

# Ionic liquid: an efficient and recyclable medium for synthesis of unsymmetrical diorganyl selenides promoted by InI<sup>†</sup>

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In an environmentally friendly protocol, InI was used as a reducing agent for the Se–Se bond to prepare unsymmetrical diorganyl selenides with very short reaction times, mild conditions and excellent yields using (bmim)BF<sub>4</sub> as a recyclable solvent.

## Introduction

Interest in organochalcogen compounds has been growing since the 1970s, when selenium based methods became a useful tool in the hands of organic chemists.<sup>1</sup> Organoselenium compounds have found such wide utility because of their effects on an extraordinary number of very different reactions, including many asymmetric transformations.<sup>2</sup> Furthermore, organoselenium compounds have been attracting considerable attention, especially for their biological and medicinal proprieties, due to their ability to mimic natural compounds with important biological properties (e.g., antioxidant, antitumor, anti-inflammatory, and anti-infective activities).<sup>3</sup> Investigation of synthetic methods for the preparation of selenocysteine,<sup>4</sup> selenium-based peptides,<sup>5</sup> selenoglycosides<sup>6</sup> and other important natural compounds<sup>7</sup> is nowadays an area of intensive research.

Recently, many reports have appeared in the literature describing the preparation of diorganyl selenides. In general, to avoid handling unstable reagents, such as selenols, diorganyl diselenides are used as starting materials and the selenium anion is generated *in situ*. Most of these procedures employed NaBH<sub>4</sub>,<sup>8</sup> Zn,<sup>9</sup> Zn/In(III),<sup>10</sup> In,<sup>11</sup> InI,<sup>12</sup> Sn/Pd,<sup>13</sup> RhCl(PPh<sub>3</sub>)<sub>3</sub>/H<sub>2</sub>,<sup>14</sup> RuCl<sub>3</sub>/Zn,<sup>15</sup> La/I<sub>2</sub>,<sup>16</sup> Cu<sup>17</sup> and others<sup>18</sup> as reducing agents. In general, most procedures often require drastic reaction conditions and/or expensive routes, which compromise any possibility of industrial development.

Although synthesis of unsymmetrical diorganyl selenides has been successfully accomplished by indium salts, it was undesirable from an environmental point of view, since organic solvents were used.

In a sustainable chemistry context, there is a need for new methods which are not only very efficient, but also eco-friendly and inexpensive. In this respect, ionic liquids seem to be a promising choice for the development of “green” chemical protocols.<sup>19</sup> So,

this prompted us to investigate the possibility of employing ionic liquids, which would function as a mild and recyclable medium, for the synthesis of unsymmetrical diorganyl selenides. Advantages such as high reactivity, their ready commercial availability, ease of preparation and handling as well the environmental aspects all justified our choice to employ them in our work.<sup>19</sup> We selected In(I) salts as reducing agents due to their well-known ability to promote the Se–Se bond cleavage.<sup>12,20</sup>

Accordingly, and in connection with our ongoing interest in the synthesis and evaluation of organochalcogen derivatives as ligands in asymmetric transformations<sup>21</sup> as well as biological screening,<sup>22</sup> we wish to highlight in this report our results on the preparation of unsymmetrical diorganyl selenides promoted by InI in ionic liquids. The desired products were obtained in high yields, in a very short time and with the advantage of being able to recycle the reaction media, which represents an environmentally benign approach.

## Results

Firstly, we investigated the effect of four different ionic liquids (Chart 1) for the synthesis of the desired products using PhSeSePh/InI and benzyl chloride as the substrate, at room temperature and with a reaction time of 30 minutes, Table 1. Commercially available (bmim)BF<sub>4</sub>, (bmim)PF<sub>6</sub>, (bmim)NTf<sub>2</sub> and (bpy)BF<sub>4</sub> were used. We found that cationic and anionic changes in the ionic liquid display an important role in the formation of the product. While in (bmim)BF<sub>4</sub> and (bmim)PF<sub>6</sub> the products were achieved in the same range of yield (entries 1 and 2), (bmim)NTf<sub>2</sub> and (bpy)BF<sub>4</sub> showed poorer results (entries 3 and 4).

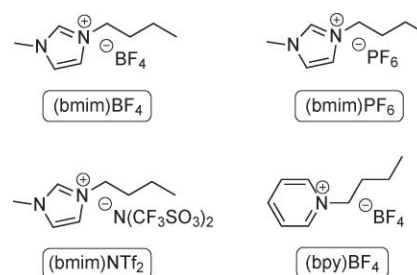


Chart 1 Room temperature ionic liquids (RTILs).

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**Table 1** Optimization of reaction conditions

| $\text{PhSeSePh} \xrightarrow[\text{IL / RT}]{\text{2 PhCH}_2\text{X} \atop \text{InX (1.0 eq)}} \text{2 PhSeCH}_2\text{Ph}$ |                        |     |                     |            |                        |
|--|------------------------|-----|---------------------|------------|------------------------|
| #  | Ionic Liquid           | InX | PhCH <sub>2</sub> X | Time (min) | Yield (%) <sup>a</sup> |
| 1  | (bmim)BF <sub>4</sub>  | I   | Cl                  | 30         | 90                     |
| 2  | (bmim)PF <sub>6</sub>  | I   | Cl                  | 30         | 86                     |
| 3  | (bmim)NTf <sub>2</sub> | I   | Cl                  | 30         | 26                     |
| 4  | (bpy)BF <sub>4</sub>   | I   | Cl                  | 30         | 64                     |
| 5  | (bmim)BF <sub>4</sub>  | Br  | Cl                  | 30         | 84                     |
| 6  | (bmim)BF <sub>4</sub>  | I   | Br                  | 30         | 93                     |
| 7  | (bmim)BF <sub>4</sub>  | I   | I                   | 30         | 98                     |

<sup>a</sup> Yields referent of pure isolated products, characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data.

**Table 2** Synthesis of unsymmetrical diorganyl selenides

| $\text{RSeSeR} \xrightarrow[(\text{bmim})\text{BF}_4 / 30 \text{ min}]{\text{2 R}'\text{X} \atop \text{InI (1.0 eq)}} \text{2 RSeR}'$ |  |   |    |                        |      |
|---|--|---|----|------------------------|------|
| #   | R  | R'  | X  | Yield (%) <sup>a</sup> | Ref. |
| 1   | Ph   | Et  | Br | 65                     | 9a   |
| 2   | Ph   | Et  | I  | 70                     | 9a   |
| 3   | Ph   | Bu  | Br | 82                     | 17   |
| 4   | Ph   | Bu  | I  | 85                     | 17   |
| 5   | Ph   | <i>t</i> -Bu  | Cl | traces                 | 12   |
| 6   | Ph   | Pentyl  | Cl | 85                     | 10   |
| 7   | Ph   | Pentyl  | Br | 89                     | 10   |
| 8   | Ph   | Allyl   | Br | 97                     | 15   |
| 9   | Ph   | Allyl   | Cl | 94                     | 15   |
| 10  | Ph   | <i>p</i> -Cl-PhCH <sub>2</sub>                            | Cl | 89                     | 12   |
| 11  | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub>  | PhCH <sub>2</sub>   | Cl | 89                     | 8c   |
| 12  | <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> | PhCH <sub>2</sub>   | Cl | 82                     | 8c   |
| 13  | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub>  | PhCH <sub>2</sub>   | Cl | 89                     | 10   |
| 14  | <i>o</i> -MeOC <sub>6</sub> H <sub>4</sub> | PhCH <sub>2</sub>   | Cl | 52                     | 8c   |
| 15  | Ph   | <i>o</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> | Br | 60                     | 18d  |
| 16  | Ph   | <i>m</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> | Br | 78                     | 18d  |
| 17  | Ph   | <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> | Br | 92                     | 18d  |
| 18  | Bn   | PhCH <sub>2</sub>   | Cl | 78                     | 15   |
| 19  | Et   | PhCH <sub>2</sub>   | Cl | 81                     | 10   |

<sup>a</sup> Yields referent of pure isolated products, characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data.

With these results in hands, we next investigated the influence of the halide, both in the indium salt and in the substrate. When we changed InI for InBr in the reaction using (bmim)BF<sub>4</sub> the product was formed in an appreciable yield, but which was lower than with InI (entries 1 and 5). Better results were found for the use of different halides in the substrate, affording the selenide in near quantitative yield (entries 6 and 7). Encouraged by our results, we next prepared a wide range of unsymmetrical diorganyl selenides using aryl or alkyl diselenides, InI, and (bmim)BF<sub>4</sub>. The results are summarized in Table 2.

Initially the experiments were carried out with alkyl or allyl halides (entries 1–9) and PhSeSePh. The yields of the products were high, even for less reactive 1-chloropentane (entries 6 and 7). Based on the results, our protocol seems to follow a S<sub>N</sub>2 type reaction, since good results were found for primary halides and just traces of product were achieved for the hindered *t*-butyl

**Table 3** Reuse of the reaction media

| $\text{PhSeSePh} \xrightarrow[(\text{bmim})\text{BF}_4 / 30 \text{ min}]{\text{2 PhCH}_2\text{Cl} \atop \text{InI}} \text{2 PhSeCH}_2\text{Ph}$ |     |          |                        |
|---|-----|----------|------------------------|
| Entry   | Run | InI (eq) | Yield (%) <sup>a</sup> |
| 1   | 1   | 1.0      | 90                     |
| 2   | 2   | 1.0      | 85                     |
| 3   | 3   | 1.0      | 82                     |
| 4   | 4   | 1.0      | 77                     |
| 5   | 5   | 1.0      | 76                     |

<sup>a</sup> Isolated yields.

chloride (entry 5). The formation of the products was not strongly influenced by the nature of halide; in most cases the products were produced with just slight differences in the yields for the same alkyl chain. Employing more reactive allyl bromide, the conversion was almost quantitative (entry 8), with a similar result found for allyl chloride (entry 9). A good result was also found for *p*-chlorobenzyl chloride, with the selenide being obtained in 89% yield (entry 10). In a new set of experiments we screened substituted diaryl diselenides with the aim of checking the influence of electronic and hindrance effects (entries 11–14). The reaction proceeded very well both for electron donating and for electron withdrawing groups attached at the *para* position of the diaryl diselenide (entries 11–13). A significant decrease in the yield was achieved by using (*o*-MeOC<sub>6</sub>H<sub>4</sub>Se)<sub>2</sub> (entry 14). Substituted benzyl bromides were also employed, the most reactive one was the *para* substituted, followed by the *meta*- and *ortho*-methyl benzyl bromides (entries 15–17). Finally we employed dibenzyl diselenide and diethyl diselenide as the source of selenium (entries 18 and 19). Once again, the desired diorganyl selenides were efficiently obtained in good yields.

To further explore the scope of our method, and in an effort toward an environmentally benign protocol, we examined the possibility of reusing the reaction media, Table 3. Accordingly, after the work-up (see ESI†) the ionic liquid was recovered.

The recovered ionic liquid was then used in another run after the addition of one equivalent of InI. To our delight, the yield was found to be similar to that obtained in the first run (entry 2). This operation was repeated three more times without appreciable loss of efficiency (entries 3–5).

## Conclusions

In summary, the present report describes a high yielding preparation of unsymmetrical diorganyl selenides, using very mild conditions and requiring a very short reaction time. Our approach employs InI as the reducing agent in (bmim)BF<sub>4</sub>, which is suitable for further reuse without loss of efficiency for at least five runs. Some important features of this method are the high reactivity, leading to the desired products in good to excellent yields, the ready commercial availability of the starting materials, as well as its environmentally benign nature. We are currently pursuing further applications of this procedure as well as investigating the use of other reducing agents.

## Experimental

### General

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 400 and 100 MHz respectively with tetramethylsilane as internal standard. Column chromatography was performed using Merck Silica Gel (230–400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF<sub>254</sub>, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. All solvents were used as purchased unless otherwise noted. The diselenides, ionic liquids and halides were used as purchased.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data of the compounds are identical to those reported.

### Representative experimental procedure to prepare unsymmetrical diorganyl selenides

In a schlenk tube, to a stirred solution of (bmim)BF<sub>4</sub> (0.5 mL) was added indium(I) iodide (121 mg, 0.5 mmol) and diphenyl diselenide (156 mg, 0.5 mmol) at room temperature under nitrogen. The mixture was allowed to stir for 5 min. Then benzyl bromide (171 mg, 1 mmol) was slowly added. The reaction mixture was stirred for another 30 min (checked by TLC), the mixture was then extracted with ether (3 × 15 mL), and the combined ether extract was washed with brine, dried (Mg<sub>2</sub>SO<sub>4</sub>), and evaporated to leave the crude product. Following purification by column chromatography over silica gel (hexane/ether 95:5) the pure benzyl phenyl selenide was obtained as a yellow liquid (224 mg, 93%).

### Representative experimental procedure to reuse (bmim)BF<sub>4</sub>

After the work-up of the first run, (bmim)BF<sub>4</sub> was diluted in dichloromethane and filtered through a celite pad to remove the inorganic materials followed by concentration to remove the organic solvents and being subjected to vacuum for 1 hour to eliminate moisture and trace organic solvents. For the following runs the recovered ionic liquid was used after addition of one equivalent of InI (121 mg, 0.5 mmol), diphenyl diselenide (156 mg, 0.5 mmol) and benzyl bromide (171 mg, 1 mmol).

### Ethyl phenyl selenide<sup>9a</sup>

Yield: 70%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.50–7.45 (m, 2H), 7.27–7.20 (m, 3H), 2.91 (q,  $J$  = 7.6 Hz, 2H), 1.43 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 132.57, 130.32, 129.0, 126.71, 21.26, 15.51.

### Butyl phenyl selenide<sup>17</sup>

Yield: 85%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.49–7.45 (m, 2H), 7.26–7.18 (m, 3H), 2.90 (t,  $J$  = 7.6 Hz, 2H), 1.71–1.64 (m, 2H), 1.46–1.37 (m, 2H), 0.90 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 132.42, 130.82, 129.02, 126.62, 32.32, 27.66, 23.02, 13.64.

### Pentyl phenyl selenide<sup>10</sup>

Yield: 89%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.47–7.44 (m, 2H), 7.22–7.14 (m, 3H), 2.87 (t,  $J$  = 7.6 Hz, 2H), 1.68 (m, 2H), 1.39–1.24 (m, 4H), 0.86 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 132.43, 130.94, 129.02, 126.61, 32.11, 30.50, 28.28, 22.27, 14.05.

### Allyl phenyl selenide<sup>15</sup>

Yield: 97%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  = 7.63–7.58 (m, 2H), 7.27–7.23 (m, 3H), 6.05–5.84 (m, 1H), 5.02–4.92 (m, 2H), 3.52 (d,  $J$  = 7.6 Hz, 2H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 134.37, 133.32, 131.51, 128.91, 127.11, 116.81, 30.65.

### (4-Chlorophenyl) methyl phenyl selenide<sup>12</sup>

Yield: 89%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 7.45–7.41 (m, 2H), 7.25–7.11 (m, 5H), 7.09–7.07 (m, 2H), 4.03 (s, 2H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 137.32, 133.38, 132.5, 130.08, 129.80, 129.04, 128.48, 127.54, 31.45.

### Benzyl 4-tolyl selenide<sup>8c</sup>

Yield: 89%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  = 7.33 (d,  $J$  = 8 Hz, 2H), 7.30–7.16 (m, 5H), 7.04 (d,  $J$  = 7.8 Hz, 2H), 4.05 (s, 2H), 2.31 (s, 3H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 138.83, 137.27, 133.93, 129.71, 128.75, 128.29, 126.68, 126.49, 32.45, 21.06.

### Benzyl 4-methoxyphenyl selenide<sup>8c</sup>

Yield: 82%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  = 7.36 (d,  $J$  = 8.6 Hz, 2H), 7.26–7.10 (m, 5H), 6.77 (d,  $J$  = 8.6 Hz, 2H), 4.0 (s, 2H), 3.79 (s, 3H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 159.55, 139.08, 136.51, 128.78, 128.29, 126.64, 120.02, 114.58, 55.22, 33.15.

### Benzyl (4-chlorophenyl) selenide<sup>10</sup>

Yield: 89%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.35–7.33 (m, 2H), 7.26–7.16 (m, 7H), 4.07 (s, 2H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 140.01, 138.42, 135.09, 130.86, 129.90, 129.45, 127.82, 126.65, 32.18.

### Benzyl 2-methoxyphenyl selenide<sup>8c</sup>

Yield: 52%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.35 (m, 1H), 7.29–7.15 (m, 6H), 6.87–6.81 (m, 2H), 4.10 (s, 2H), 3.84 (s, 3H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 50 MHz)  $\delta$  = 157.64, 138.14, 131.98, 128.83, 128.31, 127.99, 126.71, 121.24, 120.10, 110.26, 55.69, 29.43.

### 2-[(phenylseleno)methyl]toluene<sup>18d</sup>

Yield: 60%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.47–7.45 (m, 2H), 7.26–7.20 (m, 3H), 7.13–7.11 (m, 2H), 7.06–7.01 (m, 2H), 4.10 (s, 2H), 2.35 (s, 3H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 133.86, 130.47, 129.76, 128.92, 127.40, 127.21, 125.91, 30.53, 19.20.

### 3-[(phenylseleno)methyl]toluene<sup>18d</sup>

Yield: 78%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.46–7.43 (m, 2H), 7.26–7.21 (m, 3H), 7.15–7.11 (m, 1H), 7.01–6.99 (m, 3H), 4.07 (s, 2H), 2.28 (s, 3H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 138.38, 138.02, 133.45, 130.61, 129.59, 128.92, 128.30, 127.63, 127.21, 125.84, 32.23, 21.29.

### 4-[(phenylseleno)methyl]toluene<sup>18d</sup>

Yield: 92%;  $^1\text{H}$  NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.47–7.44 (m, 2H), 7.25–7.23 (m, 3H), 7.11 (d,  $J$  = 8 Hz, 2H), 7.05 (d,  $J$  = 8.4 Hz, 2H), 4.09 (s, 2H), 2.30 (s, 3H);  $^{13}\text{C}$  (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 136.34, 135.37, 133.20, 130.67, 129.02, 128.84, 128.62, 127.01, 31.84, 21.01.

### Dibenzyl selenide<sup>15</sup>

Yield: 78%; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.31–7.25 (m, 8H), 7.23–7.19 (m, 2H), 3.72 (s, 4H); <sup>13</sup>C (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 139.26, 129.01, 128.07, 126.71, 27.16.

### Benzyl ethyl selenide<sup>10</sup>

Yield: 81%; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.29–7.25 (m, 4H), 7.23–7.18 (m, 1H), 3.79 (s, 2H), 2.50 (q,  $J$  = 7.6 Hz, 2H), 1.37 (t,  $J$  = 7.2 Hz, 3H); <sup>13</sup>C (CDCl<sub>3</sub>, MHz)  $\delta$  = 132.42, 130.80, 128.90, 126.31, 27.01, 17.8, 15.9.

### Benzyl phenyl selenide<sup>12</sup>

Yield: 98%; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  = 7.50–7.42 (m, 2H), 7.28–7.14 (m, 8H), 4.10 (s, 2H); <sup>13</sup>C (CDCl<sub>3</sub>, 100 MHz)  $\delta$  = 138.60, 133.53, 130.40, 128.94, 128.82, 128.39, 127.26, 126.82, 32.21.

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