PhSeSiR₃-Catalyzed Group Transfer Radical Reactions

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A novel design for initiating radical-based chemistry in a catalytic fashion is described. The design of the concept is based on the phenylselenyl group transfer reaction from alkyl phenyl selenides by utilizing PhSeSiR₃ (1) as a catalytic reagent. The reaction is initiated by the homolytic cleavage of $C\equiv Se$ bond of an alkyl phenyl selenide by the in situ generated alkylsilyl radical ($R_3Si^+$), obtained by the mesolysis of PhSeSiR₃⁺ (1⁺). The oxidative dimerization of counteranion PhSe⁻ to PhSePh functions as radical terminator. The generation of 1⁺ is achieved by the photoinduced electron transfer (PET) promoted reductive activation of 1 through a photosystem comprising of a visible-light (410 nm)-absorbing electron rich DMA as an electron donor and ascorbic acid as a co-oxidant (Figure 1). The optimum molar ratio between the catalyst 1 and alkyl phenyl selenides for successful reaction is established to be 1:10. The generality of the concept is demonstrated by carrying out variety of radical reactions such as cyclization (10, 15–18), intermolecular addition (25), and tandem annulations (32).

Introduction

The use of tin-based reagents in free radical chemistry has dominated the scene ever since the original discovery of the radical generation by organotin hydrides (X₃SnH);¹ this dominance has been rightly referred to, recently, as “Tyrrany of Tin,”² despite their drawbacks such as cost, instability, toxicity,³ loss of valuable functionality due to the termination of radical sequence by irreversible H- abstraction,⁴ and the difficulty encountered in removing the tin byproducts from the residue⁵ whose disposal poses a hazardous problem. Although partial solution to some of these approaches invariably requires stoichiometric use of the reagents. Since there is growing demand to reduce the amount of toxic wastes and byproducts arising out of chemical reactions,¹⁰ increasing emphasis is laid on the invention and development of a catalytic and environmentally compatible strategy for initiating radical-based chemistry owing to its ever increasing popularity among synthetic chemists. Significant progress has also been made, recently, toward developing newer methodologies for initiating radical-based reactions in catalytic manner, utilizing either tin hydride reagents catalytically¹¹ or its in situ generation¹² or use of titanocene-catalyzed reductive ring opening of an epoxide;¹³ however, considering the importance of radical reactions in organic synthesis, introduction of another catalytic strategy could be a welcome addition in the repertoire of organic chemists.

We have reported¹⁴ an efficient strategy for the generation of phenyl selenide anion (PhSe⁻) and alkylsilyl radical ($R_3Si^+$) by the mesolysis¹⁵ of PhSeSiR₃⁺, produced by the visible-light (410 nm)-initiated photoinduced electron transfer (PET) activation of PhSeSiR₃ (R = tert-butylidiphenyl) through the photosystem as shown in Figure 1. The significantly higher rate constant (9.6 × 10⁷ M⁻¹ s⁻¹)⁶ for the reaction of $R_3Si^+$ with alkyl phenyl selenides and fast oxidative dimerization of PhSe⁻ to PhSePh, an excellent radical scavenger¹⁶ (the rate

⁸ (a) Curran, D. P.; Eichenberger E.; Collins, M.; Roepel, M. G.; Thoma, G. J. Am. Chem. Soc. 1994, 116, 4279. (b) For leading references, see: reference 40a and the references therein.
⁹ For leading references, see: reference 2 and the references therein.

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constant for the Si2 attack of 5-hexenyl radical upon PhSeSePh is calculated to be $1.2 \times 10^7 \text{M}^{-1} \text{s}^{-1}$,17 led us to envision that a catalytic strategy for phenylselenyl group transfer radical-based reactions might be possible to effect from a precursor of type 2 through a cycle as shown in Figure 2. Additional advantage of this strategy was perceived by the stability of the precursors as well as products and the various avenues available for the transformation of the products. The success of our effort is delineated in this article.

**Results and Discussion**

Design, Optimization and Generalization of the Concept. To introduce a concept of catalytic group transfer radical reaction in organic synthesis, a design as depicted in Figure 2 was visualized. Initially, we decided to investigate the phenylselenyl group transfer radical cyclization reaction of 10, prepared in 80% yield by the reaction of PhSeSeBr (7) with ethyl vinyl ether (6) in the presence of allyl alcohol (9).18 To ensure that the PET activation of a mixture containing 1 and 10, utilizing the photosystem as shown in Figure 1, selectively generates $1^\cdot$, $\Delta G_{et}$ values for the formation of $1^\cdot$ (–181 kJ M$^{-1}$)14 as well as $10^\cdot$ (–80 kJ M$^{-1}$) were compared. The $\Delta G_{et}$ value for the formation of $10^\cdot$ was estimated through Weller equation19 employing the values of $E_{1/2}^{red}$ (DMA) as 0.98 eV,20 $E_{1/2}^{oxid}$ of 10 as –1.4 eV, estimated by cyclic voltammetry utilizing an identical experimental setup as described elsewhere21 and $E_0$ of DMA as 3.21 eV.21 Since the selectivity of the radical ion generation from a mixture of potential electron donors/acceptors depend on the magnitude of $\Delta G_{et}$ values associated with the electron-transfer processes,22,23 the large difference between the $\Delta G_{et}$ values for the formation of $1^\cdot$ vs $10^\cdot$ indicated that there will be selectivity in the formation of $1^\cdot$ if a mixture of 1 and 10 were activated. This study coupled with the known14 mesolytic characteristics of $1^\cdot$ (producing $R_3Si^\cdot$ and PhSe$^\cdot$) and significantly higher quantum yield of disappearance of 1 ($\phi_{dis} = 0.223$)24 in comparison to $\phi_{dis}$ for –C–Se– bonds ($\approx 0.054$)25 convinced us that PET activation of a mixture of 1 and 10 through the photosystem as shown in Figure 1 would initiate a radical reaction from 10 by chalcogen transfer to $R_3Si^\cdot$ while regenerating 1 in the process as shown in Figure 2. The reorganization of the radical followed by its termination by PhSeSePh, produced by the oxidative dimerization of PhSe$^\cdot$, would set off a catalytic cycle for the formation of 11 through the steps as shown in Figure 2. With this premise, we began our study first by establishing the catalytic role of 1 in the above reaction. Toward this endeavor, PET activation of 10 at different concentrations (0.18, 0.27, and 0.35 mmol) with a fixed concentration of 1 (0.018 mmol), DMA (0.11 mmol), and $H_2A$ (0.32 mmol) was studied by irradiating 50 mL solution of each in Pyrex test tubes at 410 nm (450-W Hanovia lamp, NH3–CuSO4 solution).26 Progress of the reaction was monitored by HPLC analysis. After 45 min of irradiation (consumption of 10, =55–60%), the solutions in the test tubes were analyzed by HPLC which showed negligible change in the concentration of 1 as well as DMA in the tube having 10 and 1 in 10:1 mole ratio. This study was not performed at higher consumption of

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10 to avoid competitive reaction by the product 11. In other test tubes, the consumption of 10 was not found linearly related with the concentration of 1, probably due to the interference of 10 with the light absorbance of DMA. Therefore, based on the above study, it may be suggested that the present catalytic group transfer radical reaction strategy can be best performed at 10:1 mole ratio of the substrate (10) to catalyst (1).

Preparative PET reaction by irradiating (410 nm, 450-W Hanovia lamp, CuSO₄: NH₃ filter) a mixture containing 10 (0.76 mmol), DMA (0.30 mmol), ascorbic acid (0.88 mmol), and 1 (0.08 mmol), followed by usual workup and column chromatographic purification of the residue, gave 11 in 75% yield (Scheme 1). Although, quantitative estimation of recovered DMA and 1 was not made after column chromatography, negligible change in their concentrations, after the photolysis was completed, was established by comparing the HPLC analysis of the photolyze before and after the irradiation. The accumulated concentration of PhSeSePh in the reaction mixture at a given time, also determined by HPLC analysis of the aliquots withdrawn at different intervals of time during photolysis, was found to be very small, indicating that the combined rates of generation and cyclization of 3-oxa-5-hexenyl radical of type 10 is possibly slower than the rate of oxidative dimerization of PhSe⁺ to PhSeSePh.

To provide some conclusive support to the mechanism for the catalytic cycle as proposed in Figure 2, the possibilities of other competing reaction pathways available to the radical intermediates must be eliminated. For example, the alkyl radical 4 could possibly terminate by chalcogen transfer either from PhSePh or from 2. However, based on the comparative rate constant values of chalcogen transfer from PhSePh (k = (2.6 ± 10⁷ M⁻¹s⁻¹) and alkyl selenide (k = (1.0 × 10⁷ M⁻¹s⁻¹) to an octyl radical, reported by Curran et al., and their conclusion that diselenide would usually be the preferred reagent for the termination of an alkyl radical in such cases, the involvement of the later possibility can easily be ignored. Furthermore, if 4 is presumed to be terminating by chalcogen transfer from 2, a radical chain reaction would have set in for the transformation of 10 → 11. However, our observation that the conversion of 10 → 11 is very much dependent on the irradiation time supports the termination of 4 by chalcogen transfer by PhSePh and not by alkyl-PhSe. The PhSe⁺, generated after the termination of cyclized alkyl radical derived from 10 by PhSePh, dimerizes efficiently (kₐ = (7.0 × 10⁹ Mᵢs⁻¹) to PhSeSePh as the slower rate of reaction of PhSe⁺ with an olefinic bond and its known reversibility rules out any other competing decay mode.

The possible decay of alkyl radical 4 as well as tert-butyldiphenylsilyl radical (RSi₃) by the reaction of molecular oxygen could also be ruled out on the following considerations. The reaction of an alkyl radical with molecular oxygen is diffusion-controlled (k = (4.9 ± 0.6 × 10⁹ M⁻¹s⁻¹) for cyclopentyl radical), and the rate-determining step is the termination of the resultant peroxy radical (ROO⁻) by hydrogen abstraction and not the reaction of alkyl radical with oxygen. Therefore, the reaction of 4 with oxygen, if it occurs at all, could be reversible, as there is no possibility of H-abstraction by the corresponding peroxy radical. Moreover, we were unable to detect any product related to the peroxy radical derived from 10. Since, no kinetic data, to the best of our knowledge, is available on the reaction of R₃Si with O₂ in the solution phase (the rate constant for the reaction of Me₃Si with O₂ is reported to be (1.0 × 10¹⁰ M⁻¹s⁻¹ in gas phase), no definite statement could be made about the rate constants for the reaction of tert-butyldiphenylsilyl radical with oxygen in comparison to the oxidative dimerization rate constant of PhSe⁺ to PhSeSePh. However, in a separate study, where we were attempting to study the selenosilylation of an enone through the route as shown in Scheme 2, tert-butyldiphenylsilyl anion (R₃SiOH, 14) was obtained as the major product. The absence of 14 during the transformation of 10 → 11 suggests that the rate of chalcogenide transfer from alkyl-PhSe to R₃Si could be much higher than the reaction rate of R₃Si with molecular oxygen.

To compare the efficiency of this methodology over the one earlier reported by us by the direct PET activation of C-Se bond compounds, a control experiment was performed in a similar manner as described above but without having 1 in the reaction mixture. The comparative results indicated that, within the constant period of irradiation, the efficiency for the formation of 11 in the tube containing 1 was at least 4–5 times higher than the one without 1. This observation was expected due to the higher quantum efficiency of Se⁻Si⁻ bond dissociation from its corresponding radical anion (1⁻: φDiss = 0.223) in comparison to φDiss of C-Se⁻ bonds (≈0.054) and high rate constant of C-Se⁻ bond dissociation by R₃Si⁻ (9.6 × 10⁶ M⁻¹s⁻¹)₁b.

To establish the generality of the catalytic phenylsele- nyl group transfer radical cyclization reactions, a number of substrates (15–18) were studied, and the results are given in Table 1. The starting substrates (15–

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(28) Although, the rate constant for the oxidative dimerization of PhSe⁺ to PhSeSePh is not known, it is understood to be much higher than the oxidative dimerization of PhSeH. Encyclopedia of Reagents in Organic Synthesis; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 1, p 270.


(35) Pandey, G.; Rao, K. V. N. Unpublished result.
The spectacular success of the catalytic phenylselenyl group transfer radical cyclization reaction of 10 through the cycle, as shown in Figure 2, encouraged us to evaluate further the scope of this strategy for other contemporary radical reactions such as intermolecular additions and tandem annihilations. Intermolecular radical additions, though, are powerful tools in preparative organic chemistry, have difficulty in their execution by classical radical-based methodology due to competing bimolecular side reactions. Moreover, with stannous-based reactions the difficulty lies, apart from being ecologically noncompatible, in preventing premature H-atom transfer to the radical before it adds to the olefin. The other alternative approaches known in this context also lack flexibility in the choice of radical precursors. Therefore, it occurred to us that application of our methodology, through the sequences as shown in Figure 3, could provide an attractive route in catalytic manner for the group transfer intermolecular radical addition reaction where bimolecular radical reactions would be diminished due to fast termination of the adduct radical by phenylselenyl group transfer (k = 3 x 10^7 M^-1 s^-1 for secondary alkyl radicals). Toward this endeavor, we studied the addition of PhSeCH2COOEt (24) onto the 4-tert-butyl(dimethyl)silyloxy-1-decene (23). Considering the favorable electron pairing (electron-poor radical/electron-rich acceptor) PET reaction of a mixture containing 1 (0.18 mmol), 24 (1.85 mmol), 23 (1.85 mmol), DMA (0.63 mmol), and ascorbic acid (1.57 mmol) followed by workup and purification gave 25 as a yellow oil in 61% yield (Figure 3). Product 25 was characterized by ^1H NMR, ^13C NMR, and mass spectral data.

The exo-mode cyclization property of 5-hexenyl radicals have been widely utilized for the construction of five-membered carbocyclic rings. Curran et al. have also reported in situ generation and iodine atom transfer cyclization of 5-hexenyl radicals via addition/cyclization sequence (annulation) from 26 to a variety of simple olefins (28) to construct five-membered ring systems (Scheme 3). However, construction of six-membered carbocyclic ring systems, also widely distributed in numerous biologically active molecules, by endo-mode radical cyclizations has been known to be difficult.

The presence of silicon atom α, as well as β to a carbon-centered radical is known to reverse the regioselectivity of radical cyclizations (favoring the endo-mode) due to

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**Table 1. Phenylselenyl Group Transfer Radical Reaction**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield(%)</th>
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<tr>
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<td>21</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td>22</td>
</tr>
</tbody>
</table>

1. See Supporting Information for the preparation and characterizations of 17 and 18. Characterized by ^1H NMR, ^13C NMR, and mass spectral analyses. Isolated yield, unoptimized.

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**Figure 3. Catalytic intermolecular phenylselenyl group addition.**

**Scheme 3. Iodine Atom Transfer Strategy for the Construction of Five-Membered Rings.**

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Irradiations were performed in a specially designed double-walled photoreactor. The photoreactor consisted of three chambers. The first and outermost chamber contained irradiation solution while the second one was charged with CuSO₄·5H₂O:NH₃ filter solution. This filter solution allowed only 410 nm wavelength light to pass through.⁴⁶ A 450-W Hanovia medium-pressure mercury vapor lamp was used as light source that was housed in a water-circulated double-jacketed chamber imbedded into the second chamber, maintaining a 1 cm path length of the filter solution. The whole photoreactor was made of Pyrex glass.

**Evaluation of Catalytic Property of 1.** A 200 mL stock solution in acetonitrile containing 1 (0.07 mmol), DMA (0.42 mmol), and ascorbic acid (0.31 mmol) was prepared. Fifty milliliter amounts of this solution were distributed into three test tubes made up of Pyrex glass, and 0.05 g (0.176 mmol), 0.075 g (0.265 mmol), and 0.1 g (0.35 mmol) of 10 were introduced into each test tube resulting in mole ratios of 10 with respect to 1 as 10:1, 15:1, and 20:1, respectively. One milliliter each of this solution was analyzed before irradiation by HPLC after adding 0.5 mL of solution of Ph₃As (0.05 M) as an internal standard, and the area ratios of 10:Ph₃As and 1:Ph₃As were recorded. These tubes were irradiated externally at 410 nm wavelength light coming out of a 450-W Hanovia lamp after passing through a CuSO₄:NH₃ filter solution. Aliquots were analyzed time to time by HPLC in the same manner as described above, and the area ratios were compared. After 45 min, the irradiation was discontinued. The HPLC analysis of the test tube containing 10 and 1 in 10:1 mole ratio (first tube) indicated negligible change in the concentration of 1. Formation of 11 as the only product was noticed by HPLC analysis. The other two tubes showed no correlation between the conversion of 10 and the concentration of 11.

**Preparative PET Cyclization of 10.** A dilute solution of CH₂CN (500 mL) containing a mixture of 1 (0.07 g, 0.17 mmol), 10 (0.5 g, 1.74 mmol), DMA (0.15 g, 0.63 mmol), and ascorbic acid (0.28 g, 1.62 mmol) was irradiated in the special photoreactor (as described in the general Experimental Section) with a 450-W Hanovia medium-pressure mercury lamp at room temperature without removing dissolved oxygen from the solution. The progress of the reaction was monitored by HPLC. When substantial consumption of 10 was noticed, the irradiation was discontinued. Solvent was removed under vacuum and the crude photolyzate was purified by silica gel column chromatography to give a yellow oily product 11 (0.37 g, 75% yield).

**11.** H NMR (200 MHz, CDCl₃) δ 1.15−1.30 (3H, 3H), 1.60−1.80 (1H, 2H), 2.15−2.60 (2H, 2H), 2.90−3.17 (2H, 2H), 3.30−3.50 (3H, 3H), 3.57−3.80 (2H, 2H), 3.95−4.10 (1H, 1H), 5.10−5.17 (1H, 1H), 7.20−7.30 (3H, 3H), 7.45−7.55 (2H, 2H); ¹³C NMR (50 MHz, CDCl₃) δ 123.8, 123.8, 129.9, 129.9, 127.6, 126.9, 104.0, 103.8, 72.0, 63.0, 67.1, 39.9, 39.6, 38.6, 37.9, 32.5, 31.5, 15.4, 15.3; MS m/e (relative intensity) 286 (M⁺, 28), 250 (15), 157 (23), 91 (42), 83 (100).

Identical irradiation procedures were adopted for the PET activation of 15−18, 23, and 29, and the spectral characterization of products 19−22, 25 and 32 are given as follows:

**19.** yield: 77%; H NMR (200 MHz, CDCl₃) δ 1.45−1.90 (6H, 6H), 2.00−2.20 (1H, 1H), 2.55−2.75 (3H, 3H), 2.85−3.15 (2H, 2H), 3.30−3.50 (3H, 3H), 3.95 (d, J = 7.8, 13.5 Hz, 1H), 4.45−4.60 (1H, 1H), 7.20−7.30 (3H, 3H), 7.45−7.55 (2H, 2H); ¹³C NMR (50 MHz, CDCl₃) δ 123.9, 123.6, 130.3, 129.1, 129.0, 126.9, 126.8, 86.2, 85.1, 73.3, 72.2, 50.1, 48.1, 47.1, 43.4, 34.4, 34.0, 33.0, 30.5, 26.4, 25.9, 25.2, 24.0; MS m/e (relative intensity) 282 (M⁺, 10), 157 (15), 124 (17), 95 (78), 67 (100).

**20.** yield: 82%; H NMR (200 MHz, CDCl₃) δ 1.35−1.85 (6H, 6H), 2.00−2.15 (1H, 1H), 2.50−2.75 (3H, 3H), 2.80−3.05 (2H, 2H), 3.65−3.85 (3H, 3H), 4.05 (s, J = 7.1 Hz, 1H), 5.25 (s, J =
3.7 Hz, 1H), 7.20–7.35 (m, 3H), 7.45–7.60 (m, 2H); 13C NMR (50 MHz, CDCl3) δ 133.1, 129.5, 129.0, 127.2, 101.8, 70.1, 61.0, 41.2, 37.4, 25.8, 22.9, 19.2; MS m/e (relative intensity) 298 (M+, 6), 197 (20), 157 (15), 141 (50), 116 (42).

21: yield: 73%; 1H NMR (200 MHz, CDCl3) δ 1.25 (t, J = 7.3 Hz, 3H), 1.35–1.55 (m, 1H), 1.85–2.05 (m, 2H), 2.45–2.60 (m, 1H), 2.95 (d, J = 8.2 Hz, 2H), 4.20 (q, J = 7.3 Hz, 4H), 7.20–7.30 (m, 3H); 13C NMR (50 MHz, CDCl3) δ 172.6, 133.0, 129.3, 127.1, 61.6, 60.4, 40.9, 40.2, 33.5, 32.6, 14.3; MS m/e (relative intensity) 384 (M+ 20), 227 (52), 119 (27), 153 (100).

22: yield: 64%; 1H NMR (200 MHz, CDCl3) δ 1.50–1.65 (m, 1H), 1.90–2.05 (m, 1H), 2.21–2.37 (m, 1H), 2.60–2.85 (m, 2H), 2.95–3.05 (m, 1H), 3.15–3.55 (m, 3H), 7.20–7.30 (m, 3H), 7.35–7.65 (m, 5H), 7.70–7.85 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 133.0, 132.9, 130.4, 128.9, 128.9, 129.4, 127.2, 53.2, 47.3, 39.1, 31.6, 30.6, 29.6; MS m/e (relative intensity) 381 (M+, 4), 223 (100), 209 (13), 141 (25); HRMS calculated for C17H19NO2SSe 381.030171, found 381.032655.

23: yield: 65%; 1H NMR (200 MHz, CDCl3) δ 0.00–0.05 (s, 9H), 0.30–0.70 (m, 2H), 1.25 (t, J = 7.3 Hz, 3H), 1.87–2.05 (m, 1H), 2.10–2.50 (m, 5H), 2.65–2.83 (m, 1H), 2.95–3.05 (m, 1H), 4.2 (q, J = 7.3 Hz, 4H), 7.20–7.35 (m, 3H), 7.45–7.55 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 172.6, 133.0, 132.9, 130.4, 128.9, 126.7, 61.3, 58.9, 43.9, 40.6, 38.8, 38.7, 29.1, 16.2, 13.9, −0.1; MS m/e (relative intensity) 470 (M+, 100), 455 (34), 425 (16), 397 (16), 337 (4), 313 (57), 239 (20), 157 (10); HRMS for C22H34O4SiSe calculated 470.139159, found 470.137444.

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Supporting Information Available: Preparation and characterization details of the compounds 17, 18, 24, and 29 and 1H NMR and 13C NMR spectra of compounds 11, 19–22, 25, 29, and 32. This material is available free of charge via the Internet at http://pubs.acs.org.