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Indium-mediated mild and efficient one-pot synthesis of alkyl phenyl selenides

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Abstract—A mild and convenient one-pot process for synthesizing alkyl phenyl selenides is developed using indium metal. The reaction shows the selectivity for *tert*-alkyl, benzylic, and allylic halides over primary and secondary alkyl halides.

Organic selenides have been playing an important role in organic synthesis.[1] They have been employed widely as key intermediates for introducing new functional groups. For instance, phenyl selenides generally have been used as precursors for forming carbon–carbon double bonds. Although a number of research reports on the preparation of organoselenides have been published,[1,2] they have several drawbacks including the instability of reagents used and the strongly acidic or basic reaction conditions.[3] Therefore, a method of preparing organoselenides with stable reagents under neutral conditions is still called for.

Recently, indium metal has drawn an increasing attention for its unique properties such as low toxicity and high stability in water and air compared with other metals.[4] As part of our effort toward developing applications of indium metal in organic synthesis,[5] we provided an indium-mediated reaction for the preparation of organoselenides. We report on a mild and efficient one-pot procedure for the synthesis of alkyl phenyl selenides using indium metal under neutral conditions (Scheme 1).

$$\text{R-X} \ + \ \text{PhSeSePh} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{reflux}]{\text{In}} \text{R-SePh}$$

Scheme 1.

Table 1. Reaction of ^{t}BuCl with PhSeSePh (1 equiv) in the presence of indium

$$^t\text{BuCl} \ + \ \text{PhSeSePh} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{reflux}]{\text{In (1 equiv)}} {}^t\text{BuSePh}$$

Entry	^{t}BuCl (equiv)	In (equiv)	Temp	Time (h)	Yield (%)[a]
1	2.0	1.0	Reflux	1	95
2	2.0	1.0	rt	3	99
3	2.0	0	Reflux	1	0
4	2.0	1.0	Reflux	1	73[b]
5	2.0	0.1	Reflux	1	20
6	2.0	1.0	Reflux	1	3[c]

[a] Analyzed by GC based on ^{t}BuCl.
[b] 0.2 equiv of I_2 was added.
[c] 1.0 equiv of $InCl_3$ was used instead of In.

We first investigated the reaction of ^{t}BuCl with PhSeSePh under several reaction conditions (Table 1). When diphenyl diselenide was allowed to react with 2 equiv of ^{t}BuCl in the presence of an equimolar amount of indium in CH_2Cl_2 at reflux for 1 h, *tert*-butyl phenyl selenide was obtained in 95% yield based on ^{t}BuCl (entry 1). At room temperature, longer reaction time was required to complete the reaction (entry 2). In the absence of indium metal, the reaction did not proceed at all, which implies that indium was a promoter of the reaction (entry 3). The addition of a catalytic amount of iodine caused a decrease in the yield of alkyl phenyl selenides

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Keywords: Indium; Alkyl phenylselenides; Diphenyl diselenide; Alkyl halides.

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Table 2. Solvent effects on the reaction of ^{t}BuCl with PhSeSePh

$$\underset{\text{(2 equiv)}}{{}^{t}\text{BuCl}} + \underset{\text{(1 equiv)}}{\text{PhSeSePh}} \xrightarrow[\text{solvent, reflux, 1 h}]{\text{In (1 equiv)}} {}^{t}\text{BuSePh}$$

Solvent	Yield (%)[a]
Benzene	65
Toluene	41
THF	22
$ClCH_2CH_2Cl$	52
CH_3CN	66
CH_2Cl_2	95
CH_2Cl_2–H_2O (9:1, v/v)	42

[a] Analyzed by GC based on ^{t}BuCl.

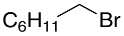
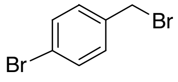
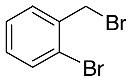
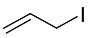
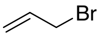
(entry 4).[6] With a catalytic amount of indium or 1 equiv of $InCl_3$ the reaction was not efficient (entries 5 and 6).

Next, we examined the solvent effects of the reaction (Table 2). The reaction of ^{t}BuCl with PhSeSePh in common organic solvents such as benzene, toluene, THF, $ClCH_2CH_2Cl$, and CH_3CN gave *tert*-butyl phenyl selenide in low to moderate yields. The reaction performed in CH_2Cl_2 was the most efficient affording a 95% yield of *tert*-butyl phenyl selenide. In aqueous CH_2Cl_2, the yield of the product decreased.

With the optimal conditions in our hand, we investigated the scope and limitations of the present method employing a variety of sterically different organic halides. The results are summarized in Table 3. Tertiary alkyl halides underwent a clean reaction to provide the corresponding alkyl phenyl selenides in high yields (entries 1–6). It is noteworthy that the reaction of *tert*-alkyl halides with metal phenyl selenoates could not be achieved even under harsh reaction conditions.[3c] Primary and secondary alkyl iodides showed high reactivity under these conditions (entries 7 and 8). On the other hand, primary and secondary alkyl bromides remained inactive (entries 9 and 10). Although the reactivity of aryl halides was very low (entry 15), benzylic and allylic halides were converted into the corresponding selenides in excellent yields (entries 11–14). Next, we applied the method to preparing alkyl phenyl chalcogenides. Treatment of ^{t}BuCl with PhSSPh or PhTeTePh in the presence of indium in CH_2Cl_2 at reflux gave the corresponding sulfide and telluride in 35% and 95% yields, respectively.

Table 3. Reaction of various alkyl halides with PhSeSePh in the presence of indium

$$\underset{\text{(2 equiv)}}{\text{RX}} + \underset{\text{(1 equiv)}}{\text{PhSeSePh}} \xrightarrow[\text{CH}_2\text{Cl}_2\text{, reflux, 1 h}]{\text{In (1 equiv)}} \text{RSePh}$$

Entry	RX	Yield (%)[a]
1	^{t}BuI	99
2	^{t}BuBr	95 (86)
3	^{t}BuCl	95
4	1-Iodoadamantane	86 (76)
5	1-Bromoadamantane	84 (74)
6	1-Chloroadamantane	90 (88)
7	^{i}PrI	98 (70)
8	$CH_3(CH_2)_{15}I$	98 (78)[b]
9	Cyclohexyl bromide	Trace[b]
10		Trace[b]
11		98 (85)
12		99 (95)
13		99 (89)
14		97 (73)
15	PhBr	Trace

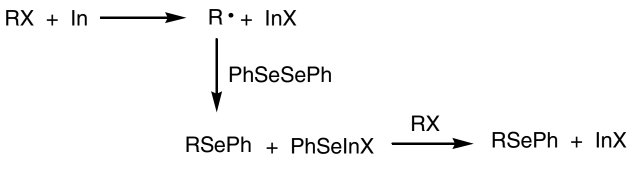
[a] Analyzed by GC based on alkyl halides. The yields in parenthesis are isolated yields.

[b] The reaction time was 3 h.

Recently, there have been reports that alkyl radicals are readily generated from alkyl halides by indium metal and are added to electron-deficient carbon–carbon double bonds.[5c,7] Compared with primary alkyl halides, tertiary alkyl halides showed high reactivity under the present reaction conditions (Table 2). We carried out some competitive experiments with mixtures of tertiary alkyl halides. A set of mixture of *tert*-butyl halides was treated with indium metal in CH_2Cl_2 at reflux for 15 min, and analyzed the remaining *tert*-butyl halides. The ratio of the remaining *tert*-butyl halides as Cl–I, Cl–Br, and Br–I was 6.5:1, 3.6:1, and 2.6:1, respectively. Thus, the relative reactivity of halides was found to follow the sequence: I > Br > Cl. It is consistent with the order of halides with respect to the reactivity under radical reaction conditions. On the basis of these findings, it might be assumed that there is a possibility of not only involving metal selenoates as suggested for the reaction using La or Zn, but also radical intermediates.

The reaction pathway for the formation of alkyl phenyl selenides is illustrated in Scheme 2. First, indium metal reduced alkyl halides to generate alkyl radicals, and then the S_H2 reaction of alkyl radicals with diphenyl diselenide formed alkyl phenyl selenides. The PhSeInX species that was generated during the reaction reacted with other alkyl halide through S_N2 pathway to give the corresponding alkyl phenyl selenides.

In conclusion, we have developed a mild and efficient one-pot method for synthesis of alkyl phenyl selenides by indium-mediated reaction of diphenyl diselenide with organic halides, which showed the selectivity for *tert*-alkyl, benzylic, and allylic halides over primary and secondary alkyl halides. Our method has some advantages including a simple experimental procedure, the



Scheme 2.

neutral reaction conditions, high yields of the desired products, and low toxicity.

A typical experimental procedure is as follows: Indium powder (0.5 mmol, 57.4 mg), diphenyl diselenide (0.5 mmol, 156.1 mg), and CH_2Cl_2 (2 mL) were placed in a two-necked flask. Organic halides (1.0 mmol) in CH_2Cl_2 (1 mL) were added to the mixture and the resulting mixture was stirred at reflux for 3 h under nitrogen. The mixture was then quenched with 1 M HCl and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and purified by column chromatography on silica gel eluting with hexane, to give the corresponding alkyl phenyl selenide.

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