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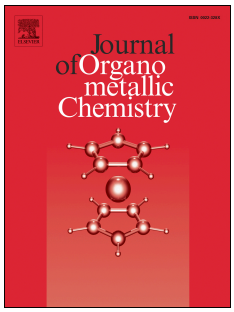

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First Use of an Organobismuth Reagent in C(sp^3)–S Bond Formation: Access to Aryl Cyclopropyl Sulfides via Copper-Catalyzed S–Cyclopropylation of Thiophenols using Tricyclopropylbismuth

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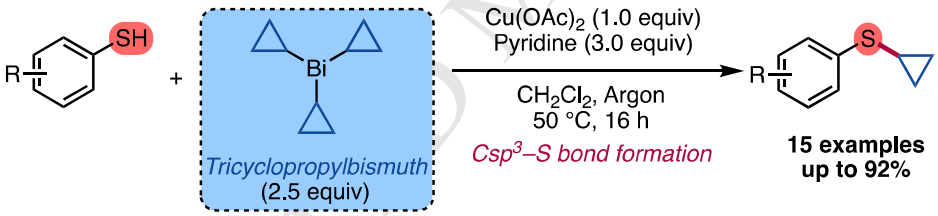
Abstract

The direct S-cyclopropylation of thiophenols using tricyclopropylbismuth is reported. The reaction is catalyzed by copper(II) acetate and operates under mild conditions to afford the corresponding aryl cyclopropyl sulfides in moderate to good yields. This reaction represents the first use of an organobismuth reagent in C(sp^3)–S bond formation.



Keywords

Organobismuth compounds, Tricyclopropylbismuth, Thiophenols, Benzenethiols, Aryl cyclopropyl sulfides, Copper catalysis

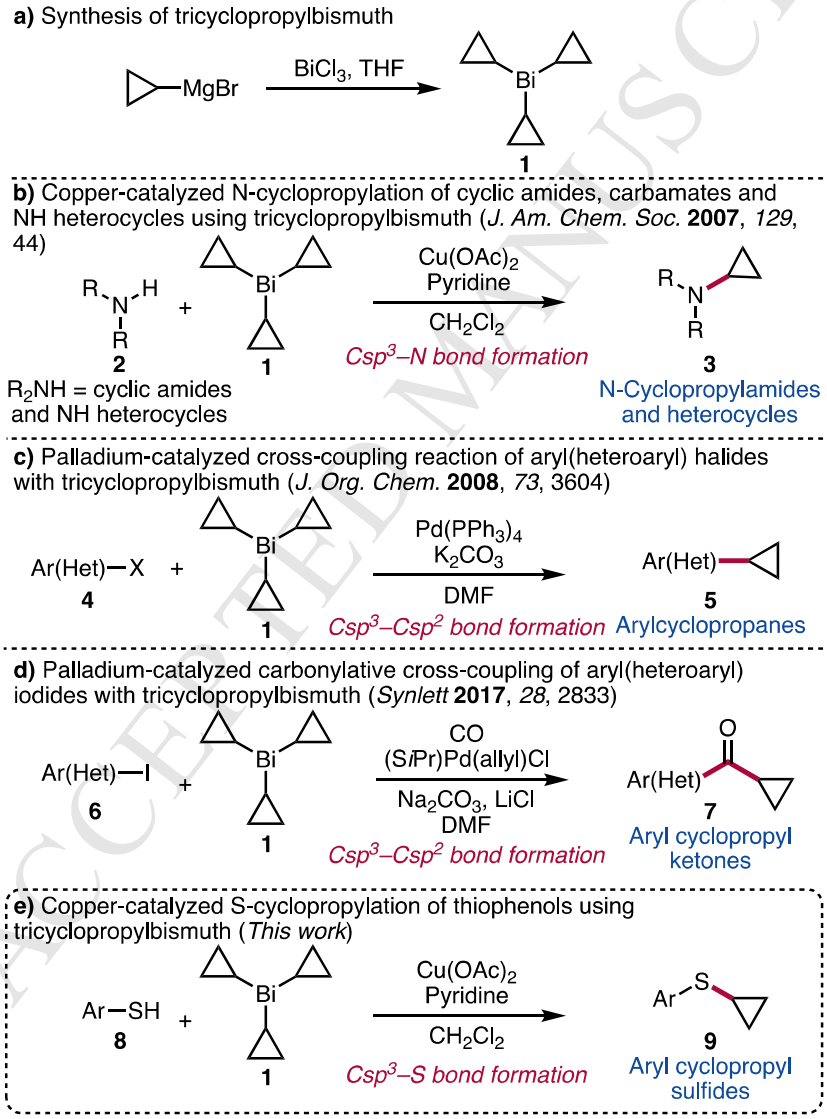
Introduction

Organobismuth compounds are organometallic species that contain a C–Bi bond and that are easily prepared from inexpensive and low-toxic inorganic bismuth salts.[1,2] Organobismuth compounds are divided in trivalent and pentavalent species where bismuth is at the +3 and +5 oxidation state, respectively. Trivalent bismuth compounds can be further subdivided into triaryl and trialkyl species. While triarylbismuthines are stable to

air and can be purified by simple silica gel chromatography, trialkylbismuthines are usually pyrophoric and must be isolated by distillation or recrystallization under inert atmosphere.[3] Triarylbismuthines have been abundantly used in metal-catalyzed reactions.[4-6] For example, our group developed a series of copper-catalyzed N- and O-arylation reactions of NH-containing heterocycles,[7] phenols[8] and amino alcohols[9,10] using triarylbismuthines. We also reported various methods for the palladium-catalyzed cross-coupling reaction between triarylbismuthines and aryl and heteroaryl halides and triflates.[11] Examples of metal-catalyzed transformations involving trialkylbismuthines are much more scarce and are limited to a few scattered reports of copper-catalyzed N-alkylation of anilines and amines,[12] and palladium-catalyzed cross-coupling reactions between alkyldiarylbismuthines and arylchlorides.[13] We also published a more comprehensive protocol for the palladium-catalyzed cross-coupling of trialkylbismuthines with aryl and heteroaryl halides and triflates and demonstrated that triarylbismuthines are not prone to β-hydride elimination.[14,15]

We disclosed in 2007 the first synthesis of tricyclopropylbismuth **1** by the addition of cyclopropylmagnesium bromide to bismuth chloride (**Scheme 1a**).[16] In sharp contrast to most trialkylbismuthines, tricyclopropylbismuth **1** was found to be surprisingly stable to air, suggesting that its chemical behavior might be closer to triarylbismuthines than trialkylbismuthines. To test this hypothesis, we evaluated the ability of tricyclopropylbismuth **1** to replicate the reactivity of triphenylbismuth in copper-catalyzed N-arylation reactions. Using conditions reported by Barton[17] and Chan[18] for the N-arylation of anilines and amides, we developed the first copper-catalyzed N-cyclopropylation reaction of cyclic amides and NH-containing heterocycles **2** leading to C(sp^3)–N bond construction and formation of N-cyclopropylated compounds **3** (**Scheme 1b**).[16] We then investigated the use of tricyclopropylbismuth **1** in the construction of C(sp^3)–C(sp^2) bonds through palladium-catalyzed cross-coupling reaction with aryl halides and triflates **4** to form arylcyclopropanes **5** (**Scheme 1c**)[19,20] and its extension to the carbonylative version to generate aryl cyclopropylketones **7** (**Scheme 1d**).[21] To further expand the scope of tricyclopropylbismuth **1** in organic synthesis, we opted to explore its use in the cyclopropylation of phenols and thiophenols, which, if successful, would result in the

formation of C(sp^3)–O and C(sp^3)–S bonds. Although we were unable to identify conditions to O-cyclopropylate phenols with tricyclopropylbismuth **1**, we discovered that thiophenols **8** could be smoothly S-cyclopropylated under conditions similar to those reported previously by us for the N-cyclopropylation of amides and azoles. We would thus like to report herein our results on the first S-cyclopropylation reaction of thiophenols using tricyclopropylbismuth **1** which also represents the first example of C(sp^3)–S bond formation using an organobismuth reagent (**Scheme 1e**).



Scheme 1. Synthesis of tricyclopropylbismuth **1** and use in metal-catalyzed N-, C- and S-cyclopropylation reactions.

Aryl cyclopropyl sulfides are present in numerous biologically active compounds, but in most cases, the sulfur is at an elevated oxidation state. These oxidized derivatives include aryl cyclopropyl sulfoxides,[22–25] sulfones[26–28] and sulfoximines,[29,30] which can all be prepared by controlled oxidation of the corresponding aryl cyclopropyl sulfides under various conditions. LY-2608204 (**10**),[31] PSN-GK1 (**11**)[32] and compounds **12**[28] and **13**[27] are investigational drugs that contain an aryl cyclopropyl sulfone and that were developed to treat type 2 diabetes through glucokinase (GK) activation (**Figure 1**). Compound **14**, which contains an aryl cyclopropyl sulfoximine, increases cytosolic GK levels through binding to glucokinase regulatory protein (GKRP).[25] Roniciclib (**15**), also named BAY 1000394, is a pan-cyclin-dependant kinase (CDK) inhibitor that contains an aryl cyclopropyl sulfoximine and that entered phase 2 clinical studies in 2019 in patients with untreated small cell lung cancer extensive disease (EC-SCLC).[30,33]

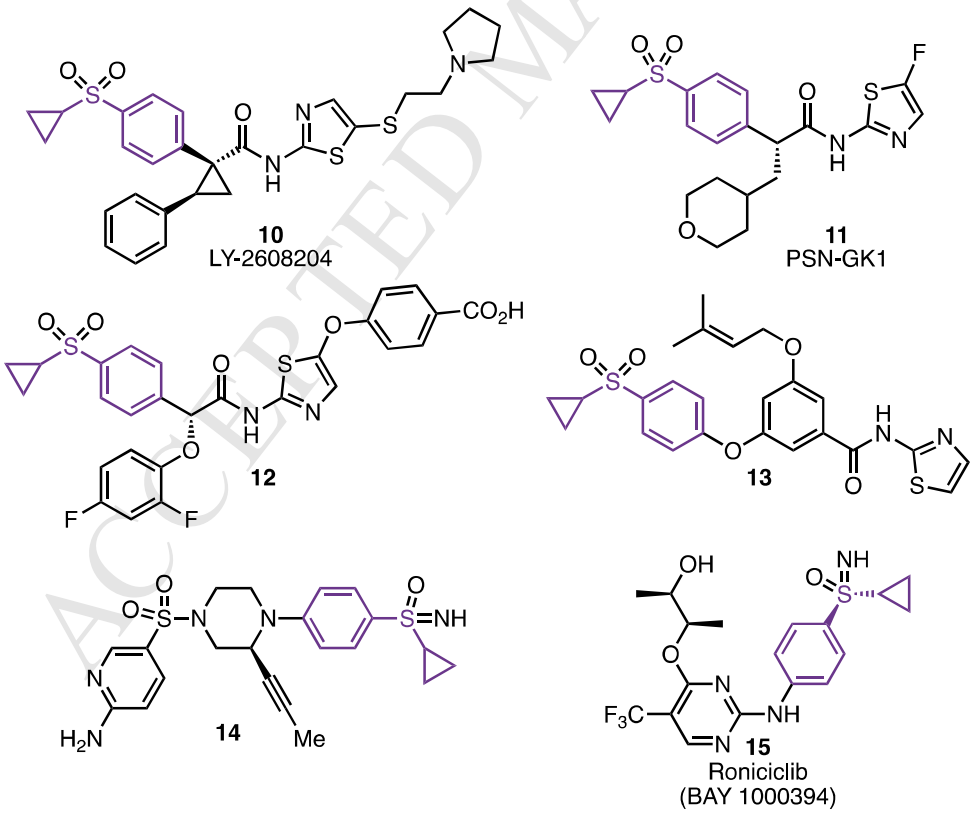


Figure 1. Biologically active compounds prepared from aryl cyclopropyl sulfides.

Aryl cyclopropyl sulfides are also very useful synthons in organic synthesis. For instance, removal of the proton alpha to the sulfur with butyllithium results in the formation of a lithium species which can then react with alkyl halides to afford the corresponding alkylated adducts that can be converted into ketones by treatment with mercuric chloride.[34] Reaction of these lithium cyclopropyl species with aldehydes leads to compounds which rearrange to cyclobutanones[35–37] and 1-arylcyclobutenes[38] by treatment with Lewis or Brønsted acids, and Burgess reagent, respectively. The acid-catalyzed ring expansion of 1-(arylthio)cyclopropylcarbinols to cyclobutanone has been used as a key step in the synthesis of natural products (±)-fragranol,[39] (±)-grandisol,[39] (±)-α-cuparenone[40] and (±)-herbertene.[40] Phenylthiocyclopropanes have also been used as donor-acceptor dipoles in the diastereoselective annulation reaction with ketene acetals, leading to complex cyclopentane scaffolds.[41]

Aryl cyclopropyl sulfides are most frequently prepared by S_N2 reaction of arylthiolates with halocyclopropanes.[27,28] However, because of geometric constraints inherent to the three-membered ring which disfavor the planar transition state, these reactions usually require a strong base and high temperatures, thus precluding the presence of many functional groups.[42] An alternative approach for the synthesis of aryl cyclopropyl sulfides consists of adding a cyclopropane thiol to an arylfluoride through a S_NAr reaction.[30] However, the necessity of having an electron-withdrawing group on the aromatic scaffold reduces the applicability of this approach in the context of medicinal chemistry and organic synthesis. Other methods to prepare aryl cyclopropyl sulfides include the addition of arylthiols to cyclopropenes,[43–46] the cyclization of 1,3-bis(phenylthio)propanes with butyllithium,[47] the Brønsted acid-catalyzed arythiol addition/ring contraction to α-hydroxybutanones,[48] and the [2+1] addition of phenylthio(trimethylsilyl)carbenes to alkenes.[49]

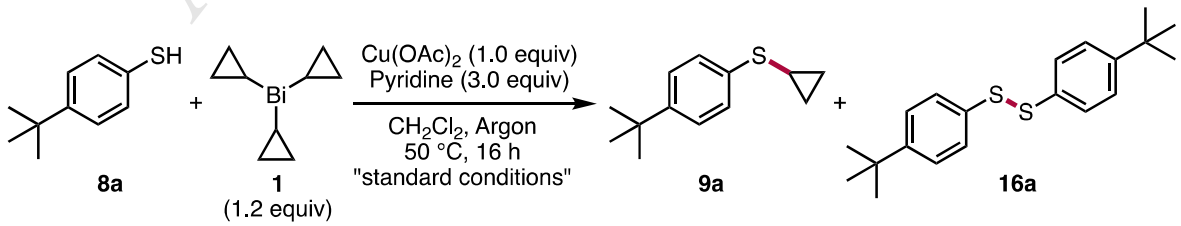
The lack of general procedures for the synthesis of aryl cyclopropyl sulfides gave us an impetus to develop a method for the direct S-cyclopropylation of benzenethiols using tricyclopropylbismuth **1**. Reported protocols for the S-arylation of thiophenols using pentavalent arylbismuth reagents[50–52] and for the S-arylation of diaryl disulfides using

triarylbismuthines[53] comforted us in our hypothesis that **1** could be used as a cyclopropylating agent towards thiophenols to form C(sp^3)–S bonds.

Results and discussion

We began by testing the feasibility of S-cyclopropylating 4-*tert*-butylbenzenethiol **8a** with tricyclopropylbismuth **1** using reaction conditions that we developed for the N-cyclopropylation of amides.[16] In the event, treating **8a** with 1.2 equivalents of tricyclopropylbismuth **1**, 1.0 equivalent of copper(II) acetate and 3.0 equivalents of pyridine under argon atmosphere in dry dichloromethane at 50 °C during 16 h provided the desired aryl cyclopropyl sulfide **9a** in 67% yield along with 4% of the diaryl sulfide **16a** (**Table 1**, Entry 1). Replacing pyridine by the more basic triethylamine was well tolerated (**Table 1**, Entry 2) but using the more hindered 2,6-lutidine led to a drastic erosion in the yield of the reaction (**Table 1**, Entry 3). Using Cs_2CO_3 completely shut down the S-cyclopropylation reaction, presumably due to the lack of coordination of the copper species, and afforded instead the corresponding disulfide **16a** in quantitative yield (**Table 1**, Entry 4). Changing the solvent for tetrahydrofuran or conducting the reaction at a higher temperature in dichloroethane negatively impacted the yield of the reaction (**Table 1**, Entry 5 and 6). Using 2.5 equivalents of tricyclopropylbismuth **1** gave a substantial improvement in the yield of the desired product **9a** (**Table 1**, Entry 7) while reducing the reaction time to 4 hours resulted in a less efficient process (**Table 1**, Entry 8). For every entry, complete consumption of the starting material was observed. This optimization shows that similar conditions can be used for the cyclopropylation of NH- and SH-containing compounds with tricyclopropylbismuth **1**.

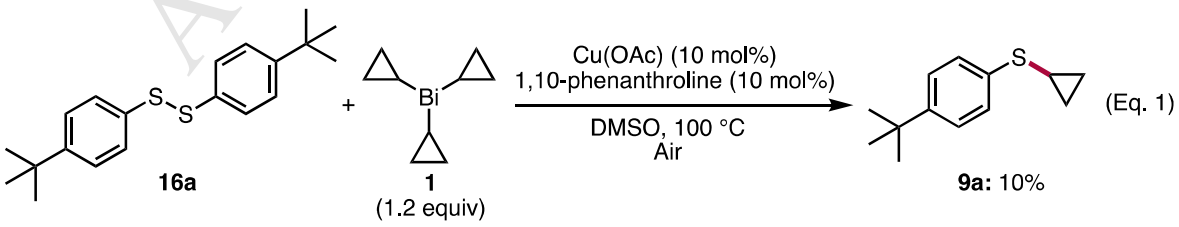
Table 1. Optimization of reaction conditions for the copper-catalyzed S-cyclopropylation of 4-*tert*-butylbenzenethiol **8a** using tricyclopropylbismuth **1**



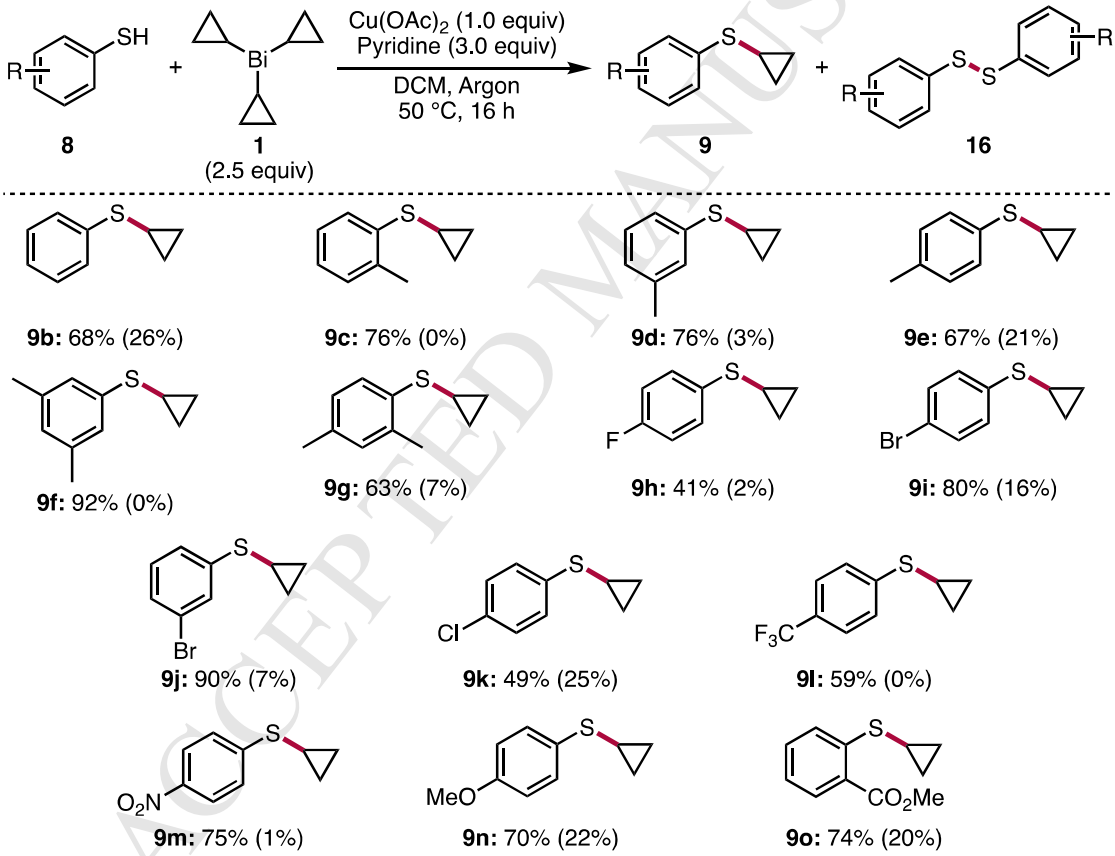
Entry	Change from "standard conditions"	Yield **9a**[b] (%)	Yield **16a**[b] (%)
1	No change[a]	67	4
2	Et_3N instead of pyridine	61	0
3	2,6-Lutidine instead of pyridine	47	0
4	Cs_2CO_3 instead of pyridine	0	99
5	THF instead of CH_2Cl_2	31	1
6	DCE at 80 °C instead of DCM at 50 °C	56	16
7	2.5 equiv of cPr_3Bi (**1**) instead of 1.2	84	14
8	2.5 equiv of cPr_3Bi (**1**) instead of 1.2 and 4 h instead of 16 h	59	12

[a] Standard conditions: 4-*tert*-butylbenzenethiol (**8a**) (1.0 equiv), cPr_3Bi (**1**) (1.2 equiv), $Cu(OAc)_2$ (1.0 equiv), pyridine (3.0 equiv), anhydrous dichloromethane (0.1 M), 50 °C, 16 h, argon. [b] Yields of isolated pure products. For every entry, no starting material was recovered.

Because diaryl disulfides are common side products in copper-catalyzed reactions involving benzenethiols and because these substrates are commercially available and do not have the unpleasant smell associated with thiophenols, we attempted the S-cyclopropylation reaction directly on bis(4-*tert*-butylphenyl)disulfide **16a**. Unfortunately, using conditions reported by Yasuike and Kurita for the S-arylation of diaryl disulfides,[53] we obtained the desired product **9a** in a meager 10% yield (Equation 1). After unsucessful attempts at improving this process through variation of the reaction conditions, we decided to pursue our work with the S-cyclopropylation directly on thiophenols.

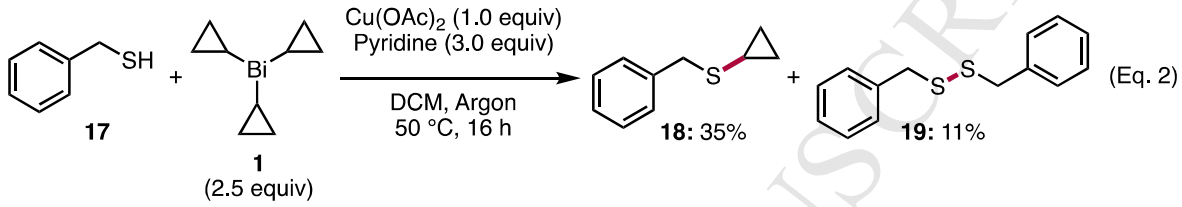


Using the optimized reaction conditions from Table 1, entry 7, we then investigated the scope of the reaction and observed that the protocol is applicable to unsubstituted as well as *ortho*, *meta*, *para* and disubstituted benzenethiols, giving the desired aryl cyclopropyl thioethers **9b–g** in yields ranging from 63 to 92% (**Scheme 2**). Thiophenols bearing electron withdrawing (compounds **9h–9m**) and donating groups (compound **9n**) were also smoothly cyclopropylated, affording the corresponding products in 41 to 90% yield. Lastly, it was found that our reaction also tolerates the presence of a methyl ester at the *ortho* position, as indicated by product **9o**. Diaryl disulfides were isolated as side products in yields ranging between 1 to 26%.



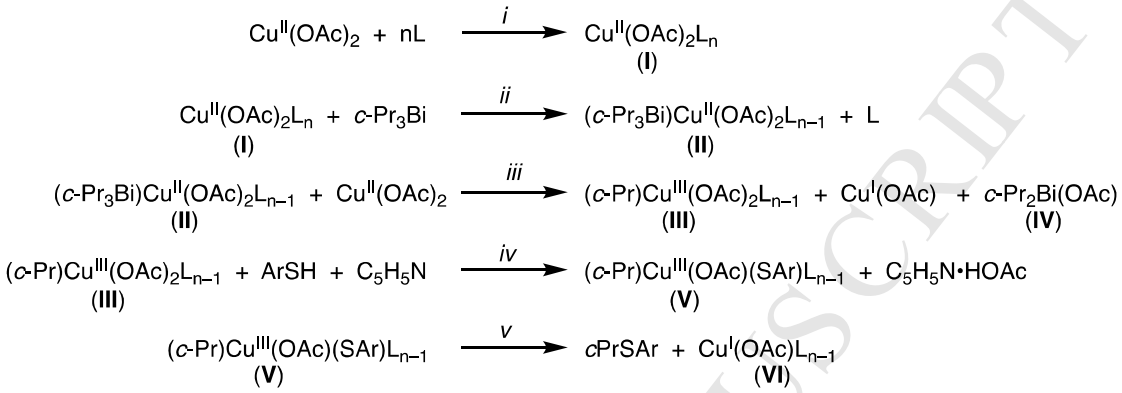
Scheme 2. Substrate scope in the copper-catalyzed S-cyclopropylation of thiophenols **8** using tricyclopropylbismuth **1**. Numbers under parentheses indicates the yield of diaryl disulfide side-product **16**.

We next investigated the efficiency of our protocol on an alkylthiol (as opposed to an arylthiol) and found that benzylthiol **17** could be S-cyclopropylated using tricyclopropylbismuth **1** to afford the desired S-cyclopropylated product **18**, albeit in only 35% yield, along with 11% of the disulfide **19** (Equation 2). Although the yield is very low, this result is nonetheless interesting since there are very few methods to S-cyclopropylate non-aromatic thiols.[43,64]



The proposed mechanism for the copper-catalyzed S-cyclopropylation of thiophenols using tricyclopropylbismuth is based on the one suggested by Barton for the N-arylation of amines using triarylbismuthines.[17] It is also modified according to mechanistic findings published by Stahl for the Evans Chan Lam reaction.[65] Thus, the process would begin by the coordination of pyridine to copper(II) acetate to give, in agreement with precedents from the literature, $Cu^{II}(OAc)_2L_n$ where L is a pyridine ligand and where n can be 1,[66,67] 2,[66] 3,[68] or 4[67] (*Step i*, **Scheme 3**). Displacement of one pyridine ligand on species (**I**) by tricyclopropylbismuth would then lead to adduct (**II**) (*step ii*) which would undergo disproportionation with copper(II) acetate to generate the copper(III) species (**III**) that has two acetate ligands and one cyclopropyl group, along with copper(I) acetate and bis(cyclopropyl)bismuth acetate (**IV**) (*step iii*). Deprotonation of the arylthiol by pyridine (most likely after complexation to a copper center to lower its pK_a) then affords an arylthiolate which displaces an acetate from species **III** to provide complex (**V**) where the copper is simulatenously ligated to an acetate, a thiolate and a cyclopropyl group (*step iv*). Reductive elimination from this species would then provide the expected S-cyclopropylated thiol along with copper(I) acetate (*step v*). In many copper-catalyzed arylation reactions, the copper(I) species can be converted back to the active copper(II) catalyst by action of oxygen. However, in our case, since oxygen was found to be detrimental (presumably due to reaction with tricyclopropylbismuth), this mechanism cannot be drawn as a catalytic cycle.

Additionally, it should be emphasized here that although reasonable, this mechanism is nonetheless speculative since there are no detailed studies on copper-catalyzed reactions involving trialkylbismuthines.



Scheme 3. Proposed mechanism for the copper-catalyzed S-cyclopropylation of thiophenols using tricyclopropylbismuth. L = pyridine (C_5H_5N); n = 1, 2, 3, 4.

Conclusion

In summary, we developed the first S-cyclopropylation reaction of thiophenols using tricyclopropylbismuth. The reaction is performed under mild conditions and affords the corresponding aryl cyclopropyl sulfides, a useful class of compounds for medicinal and synthetic organic chemistry, in moderate to good yields. This reaction constitutes the first use of an organobismuth reagent in C(sp^3)–S bond construction.

Acknowledgments

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First Use of an Organobismuth Reagent in C(sp^3)–S Bond Formation: Access to Aryl Cyclopropyl Sulfides via Copper-Catalyzed S–Cyclopropylation of Thiophenols using Tricyclopropylbismuth

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Highlights

- Arylcyclopropyl sulfides are found in biologically relevant compounds and are useful synthons for organic chemistry.
- Efficient methods to prepare arylcyclopropyl sulfides are needed.
- The direct S-cyclopropylation of thiophenols can be accomplished using tricyclopropylbismuth.
- The reaction is catalyzed by copper(II) acetate, operate under simple conditions and affords the desired arylcyclopropyl sulfides in good yields.
- This reaction is the first example on the use of an organobismuth species to form C(sp^3)–S bonds.