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Oxy- and aminoselenation of alkenes utilizing an isolable selenenyl iodide

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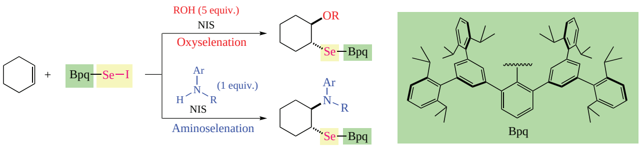
Application of an isolable selenenyl iodide BpqSeI (Bpq denotes 5′,5‴-bis(2,6-diisopropylphenyl)-2,6,2⁗,6⁗-tetraisopropyl-1,1′:3′,1″:3″,1‴:3‴,1⁗-quinquephenyl-2″-yl) to selenofunctionalization of alkenes with external oxygen or nitrogen nucleophiles was investigated. In the presence of *N*-iodosuccinimide as an additive, alcohols, a carboxylic acid, or aromatic amines were smoothly introduced to alkenes to give the corresponding β-oxy or β-amino selenides in moderate to high yields.



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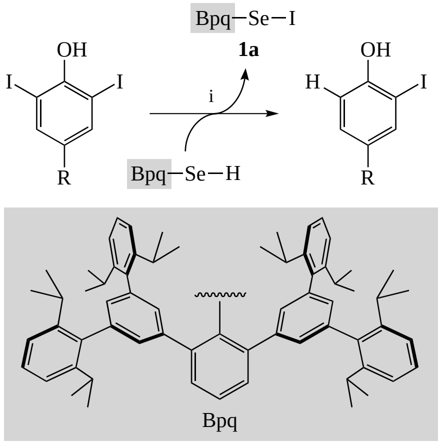
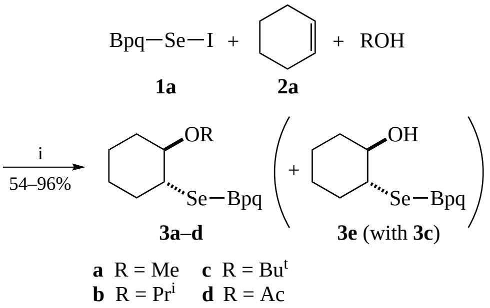
Introduction of selenium atoms into organic compounds is an important research topic because the resulting selenides can be applied to a variety of synthetically useful transformations such as oxidative *syn*-elimination and radical reactions.[1–5] Among the methods developed so far, selenofunctionalization of unactivated alkenes utilizing selenenyl chlorides (RSeCl) or bromides (RSeBr) with various external nucleophiles is an attractive one for the rapid construction of vicinal functional groups.[6–21] However, in sharp contrast to the selenenyl chlorides and bromides, the use of selenenyl iodides (RSeI) remains elusive because they are notoriously unstable due to their facile disproportionation to the corresponding diselenide and diiodine.[22–26] Although reactions in which generation of selenenyl iodides was assumed *in situ* have been investigated,[27–29] it is desirable to elucidate the characteristic reactivity of this species by utilizing a stable compound that can be isolated in pure form.

For the synthesis of an isolable selenenyl iodide, introduction of a sterically demanding substituent[30,31] or an intramolecular coordinating group around the selenium center has been reported.[32–34] During our studies concerning biologically relevant organoselenium intermediates,[35–43] we have succeeded in the synthesis and isolation of the stable selenenyl iodide **1a** bearing a cavity-shaped substituent, a Bpq group.[39] By utilizing compound **1a**, we demonstrated the formation of a selenenyl iodide in the deiodination of a thyroxine derivative with the corresponding organoselenol (Scheme 1),[39] which has been proposed as a key step in thyroid hormone deiodination by iodothyronine deiodinases.[44,45] We also reported that this selenenyl iodide had intrinsically high thermal stability so far as the formation of the corresponding diselenide is sterically prevented[39,40] and that the high affinity between selenium and iodine can be applied to iodide-promoted deselenylation reactions.[46] Due to the reliable stability of **1a**, it has a potential as a benchmark compound to evaluate reactivity of selenenyl iodides as the class of chemical compounds. Herein, we report the application of this selenenyl iodide **1a** to selenofunctionalization of alkenes with alcohols, a carboxylic acid, and aromatic amines.



Scheme 1 *Reagents and conditions*: i, NEt_3, $CDCl_3$, 50 °C, 7 days (see ref. 39).

In the presence of MeOH as the oxygen nucleophile, oxyselenation of cyclohexene **2a** was investigated (Scheme 2, Table 1). When these reactants were stirred in $CDCl_3$ at room temperature, product **3a**[46] was obtained quantitatively after 72 h (entry 1). It is noteworthy that this reaction yielded the methoxyselenated product **3a** quantitatively by using 160 equiv. of MeOH without the formation of the corresponding β-iodo

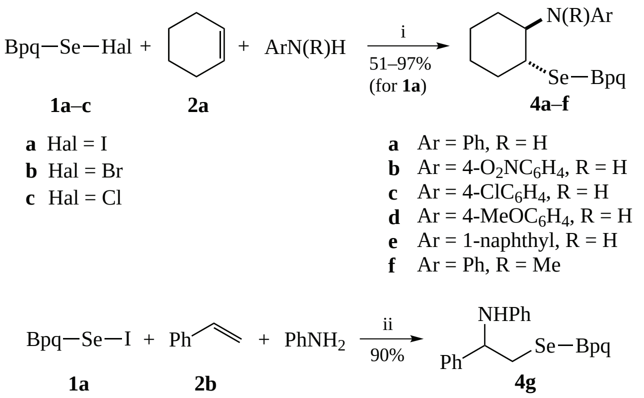


Scheme 2 *Reagents and conditions*: i, **1a** : **2a** = 1 : 6, ROH (5 equiv.), NIS (1 equiv.), MeCN/$CHCl_3$ (1 : 1), 25 °C, 0.5 h (optimal, see also Table 1).

Table 1 Oxy- and aminoselenation of cyclohexene **2a** using BpqSeI **1a**.[a]

Entry	Nucleophile	Solvent	*t*/h	Product	Yield (%)
1	MeOH	$CDCl_3$	72[b] (1,[c] 0.33[d])	**3a**	>99
2	MeOH	$CHCl_3$	1	**3a**	60
3	MeOH	EtOAc/$CHCl_3$[e]	1	**3a**	69
4	MeOH	acetone/$CHCl_3$[e]	1	**3a**	71
5	MeOH	MeCN/$CHCl_3$[e]	0.5–1	**3a**	96
6	Pr^iOH	MeCN/$CHCl_3$[e]	0.5	**3b**	88
7	Bu^tOH	MeCN/$CHCl_3$[e]	0.5	**3c**	54
8	AcOH	MeCN/$CHCl_3$[e]	0.5	**3d**	92
9[f]	$PhNH_2$	MeCN/$CHCl_3$[e]	0.17	**4a**	>99 (84,[g] traces[h])
10	$PhNH_2$	MeCN/$CHCl_3$[e]	0.17	**4a**	92
11	$4\text{-}O_2NC_6H_4NH_2$	MeCN/$CHCl_3$[e]	0.17	**4b**	71
12	$4\text{-}ClC_6H_4NH_2$	MeCN/$CHCl_3$[e]	0.17	**4c**	93
13	$4\text{-}MeOC_6H_4NH_2$	MeCN/$CHCl_3$[e]	1	**4d**	62
14	1-naphthylamine	MeCN/$CHCl_3$[e]	1	**4e**	51
15	PhN(Me)H	MeCN/$CHCl_3$[e]	0.17	**4f**	97

[a] Optimized reaction conditions: cyclohexene **2a** (6 equiv. for **3a**–**d** and 1 equiv. for **4a**–**f**), nucleophile (5 equiv. for **3a**–**d** and 1 equiv. for **4a**–**f**), NIS (1 equiv. for **3a**–**d** and 0.9 equiv. for **4a**–**f**), 25 °C. [b] 160 equiv. of MeOH, without NIS. [c] 160 equiv. of MeOH, 3.2 equiv. of I_2 instead of NIS. [d] 160 equiv. of MeOH, 3.2 equiv. of NIS. [e] 1 : 1 (v/v). [f] 1 equiv. of **1a**, 6 equiv. of **2a**, 5 equiv. of $PhNH_2$, 0.5 equiv. of NIS. [g] With BpqSeBr. [h] With BpqSeCl.



Scheme 3 *Reagents and conditions*: i, **1** : **2a** = 1 : 1, NIS (0.9 equiv.), ArN(R)H (1 equiv.), MeCN/$CHCl_3$ (1 : 1), 25 °C, 0.17–1 h (optimal, see also Table 1); ii, **1a**/**2b** = 1 : 6, NIS (1 equiv.), $PhNH_2$ (5 equiv.), MeCN/$CHCl_3$ (1 : 1), 25 °C, 24 h.

selenide. This is in sharp contrast to methoxyselenation using selenenyl chlorides or bromides, which usually requires a solvent amount of MeOH to avoid the formation of the corresponding β-halo selenides. The addition of an iodinating reagent (I_2 or *N*-iodosuccinimide, NIS) drastically accelerated the reaction rate (see entry 1). Solvent screening revealed that a mixed solvent of MeCN and $CHCl_3$ was optimal, and the target compound **3a** was produced in 96% yield after 1 h (entries 2–5). Under these conditions, the use of only 5 equivalents of MeOH was found to be enough. Under optimized reaction conditions (1 equiv. of **1a**, 6 equiv. of **2a**, 5 equiv. of oxygen nucleophile, 1 equiv. of NIS, MeCN/$CHCl_3$, 25 °C, 30 min), the substrate scope of oxygen nucleophile was examined. Reactions of MeOH and Pr^iOH smoothly proceeded to give the corresponding products **3a** and **3b** in 96 and 88% yields, respectively (entries 5 and 6). When bulky Bu^tOH was tested, β-alkoxy selenide **3c** was obtained in moderate yield, and β-hydroxy selenide **3e** was detected as byproduct (entry 7). In addition to alcohols, acetic acid was also applicable to give ester **3d** in 92% yield (entry 8).

Among the limited examples of aminoselenation, the use of free amines is rare due to their high nucleophilicity.[29,47–49] For the expansion of generality of selenofunctionalization utilizing selenenyl iodide **1a**, aniline was selected as a candidate of nitrogen nucleophile (Scheme 3). Under the similar reaction conditions for the above oxyselenation, the aminoselenation also proceeded smoothly to generate β-amino selenide **4a** in >99% yield (see Table 1, entry 9). Interestingly, comparison of BpqSeI **1a**, BpqSeBr **1b** and BpqSeCl **1c** revealed that **1a** was the most effective for the aminoselenation. This result suggests an unexplored utility of selenenyl iodides in synthetic organic chemistry. The substrate scope of the reaction of nitrogen nucleophile was investigated. Primary aromatic amines bearing either an electron-donating or an electron-withdrawing group on the benzene ring gave the corresponding products in good yields (entries 10–13). Bulky 1-naphthylamine was proven to be a suitable substrate for this aminoselenation (entry 14). In addition to the primary aromatic amines, secondary amine also afforded β-amino selenide **4f** in 97% yield (entry 15). For the scope of alkenes, styrene **2b** could be applied to give the target product **4g** in 90% yield (see Scheme 3). In the experiments described in Table 1, reactions of **1a** with added nucleophiles were not observed.

In summary, application of an isolable selenenyl iodide to selenofunctionalization of alkenes with external oxygen or nitrogen nucleophiles was demonstrated for the first time by utilizing a cavity-shaped molecule. By the aid of the selenenyl iodide, various alcohols, a carboxylic acid, or aromatic amines were introduced to alkenes to give the corresponding β-oxy selenides or β-amino selenides in moderate to high yields. These results indicate that a selenenyl iodide is effective for the introduction of external nucleophiles in the selenofunctionalization of alkenes. Further investigations on the use of selenenyl iodides in synthetic chemistry are currently underway.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.01.026.

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