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Visible-Light-Promoted Selenofunctionalization of Alkenes

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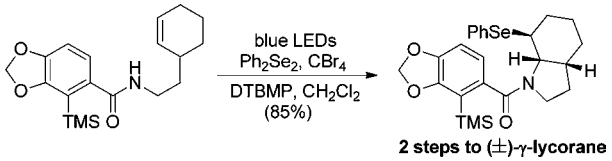
ABSTRACT



A visible-light-promoted method for the selenofunctionalization (and tellurofunctionalization) of alkenes has been developed. This method obviates the prepreparation of moisture-sensitive chalcogen electrophiles. The experimental setup is simple, and superior yields are obtained in the case of selenofunctionalization (up to 99%) while moderate to good yields are obtained in the case of tellurofunctionalization (53−75%). A variety of intra- and intermolecular processes and a short synthesis of the Amaryllidaceae alkaloid (±)-γ-lycorane are demonstrated with this method.

Since the publication of seminal reports in the late 1950s and early 1960s,[1] selenofunctionalization and tellurofunctionalization have served as versatile methods for the synthetic elaboration of alkenes. These methods have been used in the synthesis of numerous non-natural and natural products. The preparation of reagents and the synthesis of target molecules have been the subject of a number of reviews.[2] Organoselenide products of selenofunctionalization are useful synthetic intermediates as they can be manipulated further (e.g., with selenoxide elimination,[3] C−Se bond homolysis,[4] Pummerer rearrangement,[5] and selenone manipulation[6]). Further, a surge of interest in organoselenides and organotellurides as potential anticancer agents has been kindled in recent years.[7]

Selenofunctionalization and tellurofunctionalization are traditionally accomplished with the use of selenium and tellurium electrophiles with the general structures ArSeX and $ArTeX_3$ where "X" is typically a halogen.[1,2] These reagents suffer from numerous shortcomings including moisture sensitivity and a short shelf life. As such, the *in situ* preparation of reagents in this class has become a method of choice in accomplishing these transformations. Unfortunately, the use of electrophiles such as molecular bromine in the formation of electrophiles such as PhSeBr from bench-stable and easily handled PhSeSePh preclude the generation of these electrophiles in the presence of an alkene substrate. Methods allowing for the *in situ* generation of "ArSeX" and "$ArTeX_3$" in the presence of alkene substrates are very desirable to accomplish these transformations.

Unfortunately, methods to form "ArSeX" in the presence of nucleophile-tethered alkene substrates are scarce and include chemical,[8] electrochemical,[9] and UV photochemical[10] protocols. We now report on a mild, *visible-light-promoted* method for the seleno- and

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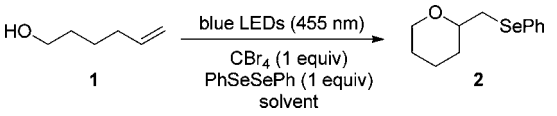
tellurofunctionalization of alkenes via the *in situ* preparation of chalcogen electrophiles in the presence of alkene substrates. This method uses bench-stable reagents (PhSeSePh, PhTeTePh, and tetrahalomethanes) with low reactivity in the absence of blue light and is marked by operative simplicity and high (often near quantitative) yields without the use of an inert atmosphere.

Recently, we have demonstrated the visible-light-promoted activation of selenoglycosides for *O*-glycosylation and determined through ^{77}Se NMR studies that the combination of PhSeSePh and CBr_4 with blue LED irradiation results in the formation of PhSeBr.[11] We recognized the potential for these conditions to provide a method for the *in situ* generation of PhSeBr in the presence of alkene substrates. To explore this possibility, we studied the selenocyclization of 5-hexen-1-ol (**1**, Table 1; see Supporting Information for a photo of the experimental setup, Figure S1). Initial experiments involving the blue LED irradiation of 1 equiv each of PhSeSePh and CBr_4 at a concentration of 200 mM resulted in long reaction times (>24 h) with low and variable yields. Increasing the dilution to 50 mM resulted in reaction times of 1 day or less and a marked improvement in yield. Reactions run in THF or diethyl ether resulted in relatively long reaction times (24.5 h) but high yields of the selenocyclized product **2** (entries 1, 2). Dichloromethane and acetonitrile reduced the reaction time substantially and resulted in excellent yields of **2** (entries 3, 4). Finally, the use of undistilled alcohol solvents resulted in the shortest observed reaction times (3.5−5.5 h) and, in the case of methanol, a nearly quantitative yield of **2** (entries 5−7). Somewhat surprisingly, we never observed products of intermolecular alkoxyselenation resulting from solvent attack on the intermediate seleniranium ion.

We also observed (entry 8) that the tetrahalomethane Cl_3CBr is interchangeable with CBr_4, providing a lowered yield of **2** in MeOH with an increased reaction time. Importantly, controls run in the absence of both light and CBr_4 (entries 9 and 10) demonstrated the necessity of both. Finally, none of these experiments were run under an inert atmosphere (which did nothing to improve yields).

To demonstrate the substrate scope of this method, we screened a number of alkene substrates for the intra- and intermolecular selenofunctionalization of alkenes (Table 2). Formation of the five-membered ether **4a** (entry 1) proceeded in 94% yield while the Boc-protected pyrrolidine **4b** was formed in a modest 62% yield in CH_2Cl_2 (entry 2) and not at all in MeOH. Surmising that HBr generated during the course of selenofunctionalization might result in degradation of both substrate **3b** and product **4b**, we performed the selenocyclization of methoxycarbonyl-protected analog **3c** that proceeded in an improved 78% yield, demonstrating the efficacy of this method for the formation of pyrrolidine derivatives (entry 3). The selenocyclization of 4-pentenoic acid (**3d**) in methanol resulted in substantial quantities of

Table 1. Solvent Screen for Visible-Light-Promoted Selenocyclization[a]



entry	solvent	irradiation time (h)	yield (%)
1	THF	24.5	70
2	Et_2O	24.5	84
3	CH_2Cl_2	11	93
4	CH_3CN	6	91
5	*i*PrOH	3.5	85
6	EtOH	5.5	90
7	MeOH	4	98
8[b]	MeOH	7	82
9[c]	CH_2Cl_2	120	0
10[d]	CH_2Cl_2	120	0

[a] All reactions were performed on a 0.6 mmol scale at a concentration of 50 mM. [b] Used $CBrCl_3$ instead of CBr_4. [c] Performed in the absence of light. [d] Performed in the absence of CBr_4.

products of methoxyselenation. The same reaction in dichloromethane resulted in a 95% yield of γ-butyrolactone product **4d** (entry 4). The intermolecular methoxyselenation of cyclohexene resulted in a 97% yield of the product **4e** as a single diastereomer (entry 5), whereas the Ritter reaction[12] of cyclohexene resulted in a sluggish reaction and a disappointing 43% yield of amide **4f** (entry 6). Methoxyselenation of 1-hexene resulted in a 97% yield of a 3.3:1 mixture of products favoring the Markovnikov product **4ga** (entry 7). Finally, selenocyclization of 2° alcohol **3g** resulted in a 1:1 mixture (99%) of diastereomeric products **4h** (entry 8).

Tellurocyclization (Table 3) was also performed on alkenols in the presence of CBr_4 and PhTeTePh. While methanol gave high yields with selenocyclization, this same solvent afforded none of the predicted tellurofunctionalization products. On the other hand, dichloromethane afforded 75% and 53% yields of **5** and **6**, respectively. The structure of **5** was confirmed by X-ray crystallography (Supporting Information, Figure S2).

The mechanism of these chalcogenofunctionalizations is a subject of continuing investigation. Controls have demonstrated that these reactions are dependent on both light and tetrahalomethane. Reaction temperatures are consistently in the range 25−29 °C, demonstrating that adventitious heating by the light source does not explain the reactivity. As mentioned before, we have observed the formation of PhSeBr upon blue LED irradiation of PhSeSePh and CBr_4 using ^{77}Se NMR. We propose that blue LED irradiation of PhTeTePh in the presence of CBr_4 results in the formation of $PhTeBr_3$, a reagent known to promote tellurofunctionalization.[13] However, CBr_4 does not absorb at the wavelengths (λ_{max} = 455 nm) of blue

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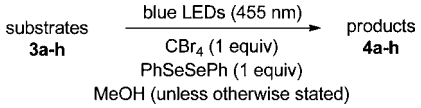
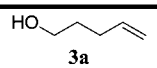
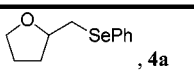
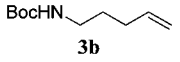
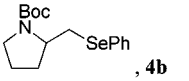
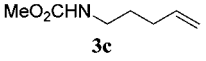
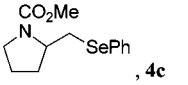
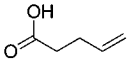
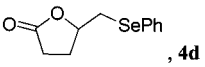
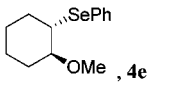
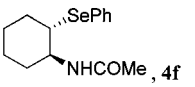
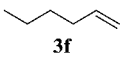
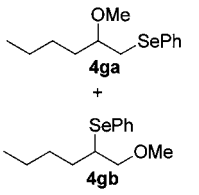
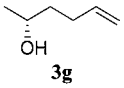
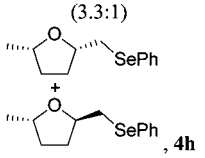
Table 2. Substrate Scope of Visible-Light-Promoted Selenofunctionalization[a]

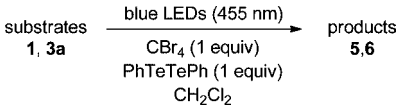


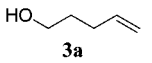
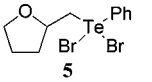
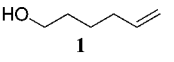
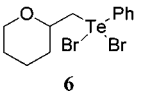
entry	substrate	product	yield (%)
1	 **3a**	 , **4a**	94
2[b]	 **3b**	 , **4b**	62
3	 **3c**	 , **4c**	78
4[b]	 **3d**	 , **4d**	95
5	 **3e**	 , **4e**	97
6[c]	 **3e**	 , **4f**	43
7	 **3f**	 **4ga** + **4gb** (3.3:1)	97
8	 **3g**	 , **4h** (1:1)	99

[a] All reactions were performed on a 0.6 mmol scale at a concentration of 50 mM. [b] Reaction performed in CH_2Cl_2. [c] Reaction performed in CH_3CN/H_2O (13 μL of H_2O added to 12.0 mL of CH_3CN).

LED irradiation.[14] On the other hand, PhSeSePh absorbance does tail into the wavelengths produced by blue LEDs[15] while the absorbance of PhTeTePh at 455 nm is substantial.[16] We initially considered the possibility of a light-promoted homolysis of PhSeSePh and PhTeTePh preceding abstraction of halogen from tetrahalomethane by a chalcogen radical (Mechanism 1, Scheme 1). Indeed, Gaussian 2009 calculations at the 6-311G** level of theory indicate that phenylselenyl radical abstraction of bromine from CBr_4 to generate phenylselenyl bromide and the tribromomethyl radical is favorable by −9.3 kcal/mol

Table 3. Visible-Light-Promoted Tellurofunctionalization[a]

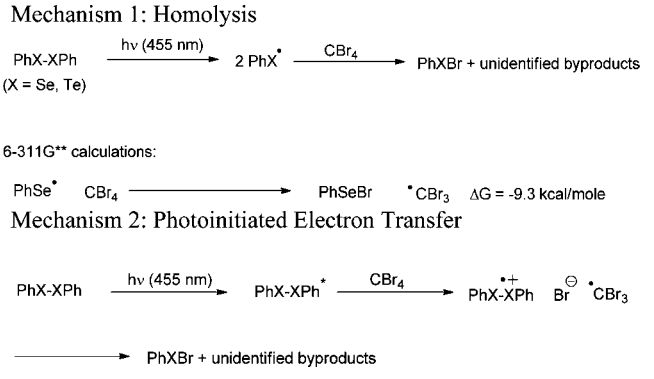


entry	substrate	reaction time (h)	product	yield (%)
1	 **3a**	47	 **5**	75
2	 **1**	44	 **6**	53

[a] Reactions were performed on a 0.6 mmol scale at a concentration of 50 mM.

(Scheme 1). Nevertheless, a photoinitiated electron transfer[10] from diaryldichalcogenide to CBr_4 (Mechanism 2, Scheme 1) is an alternative scenario that cannot be ruled out at this time. The fate of carbon and the remaining bromine atoms of CBr_4 is also unclear at this time; the formation of volatile byproducts may explain the lack of isolable byproducts from these reactions. To this end, GC/MS analysis of irradiated mixtures of **1**, PhSeSePh and CBr_4 has been inconclusive regarding the fate of the tribromomethyl radical.

Scheme 1. Possible Mechanistic Scenarios



We sought to demonstrate the efficacy of this method in the synthesis of a complex natural product and recognized its potential to provide a short synthesis of the Amaryllidaceae alkaloid (±)-γ-lycorane[17,18] (Scheme 2, Part I). Reduction of known nitrile **7**[19] to amine **8** followed by coupling to commercially available acid chloride **9** afforded a 63% yield of cyclization substrate **10** (two steps).

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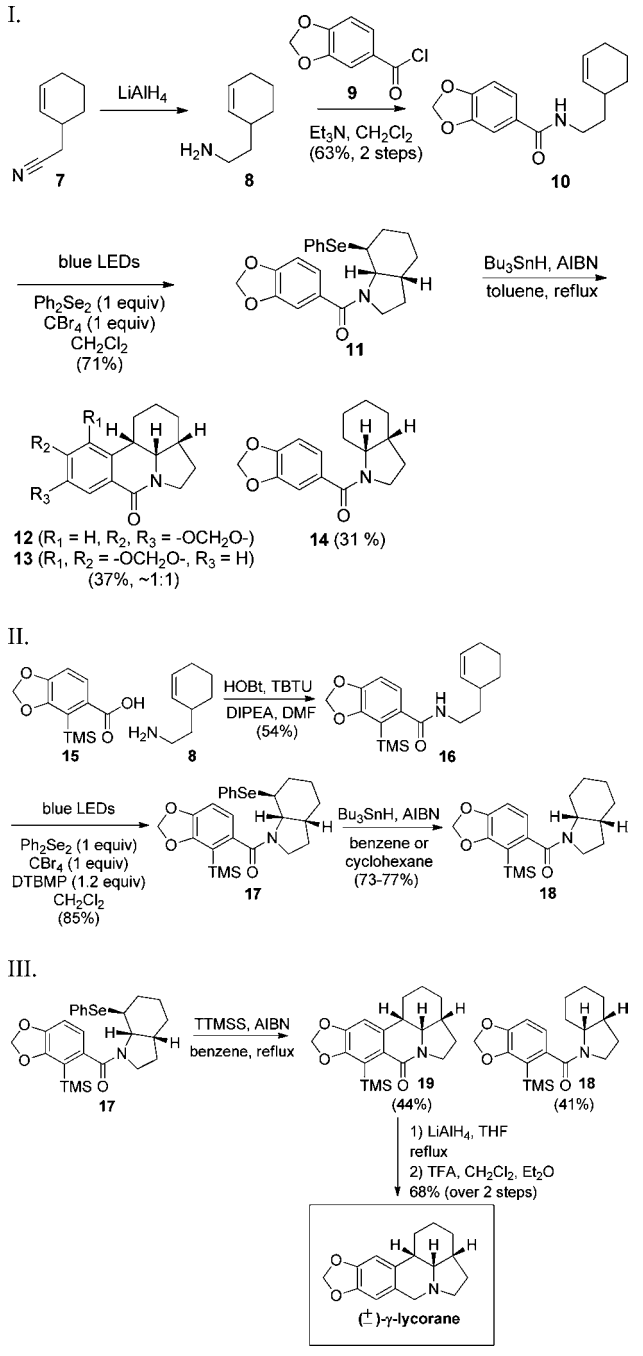
(18) For recent syntheses of γ-lycorane, see: (a) Huntley, R. J.; Funk, R. L. *Tetrahedron Lett.* **2011**, *52*, 6671–6674. (b) El Bialy, S. A. A. *Nat. Prod. Res.* **2008**, *22*, 1176–1188. (c) Chapsal, B. D.; Ojima, I. *Org. Lett.* **2006**, *8*, 1395–1398. (d) Fujioka, H.; Kenichi, M.; Ohba, Y.; Hirose, H.; Kita, Y. *Chem. Commun.* **2006**, 832–834. (e) Gao, S.; Tu, Y. Q.; Song, Z.; Wang, A.; Fan, X.; Jiang, Y. *J. Org. Chem.* **2005**, *70*, 6523–6525.
(19) Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 5039–5042.

Scheme 2. Synthesis of (±)-γ-Lycorane



Visible-light-promoted selenocyclization worked best in CH_2Cl_2 and afforded a 71% yield of perhydroindole **11**, the stereochemistry of which was confirmed with 2D NMR (see Supporting Information). Formation of the γ-lycorane skeleton proceeded via tin-promoted radical cyclization to produce a 37% yield of an inseparable ~1:1 mixture of desired **12** and undesired constitutional isomer **13** in addition to uncyclized **14**. Zard and co-workers have observed a similar effect in an alternative synthesis of (±)-γ-lycorane.[20]

To circumvent this selectivity problem (Scheme 2, Part II), we synthesized blocked substrate **16** from the requisite carboxylic acid **15**[21] and amine **8** in 54% yield. Selenocyclization of **16** in the absence of base was successful; however, the generation of HBr resulted in protiodesilylation and none of the desired TMS-protected product **17**. Buffering with the base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), on the other hand, resulted in the generation of **17** (85%). Attempted tin-promoted cyclization of **17** (Bu_3SnH) resulted in hydrogen abstraction product **18** (73−77%). Recognizing that Bu_3SnH is too reactive as a hydrogen donor, we turned to the less reactive tris(trimethylsilyl)silane (TTMSS, Scheme 2, Part III). Refluxing a solution of TTMSS, AIBN, and selenide **17** in benzene resulted in a 44% yield of the desired cyclized product **19** along with 41% of uncyclized product **18** (the formation of which we were never able to suppress). Importantly, **13** was never observed in product mixtures of **18**/**19**. $LiAlH_4$ reduction of amide **19** preceded TFA-promoted protiodesilylation to furnish (±)-γ-lycorane in 68% (two steps).

In summary, we have developed a mild method for seleno- and tellurofunctionalization of alkenes via the visible-light-promoted *in situ* generation of chalcogen electrophiles. These transformations are marked by high yields and ease of performance (reactions proceed at room temperature, and an inert atmosphere is not necessary). We have performed the seleno- and tellurofunctionalization of a variety of substrates, demonstrating that inter- and intramolecular processes are possible. The mechanism of these reactions is still under investigation, and the utility of this method has been demonstrated in a short synthesis of the Amaryllidaceae alkaloid (±)-γ-lycorane.

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Supporting Information Available. Experimental procedures and characterization for all intermediates and products, 1D and 2D NMR spectra, and X-ray crystal structures for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.