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−Se3 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−Si4 and C−Sn5 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 or 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.

Recently, TM-free versions of aryl C−Het bond formations have been successfully realized by McNally,11a,b Cornella,11c and our11d,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, and alkoxycarbonylation under different TM catalysis conditions (Scheme 1c).14 However, transformations of arylsulfoniums through a SNAr mechanism without the TM catalyst have been barely reported, except for a few examples of 18F-radiolabeling reactions.15

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

Received: July 24, 2019
First, we examined the model reaction between 4-cyanophenylidimethylsulfonium salt (1a) and \( \beta \)-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$_2$CO$_3$ 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 arylsulfoxoniums 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-phenylidimethylsulfonium salt) gave no products (for details, see Supporting Information 3.7). To further explore the synthetic utility of this method, we treated arylsulfoxonium 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, fluoroinated alcohols were much more reactive toward arylsulfoxoniums as well, giving fluoroalkyl ethers 3j and 3k in 90% and 71% yields, respectively. To illustrate the robustness and scalability of this method, the reaction of arylsulfoxonium 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, arylsulfoxonium substrates bearing a cyano (1a, 1e), acyl (1f), carboxyl (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 \(-\text{SH}\) moiety (4e–h) to react with 1a. All of the reactions occurred readily to provide desired aryl sulfoxides 5j–m in 60–72% yields. We also obtained captopril derivative 5n from arylysulfoxonium 1b in 75% isolated yield in a gram scale. Unfortunately, arylysulfoxoniums bearing electron-neutral or electron-donating groups showed no reactivity toward thiols. Instead, demethylation 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 arylysulfoxoniums 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 arylysulfoxonium 1a with dimethylselenosilane (MeSeSeMe), hexamethyldistannane (Me$_3$SnSnMe$_3$), or tetramethyl-1,2-diphenyldisilane (PhMe$_2$SiSiMe$_2$Ph). 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 KBF$_4$ 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 arylysulfoxoniums and different nucleophiles including RSeR (R = Ph, Bn, Me, Et), Me$_5$Sn-SnMe$_5$, and Me$_2$PhSi-SiMe$_3$. As shown in Scheme 4, arylysulfoxoniums bearing a cyano (1b), acyl (1e), 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 \(-\text{OH}\) 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 \( \beta \)-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 \(-\text{OH}\) and \(-\text{SH}\) were employed as well to react with 1b. The SH was found to...
preferably attack the arylsulfoinium substrate, and the corresponding products \(5_0\) and \(5_p\) 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 \(\beta\)-citronellol (\(2a\)) or \(\alpha\)-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 \(^1\)H 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.

**ACKNOWLEDGMENTS**

We appreciate the support from the Chinese NSF (21702216, 81773565), NST Major Project “Key New Drug Creation and Manufacturing Program” China (No. 2018ZX09711002-006-003), China Postdoctoral Science Foundation (2018T110416, 2017M621566), and Sano-SIBS 2017 Postdoctoral Fellowship.

**REFERENCES**

(c) Touni, M.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* 2007, 46, 572.


(b) Engman, L.; Stern, D.; Friessl, H.; Vessman, K.;