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# Bimetallic system for the synthesis of diorganyl selenides and sulfides, chiral β-seleno amines, and seleno- and thioesters

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ABSTRACT

The bimetallic reagent Sn(II)/Cu(II) in [bmim]$BF_4$ was efficiently used for the cleavage of diaryl diselenides and disulfides and reacts with a variety of organic substrates, such as organic halides, acid chlorides, and β-amino mesylates affording the diorganyl selenides and sulfides within very short reaction times, under mild conditions and with excellent yields, using BMIM-$BF_4$ as a reusable solvent.



Interest in organochalcogenides has increased continuously due to their important role in the areas of heterocyclic, radical chemistry, particularly in stereo-controlled processes in asymmetric synthesis.[1] For instance, the organo-selenium nucleus is one of the most abundant structural nucleus found in natural products and biologically active molecules (e.g., seleno-carbohydrates,[2] selenoamino acids,[3] and seleno-peptides[4]). Moreover, organoselenium compounds have emerged as an exceptional class of structures that exemplify a role in biochemical processes, serving as important therapeutic compounds ranging from antiviral and anticancer agents to a variety of situations where free radicals are involved.[5] On the other hand, organo-sulfur compounds have interesting characteristics in organic chemistry and are often used as effective reagents or convenient intermediates in organic synthesis.[6,7] The emerging biological importance of organo-sulfur compounds has led to extensive studies aimed toward the synthesis of this class of compounds.[8]

In general, symmetrical and unsymmetrical diorganyl selenides and sulfides are prepared by the reductive cleavage of Se–Se or S–S bonds, employing the common reducing agents, such as $LiAlH_4$,[9a] $NaBH_4$,[9b] La,[9c] InI,[9d,e] CsOH,[9f] $Na/NH_3$,[9g] Yb,[10a] $SmI_2$,[10b] Cu/bpy,[10c] In,[10d,e] $ArB(OH)_2/CuI$,[10e] $RhCl(PPh_3)/H_2$,[10f] Zn,[11] Sn/Pd,[9g,12a] Zn/In(-III),[12b] in photochemical reactions,[12c] bimetallic Cu(II)/Sn(II) system in common organic solvents,[13] and others.[14] Because of potential biological, pharmacological and synthetic applications of organochalcogen compounds, it is considered worthwhile to develop a general and effective method for the construction of compound libraries.

Ionic liquids as versatile and novel reaction media for organic transformations[15,16] have resulted in many diverse and flexible platforms to establish highly effective and easily separable systems. The most attractive properties of ionic liquids are very low vapor pressure, nonflammability, ease of handling, reasonable thermal stability and the fact that they remain liquid within a wide range of temperatures.[17] From the sustainable chemistry point of view, there is a need for new methods which are not only very efficient but also high yielding under mild reaction conditions. In this context, ionic liquids have appeared as suitable solvents for many organic transformations, showing greater efficiency compared with the conventional organic solvents.[18]

The search for efficient, convenient and recyclable reaction media based on ionic liquids remains a major challenge. Our interest in this area[18] and in organochalcogen chemistry[19] have prompted us to explore an efficient protocol, wherein Cu(II)/Sn(II) is used as a reducing agent for the Y–Y bond (Y = S, Se) to prepare unsymmetrical diorganyl selenides and sulfides, with very short reaction times, under mild conditions, in a variety of substrates, at room temperature and with excellent yields, using an ionic liquid as a reusable solvent (Scheme 1).

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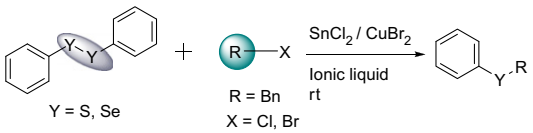



**Scheme 1.** General methodology for the synthesis of diorganyl selenides and sulfides.

To understand the influence of different variables in this reaction, several components were studied to optimize our procedure. Initially, we investigated the effect of ionic liquids on the reaction course, using a standard model for the synthesis of diorganyl chalcogenides. To this aim, five different ionic liquids (Fig. 1) were used for the synthesis of the desired products.

Benzyl phenyl selenide and sulfide were afforded in a standard protocol using 0.5 equiv of diphenyl diselenide and disulfide in the presence of 1.2 equiv of $SnCl_2$, 0.2 equiv of $CuBr_2$ and 1.1 equiv of benzyl chloride as a halide, using different ionic liquids (Table 1).

The changes in the cationic and anionic moieties in the solvent/ionic liquid have a remarkable effect, as shown in Table 1. Using [bmim]$BF_4$ the desired products were achieved in good yield, followed by [bmim]$BF_4$ and [bmim]$PF_6$. The use of [bmim]$NTf_2$ and [bpy]$BF_4$ led to a significant decrease in the yield (Table 1, entries 1–6). Using $CuCl_2$, the yield was lower compared with the use of $CuBr_2$ (Table 1, entries 1 and 2). In the absence of $CuBr_2$ the reaction of benzyl chloride with diphenyl diselenide and disulfide gave only trace amounts of the corresponding product (Table 1; entry 7). Thus, a combination of $SnCl_2$ and $CuBr_2$ in ionic liquid is essential for this transformation.

The amount of $CuBr_2$ and the reaction time (ranging from 180 to 30 min) required to promote the transformation were also evaluated. On analyzing Table 1, it is possible to verify that sulfide afforded the desired compound in a shorter time than selenide and with better yields (Table 1, entries 1–9). In terms of reaction time, ranging it as depicted in the Table 1 (entries 1 and 8) was possible verify not considerable modifications in the yield. By changing the substrate from benzyl chloride to bromide both diselenide and disulfide were obtained in better yields (Table 1, entry 9). This can be attributed to the greater leaving group ability of bromide compared with chloride.

Therefore, the optimum combination for this transformation was found to be 0.5 equiv of diaryl chalcogenide with 1.1 equiv of organic halide, which requires 1.2 equiv of $SnCl_2$, 0.1 equiv of $CuBr_2$, and 0.5 mL of [bmim]$BF_4$ at room temperature, in 60 min of reaction time to afford the diorganyl selenide or 30 min the diorganyl sulfides. In this way the use of the solvent/[bmim]$BF_4$ yields diorganyl selenide and sulfides in a short time, at room temperature, and under neutral and very mild conditions with good to excellent yields (Table 2). With the optimized results in hand, we next turned to exploring the versatility of the substitution reaction for the synthesis of aryl alkylselenides and sulfides using diphenyl dichalcogenide and a variety of alkyl halides as starting materials. The results are summarized in Table 2.

In general, the diorganyl sulfides were obtained in better yield than the diorganyl selenides. Although the selenolate intermediate is more reactive than the respective thiolate, the lower stability of the selenium species can explain their lower efficiency in the selenide synthesis. Initially, the experiments were carried out with alkyl halides, with different chain lengths and halides. From Table 2

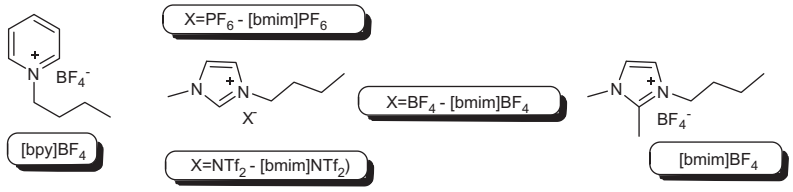
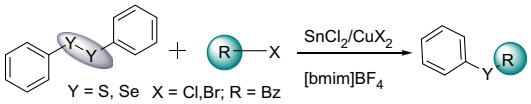



**Figure 1.** Room temperature ionic liquids.

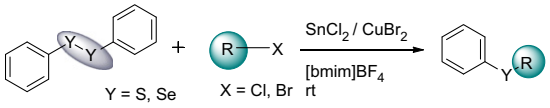
**Table 1**
Optimization of reaction time and temperature

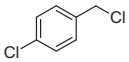
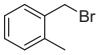
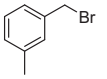
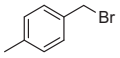



| | $SnCl_2$ (mmol) | Catalyst[a] (mmol) | Ionic liquid[b] | Time (min) | | Yield[c] (%) | |
|---|---|---|---|---|---|---|---|
| | | | | Y = Se | Y = S | Y = Se | Y = S |
| 1 | 1.2 | A | [bmim]$BF_4$ | 180 | 120 | 85 | 88 |
| 2 | 1.2 | B | [bmim]$BF_4$ | 180 | 120 | 79 | 83 |
| 3 | 1.2 | A | [bmim]$PF_6$ | 180 | 120 | 58 | 65 |
| 4 | 1.2 | A | [bmim]$NTf_2$ | 180 | 120 | 28 | 37 |
| 5 | 1.2 | A | [bmmim]$BF_4$ | 180 | 120 | 63 | 70 |
| 6 | 1.2 | A | [bpy]$BF_4$ | 180 | 120 | 34 | 38 |
| 7 | 1.2 | — | [bmim]$BF_4$ | 180 | 120 | Traces | |
| 8 | 1.2 | A | [bmim]$BF_4$ | 60 | 30 | 81 | 85 |
| 9[d] | 1.2 | A | [bmim]$BF_4$ | 60 | 30 | 88 | 92 |

[a] Catalyst A = $CuBr_2$, B = $CuCl_2$.
[b] Ionic liquids were prepared using a procedure available in the literature [Ref. [16c]] and were subjected to vacuum before use.
[c] Yields refer to pure isolated products.
[d] X = Br.

**Table 2**
Synthesis of diorganyl selenides and sulfides using Sn(II)/Cu(II) in [bmim]$BF_4$




| Entry[a] | RX | Yield (%)[b] | |
|---|---|---|---|
| | | Y = S[c] | Y = Se[d] |
| 1 |  | 75 | 68 |
| 2 |  | 80 | 75 |
| 3 |  | 79 | 74 |
| 4 |  | 85 | 80 |
| 5 |  | 65 | 58 |
| 6 |  | 82 | 80 |
| 7 |  | 89 | 84 |
| 8 |  | 77 | 72 |
| 9 |  | 99 | 98 |
| 10 |  | 97 | 93 |
| 11 |  | 92 | 83 |
| 12 |  | 75 | 67 |
| 13 |  | 84 | 79 |
| 14 |  | 98 | 94 |

[a] Ionic liquids were subjected to vacuum before use.
[b] Yields refer to pure isolated products.
[c] Y = S reaction time 30 min.
[d] Y = Se reaction time 60 min.

it is possible to verify that, in all cases, bromides furnished the respective selenides and sulfides in higher yields than the corresponding chlorides and mesylates (Table 2, entries 3–7) and the best leaving group ability could be evidenced as an important factor in the reaction yield. This protocol shows high tolerance in terms of chain length and the corresponding chalocogenides could be prepared in good yield with 2–12 carbon atoms in the organic chain (Table 2, entries 1–8). The use of more reactive allyl iodide allowed near quantitative conversion (Table 2; entry 9) with a similar result found for allyl bromide (Table 2; entry 10) showing the influence of the substrate on the reaction yield. Substituted benzylic systems were studied in the chalcogenide synthesis. A good result was obtained in the reaction of 4-chloro benzyl chloride, with diphenyl diselenide and disulfide (Table 2; entry 11). Notably, a steric effect by the aromatic substituents could be observed in the course of the reaction. For instance, with the more hindered *o*-methyl substituent the respective selenide and sulfide were obtained in lower yield comparing with the corresponding *m*- and *p*-methyl substituents (Table 2, entries 12–14).

In order to extend the scope of our methodology, we attempted to synthesize interesting functionalities, such as seleno- and thioesters and chiral β-aminochalcogenides. Selenoesters have been extensively applied as mild acyl transfer agents, both as acyl radicals or anions, to promote the synthesis of carbonyl compounds.[20] On account of this, they have been the method of choice applied in the acylation step in the synthesis of many natural products.[21] This class of compounds has also found application as liquid crystals,[22] as precursors for the synthesis of *N*-aminoacyl sulfonamides, for lactonizations and as selenating agents.[23] There are a number of methods reported in the literature to synthesize selenoesters using different metals, including palladium complexes (such as $Pd(PPh_3)_4$), Sm, In, InI, $Hg(SePh)_2$, $PhSeSnBu_3$/Pd, and $Rh/H_2$ systems.[9d,9e,24]

On the other hand, thioesters are one of the most useful building blocks for organic transformations. They have found application in C–C coupling,[25] for the synthesis of carbonyl compounds,[26] in asymmetric aldol reactions[27] and more recently, their α–β unsaturated analogs have been successfully applied for asymmetric 1–4 additions, which allow access to chiral intermediates for the synthesis of more complex compounds.[28] Furthermore, they have been applied in the natural product synthesis and can act as biologically relevant substances for in vivo tumor suppression and as anti-HIV agents.[29] Many methods have been described in the literature for the synthesis of this valuable class of compounds.[30] Employing our standard reaction conditions, seleno- and thioesters were synthesized and the results are summarized in Figure 2.

The use of benzoyl chloride, which reacts with diphenyl diselenide, gave the respective selenoester in 79% yield whereas with diphenyl disulfide afforded the thioester in 84% yield (Fig. 2, entry 2). A drastic decrease in yield was obtained for reactions with aliphatic acyl chloride (Fig. 2, entry 4). Electron withdrawing groups attached to the acyl chloride moiety afford better yields when compared with the electron donating groups (Fig. 2, entries 1 and 3). This can be rationalized due to the highest electrophilicity in the carbonyl center to electron withdrawing groups. A more complex challenge in organochalcogenium chemistry is the development of new methods for the introduction of selenium or sulfur-containing groups into organic molecules, particularly in a stereocontrolled manner. Synthesis using bimetallic reagents in ionic

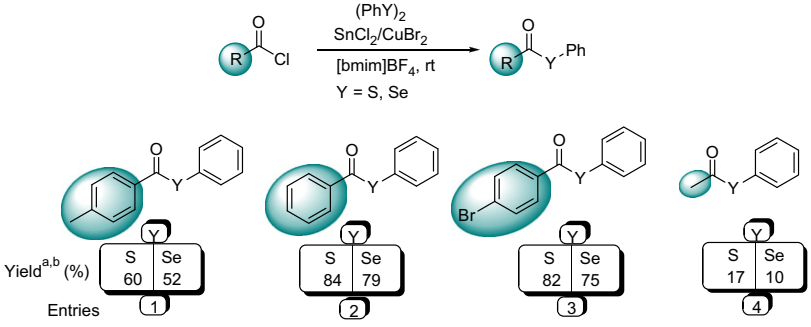



**Figure 2.** Synthesis of seleno- and thioesters using Sn(II)/Cu(II) [bmim]$BF_4$. [a]Ionic liquids were subjected to vacuum before use. [b]Yields refer to pure isolated products. [c]Y = S reaction time 30 min. [d]Y= Se reaction time 60 min.

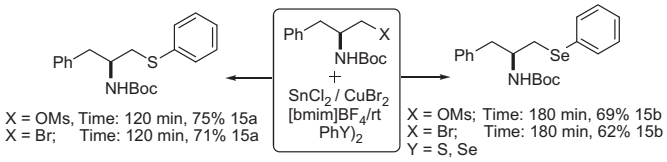



**Figure 3.** Synthesis of chiral β-sulfur and seleno amines.

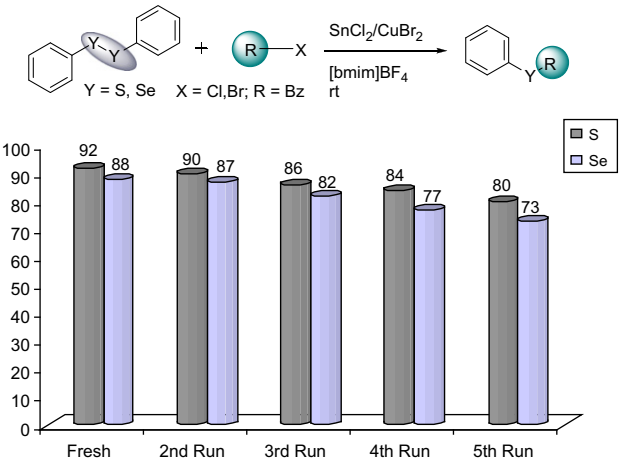



**Figure 4.** Recyclability of $[bmim]BF_4$.

liquids is a highly versatile way to create C–Se and C–S bonds in a stereo-controlled manner.[3,19] Hence, we focused our attention on the synthesis of chiral β-sulfur and seleno amines which can be obtained from the reaction of β-amino mesylate and bromo derivative[31] with diphenyl diselenide/disulfide to give the corresponding β-amino sulfur and seleno derivatives, as depicted in Figure 3.

Using our standard reaction conditions it was possible to verify the versatility of the methodology, allowing the synthesis of diverse organochalcogenium compounds from different functionalities. The results revealed the same behavior affording sulfide derivatives in higher yield as compared with selenides.

To further explore the scope of our method, and in an effort to obtain an environmentally benign protocol, we examined the possibility of reusing the reaction media. Accordingly, after the work-up (see Supplementary data) the ionic liquid was recovered and then used in additional runs. In a positive response, the yield was found to be similar to that obtained in the first run (Fig. 4; run 2). This operation was repeated three more times as depicted in Figure 4.

In summary, herein we describe an efficient methodology for the preparation of diorganyl selenides and sulfides from the corresponding alkyl and aryl halides. Some important aspects of this methodology are the high reactivity in the preparation of the different organochalcogen compounds, with very short reaction times, mild reaction conditions, room temperature, and excellent yields using an ionic liquid as a reusable solvent. The methodology shows a wide versatility, allowing the synthesis of different classes of organochalcogen compounds. Ongoing investigations into the application of this methodology are underway in our laboratory.

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## Supplementary data

Supplementary data (synthetic procedures and compounds characterisation data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.003.

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