reasonably reactive, they can be viewed as an activated form of the inert C−S bond with potential for further functional transformation.[12] In fact, TM-catalyzed transformation of aryl sulfoniums to diverse arenes was reported. In 1997, Liebeskind and colleagues reported the first example of TM-catalyzed cross-coupling of aryl sulfoniums with different organometallic species including organozinc, -tin, and -boron reagents.[13] Subsequently, arylsulfoniums have been widely used for arylation, alkenylation, alkynylation, borylation, and alkoxycarbonylation under different TM catalysis conditions (Scheme 1c).[14] However, transformations of arylsulfoniums through a S_NAr mechanism without the TM catalyst have been barely reported, except for a few examples of ^{18}F-radiolabeling reactions.[15]

In this regard, we recently re-examined the functionalization of arylsulfoniums in the absence of TM-assistance and established a universe method to transfer the aryl C−S bond to diverse C−Het bonds through an S_NAr mechanism (Scheme 1d).

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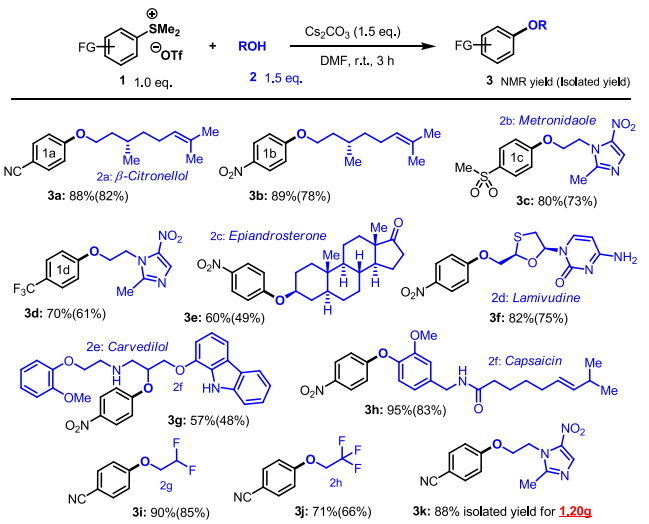
First, we examined the model reaction between 4-cyanophenyldimethylsulfonium salt (**1a**) and β-citronellol (**2a**) for different reaction conditions without TM catalyst. After extensive experimentation (see Supporting Information Table S1 for details), we established the optimum conditions as using 1.5 equiv of alcohol **2**, Cs_2CO_3 as the base, and DMF as the solvent within 3 h at room temperature. Under these standard conditions, formation of a demethylation byproduct was effectively suppressed.

After establishing the standard conditions, we then investigated the synthetic scope and compatibility of functional groups for this reaction (Scheme 2). It was found that

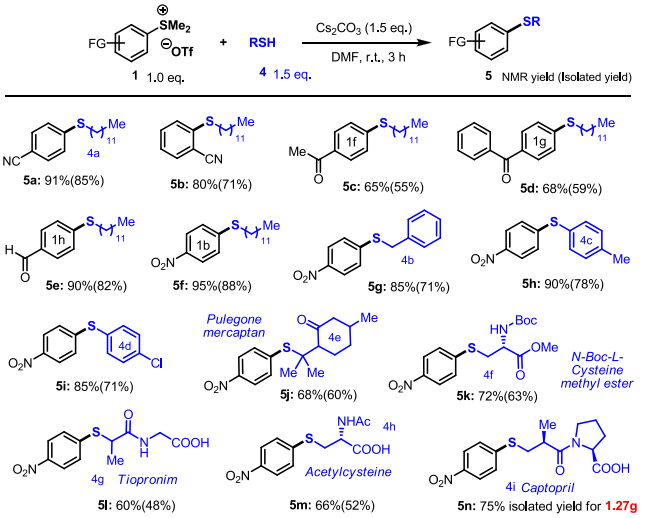
Scheme 2. Substrate Scope of C−O Bond Construction



arylsulfoiniums with an electron-deficient substituent, including cyano (**1a**), nitro (**1b**), sulfonyl (**1c**), or trifluoromethyl (**1d**) groups, showed good reactivity, and the desired products **3a−d** were obtained in 70−89% yields, whereas substrates containing electron-donating groups (e.g., 4-MeO- or 4-Me-phenyldimethylsulfonium salt) gave no products (for details, see Supporting Information 3.7). To further explore the synthetic utility of this method, we treated arylsulfoiniums **1b** with diverse OH-containing pharmaceuticals and natural products. It was found that both primary alcohols (**2b**, **2d**) and secondary alcohols (**2c**, **2e**) and phenol (**2f**) reacted with **1b** smoothly to afford the corresponding etheric products **3e−h** in 57−95% yields. Notably, fluorinated alcohols were much reactive toward arylsulfoiniums as well, giving fluoroalkyl ethers **3i** and **3j** in 90% and 71% yields, respectively. To illustrate the robustness and scalability of this method, the reaction of arylsulfonium salt **1a** was treated with metronidazole (**2b**) in a gram scale under the standard conditions. The corresponding product **3k** (1.20 g) was obtained in 88% yield.

We next examined the feasibility of thioetherification under the standard conditions. As shown in Scheme 3, arylsulfoinium substrates bearing a cyano (**1a, 1e**), acyl (**1f**), carbonyl (**1g, 4e**), formyl (**1h**), and nitro (**1b**) were well compatible to this reaction. Meanwhile, thiol nucleophiles bearing a substituent such as halogen (**4d**), ester (**4f**) or carboxylic (**4g, 4h**) group and the bulky thiol **4e** all participated in the reaction smoothly, affording the desired thioethers in 60−95% yields. To further investigate the substrate scope, we selected several bioactive compounds or clinically used drugs containing an −SH moiety

Scheme 3. Substrate Scope of C−S Bond Formation



(**4e−h**) to react with **1a**. All of the reactions occurred readily to provide desired aryl sulfides **5j−m** in 60−72% yields. We also obtained captopril derivative **5n** from arylsulfoiniums **1b** in 75% isolated yield in a gram scale. Unfortunately, arylsulfoniums bearing electron-neutral or electron-donating groups showed no reactivity toward thiols. Instead, demethylated byproducts were detected (for details, see Supporting Information 3.7).

Encouraged by the successful construction of C−O/C−S bonds, we continued to investigate the potential of forming C−Se/C−Sn/C−Si bonds using arylsulfoiniums as the substrate under similar conditions. It was found that the optimum conditions used above for C−O/C−S bond formation did not promote the C−Se/C−Sn/C−Si bond formation in the model reaction of arylsulfoinium **1a** with dimethyldiselane (MeSeSeMe), hexamethyldistannane ($Me_3SnSnMe_3$), or tetramethyl-1,2-diphenyldisilane ($PhMe_2SiSiMe_2Ph$). Therefore, a brief screening of the reaction conditions was conducted and the optimal condition for C−Se/Sn/Si bond construction was determined: CsF or KBH_4 as the base, DMF as the solvent in 3−8 h at room temperature (see Supporting Information Table S3−S5 for details).

Subsequently, we investigated the substrate scope employing a few arylsulfoiniums and different nucleophiles including RSe-SeR (R = Ph, Bn, Me, Et), Me_3Sn-$SnMe_3$, and Me_2PhSi-$SiPhMe_2$. As shown in Scheme 4, arylsulfoiniums bearing a nitro (**1b**), cyano (**1a**), ester (**1i**, **1j**), or carbonyl (**1g**) substituent were compatible in the reactions, affording the desired C−Se/Sn/Si products **6−8** in 45−98% yields.

To investigate the chemoselectivity of this method, substrates with multiple nucleophilic groups were used. Compounds containing two different −OH groups (**2i**, **2j**, and **2k**) were found to react with **1a** selectively at the less bulky position to give **3l**, **3m**, and **3n** in 85%, 93%, and 60% yields, respectively, as the sole etherification products (Scheme 5a−c). The sex hormone drug β-estradiol (**2l**) containing a phenolic hydroxyl and a secondary hydroxyl was also tested to react with **1b**, and we found that the substitution reaction occurred exclusively on the aromatic hydroxyl to provide **3o** as the sole etherification product in 82% yield (Scheme 5d). In addition, compounds **2m** and **2n** bearing both −OH and −SH were employed as well to react with **1b**. The SH was found to

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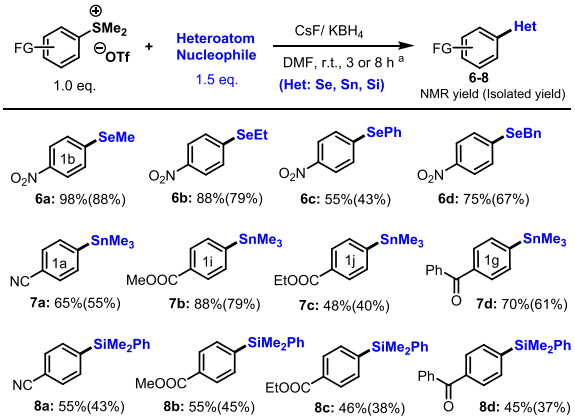
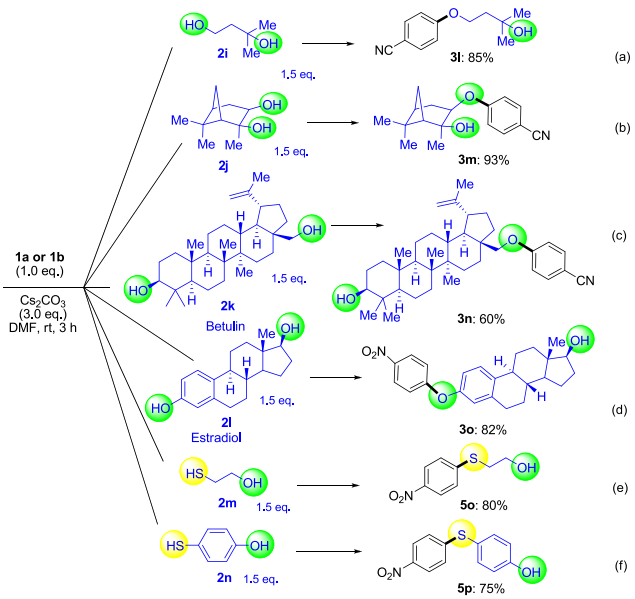
Scheme 4. Substrate Scope of C−Se/Sn/Si Bond Construction*



*For the selenation reaction: diselenides and KBH_4 (3.0 equiv) were used. For the stannylation reaction: $Me_3SnSnMe_3$ and CsF (1.5 equiv) were used. For the silylation reaction: $PhMe_2SiSiMe_2Ph$ and CsF (1.5 equiv) were used. Yields were obtained based on ^1H NMR and chromatography purification (in parentheses). [a]For both stannylation and silylation reactions: 8 h.

Scheme 5. Scope of the Reactions of Substrates[a]



[a]Yields shown are isolated yields.

preferably attack the arylsulfoinium substrate, and the corresponding products **5o** and **5p** were obtained in 80% and 75% yields, respectively (Scheme 5e,f). No nucleophilic attacking product by OH was detected, indicating the SH− is more reactive than OH.

In regard to the mechanism, we found that when the reaction of arylsulfonium salt **1a** with *β*-citronellol (**2a**) or 1-dodecanethiol (**4a**) was performed with 1,1-diphenylethylene or TEMPO as a radical scavenger, the yields of **3a** and **5a** were hardly changed, thus excluding radical involvement.[11d−f] In addition, release of dimethyl sulfide was detected in the reaction mixture based on ^1H NMR analysis (for details, see Supporting Information 4). Moreover, using the reaction to produce **3k** as an example, we performed the ICP-MS analysis of the reaction to determine the possible involvement of trace amount of metal catalysts such as Pd, Ni, Cu, Fe, Co, Ru, Rh, Ag, Pt, Ir, and Au. We found that all of the tested metals were below the detection limit (1 ppb). Therefore, based on our findings and the literature report,[15] we envisioned that current reaction occurs through an S_NAr mechanism. Additional control experiment was also performed with *p*-CN- or *p*-NO_2-substituted arylmethyl thioethers as substrates in our standard reaction conditions (for details, see Supporting Information 4), but no etherification product was obtained, thus excluding the possibility of demethylated products arylmethyl thioethers as intermediates.[11f] Further detailed mechanistic studies using both experimental and theoretical methods are in progress.

In conclusion, we have developed a convenient method to realize various C−Het bonds via C−S bond cleavage using arylsulfonium salts as the substrate with appropriate heteroatom-containing nucleophiles. By slightly tailoring the reaction conditions, these transformations performed selectively and efficiently at room temperature without assistance from any TM catalyst, thus facilitating the readily construction of C−O, C−S, C−Se, C−Si, and C−Sn bonds. Arylsulfonium substrates bearing diverse electron-withdrawing substituents and a number of bioactive natural products and clinically used drug-related nucleophiles were compatible with this protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02584.

Experimental information, detailed experimental procedures, and full spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: dongyu.wang@simm.ac.cn.
*E-mail: aozhang@simm.ac.cn.

ORCID

Ao Zhang: 0000-0001-7205-9202

Notes

The authors declare no competing financial interest.

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