

## Ligand coupling based on heteroatom chemistry

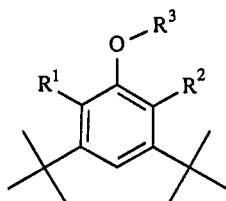
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### Abstract

Examples of ligand coupling that lead to very highly hindered compounds are discussed. A reaction for the oxidation of phenols to phenylselenoaminoquinones has been studied. Comparative reactivity data show the amazing power of the phenylselenoaminating process to make very hindered compounds. Mechanistically it is classified as ligand coupling based on  $\text{Se}^{\text{IV}}$ .

The concept of ligand coupling has been reviewed in depth.<sup>1-3</sup> One of the most interesting aspects of this mechanism is that very hindered compounds can be synthesized under mild conditions with excellent yields. For example 3,5-di-*tert*-butylphenol **1** can be arylated to give the 2,6-diphenyl derivative **2** (77%) by  $\text{Bi}^{\text{V}}$  reagents.<sup>2</sup> An even more striking example is provided<sup>4</sup> by some recent  $\text{Pb}^{\text{IV}}$  chemistry. Pinhey<sup>3</sup> had shown that 2,4,6-trimethoxyphenyllead triacetate is an arylating agent for phenols. We decided to study the limits of hindrance for ligand coupling by reacting **1** with this  $\text{Pb}^{\text{IV}}$  reagent. At room temperature over 24 hrs in  $\text{CHCl}_3$ -pyridine the diarylated derivative (87%) **3** was formed, as well the monoarylated analogue (10%). Acetylation of phenol **3**

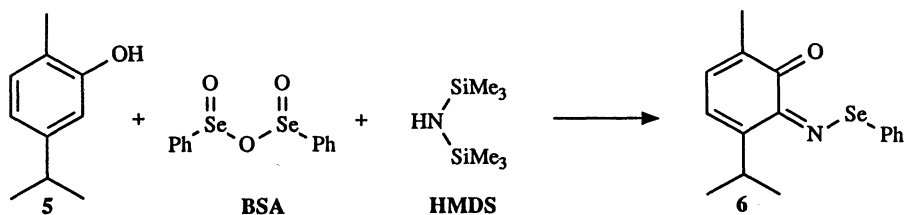


- 1  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$
- 2  $\text{R}^1 = \text{R}^2 = \text{Ph}, \text{R}^3 = \text{H}$
- 3  $\text{R}^1 = \text{R}^2 = 2,4,6\text{-(MeO)}_3\text{C}_6\text{H}_2, \text{R}^3 = \text{H}$
- 4  $\text{R}^1 = \text{R}^2 = 2,4,6\text{-(MeO)}_3\text{C}_6\text{H}_2, \text{R}^3 = \text{Ac}$

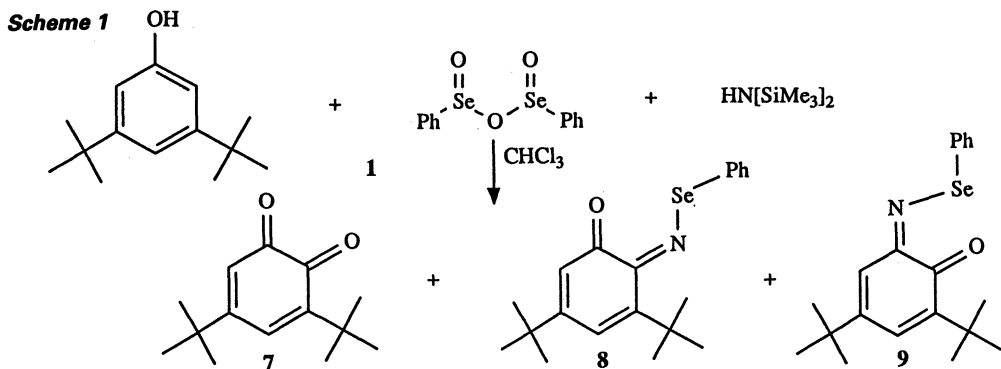
proved to be much more difficult. Heating with pyridine-acetic anhydride under reflux (140 °C) for 24 hrs finally gave the desired monoacetate **4** (94%), whose structure was confirmed by physical methods including X-ray crystallography. Other examples of  $\text{Pb}^{\text{IV}}$  ligand coupling in the synthesis of natural products (in the collaboration with Prof. D. M. X. Donnelly and Dr. J.-P. Finet) have recently been reported.<sup>5</sup>

Some years ago we introduced the reagent benzeneseleninic anhydride (BSA) for the *ortho*-hydroxylation of phenols<sup>6</sup> and for the synthesis of *ortho*-quinones<sup>7</sup> from phenols. The mechanism of these reactions was proposed to involve the rearrangement of a phenolic phenylseleninite. Some spectacular applications of the reagent have been made.<sup>8</sup>

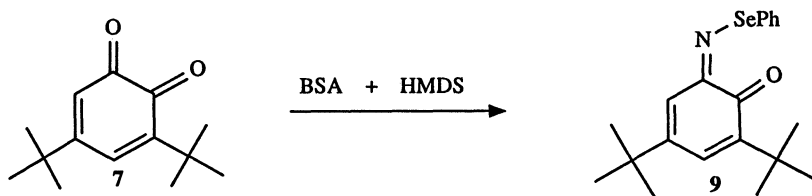
During the course of these investigations, an unexpected new reaction was discovered when the reagent (BSA) was added to hexamethyldisilazane (HMDS) and a phenol. The major product of this reaction was an *ortho*-phenylselenimine<sup>9</sup> as in the reaction **5** → **6**. These deeply red colored phenylselenium derivatives were a new class of compounds. We have always been intrigued by the nature of the reagent responsible for the reaction and the mechanism involved. In the sequel we present an in depth study of this subject which will shortly be submitted for publication.



**Discussion:** We chose 3,5-di-*tert*-butylphenol **1** as the substrate because it is symmetrical and also possesses relatively hindered *ortho* positions which would be a good measure for the efficiency of the reaction for *ortho* oxidation. The reaction gave up to 91% conversion of the phenol.<sup>10</sup> The product mixture revealed (as shown in Scheme 1), the presence of three products **7** - **9** in different



ratios depending upon the reaction conditions employed. The *ortho* quinone **7** was found to be in much greater amounts when phenol and BSA were mixed first and HMDS was added after 30 minutes of reaction time. The iminoquinone **8** formed in largest amounts when BSA and HMDS were mixed together first and allowed to react for about 30 minutes and phenol was added subsequently. The isomeric selenoimine **9** formed only in small amounts and was completely absent when the phenol was added at a much later stage (after 4 hours of reaction time with 12 equivalents of HMDS and 1 equivalent of BSA). We also carried out the reaction of 3,5-di-*tert*-butyl-1,2-quinone **10** with BSA and HMDS and found the isomeric selenoimine **9** as the major product.



The selenoimine **8** did not form indicating that its formation from the corresponding phenol **1** does not go through quinone formation. The reaction of BSA and HMDS was carried out in the absence phenol and found to produce quantitative amounts of diphenyldiselenide based on the amount of BSA used. The amount of gas evolved was also measured with respect to time and about 98% of the calculated amount of gas (nitrogen) was generated at the end of 31 hrs when 2.08 equivalents of HMDS was employed. On a formal basis this reaction can be written as in equations (1) and (2).

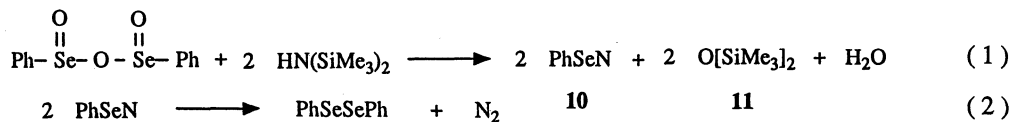


Table 1 Chemical shift values<sup>a</sup> of various observed species *via* NMR

| R               | Se-77 $\delta$ values <sup>b</sup> (and Si-29 $\delta$ values <sup>c</sup> ) |                |                |        |                      |                                     |
|-----------------|--|----------------|----------------|--------|----------------------|-------------------------------------|
|                 | [RSe(O)] <sub>2</sub> O  | Intermediate A | Intermediate B | RSeSeR | Me <sub>3</sub> SiOH | [Me <sub>3</sub> Si] <sub>2</sub> O |
| Ph              | 1241   | 1227 (26.3)    | 953            | 475    | (16.0)               | (7.1)                               |
| <sup>i</sup> Pr | 1314   | 1298 (26.0)    | 990            | 413    | (16.0)               | (7.1)                               |
| Me              | 1296   | 1270 (25.8)    | 910            | 279    | (16.0)               | (7.1)                               |

a = In a typical experiment 1 eq. of [RSe(O)]<sub>2</sub>O was treated with 6 eq. of HN(SiMe<sub>3</sub>)<sub>2</sub> [ $\delta$  Si-29 2.4] in CDCl<sub>3</sub>

b = Diphenyldiselenide was used as an external reference [ $\delta$  475ppm]

c = TMS was used as an internal reference [ $\delta$  0.00 ppm]

In this case the species responsible for phenylselenoamination of phenols would be phenylselenoazyl (PhSeN), **10**. We studied the reaction using various spectroscopic techniques. Proton and <sup>13</sup>C NMR studies were not informative. Selenium-77 NMR spectra on the other hand showed the presence of two observable intermediates A and B, (Table 1) during the course of the reaction which eventually collapsed to give the product diphenyldiselenide. Silicon-29 NMR analysis (Table 1) also showed two transient species which disappeared over a period of time to give hexamethyldisiloxane, **11**. All attempts to isolate any other identifiable species (besides the diselenide and the siloxane) from the reaction mixture failed in our hands and hence it seemed only logical to trap the reactive intermediate **10** with a suitable chemical trapping agent. We attempted cycloaddition reactions with various dienes (tetraphenylcyclopentadienone, isoprene, etc. 4+2) and dipoles (phenylazide, dichloromesitylnitrile-*N*-oxide, diphenylnitron, etc. 3+2) to no avail. The most promising case was that of phenyl azide where a red color resulted upon addition of PhN<sub>3</sub> to a stirred mixture of BSA and HMDS and an additional Se-77 signal appeared in the region characteristic of tetravalent selenium bonded to two nitrogens but we could not isolate what was believed to be the adduct.

Infrared and UV/VIS absorption spectra of the reaction were also not helpful.<sup>11</sup> We measured (nitrobenzyl alcohol matrix assisted) FAB-mass spectra of the reaction mixture at a point where there was a maximum concentration of the reactive intermediates and what we found were several low intensity signals at much higher *m/e* values than any of the proposed species.<sup>12</sup> This suggested the possibility of an associative nature of the phenylselenoazyl and there appeared to be successive loss of a definite mass unit in the fragmentation patterns. When matrix assisted laser desorption (TOF) mass spectroscopy was attempted we saw similar results repetitively.

It was interesting to note that the first intermediate containing Se appeared to be similar (comparable chemical shifts, see Table 1) to the starting material BSA in terms of the stereoelectronic environment around selenium.<sup>13</sup> Lowering the temperature of the reaction mixture to -20 °C slowed the rate of the reaction but no additional signals were observed. Upon addition of the phenol the second intermediate B ( $\delta$  <sup>77</sup>Se 953ppm) disappeared first followed by the signal for intermediate A at 1227ppm. This gave rise to stable signals of the products the iminoquinone **8** and the diselenide at 1064ppm and 475ppm respectively. We employed two other seleninic anhydrides in similar manners and observed identical results. The chemical shifts of both the transient species in all the cases were comparable, see table 1. This time however, <sup>1</sup>H (to a lesser extent) and <sup>13</sup>C (to a greater extent) spectral studies gave useful information. The <sup>13</sup>C spectra showed two types of

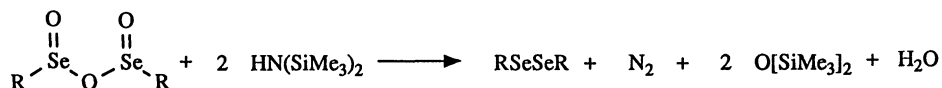
alkylselenyl groups emerge as transient species which eventually collapsed to give the corresponding diselenides. The rate of formation and disproportionation of both these entities were the same as those seen for the two intermediates observed *via* selenium-77 NMR investigations.

In all these studies both the observed intermediates appeared to be symmetrical entities even at low temperatures ( $-20\text{ }^{\circ}\text{C}$ ) *via* NMR. Hence we decided to probe further the nature of these species by employing a mixture of two different seleninic anhydrides in reaction with HMDS. The selenium-77 analysis now revealed twelve major signals (singlets) in the region of 900 to 1000 ppm, the range where intermediate B normally appeared, whereas, there were only two signals at their respective chemical shifts for the corresponding intermediates A and no other additional signals were observed. This was true for any combination of two seleninic anhydrides (of the three listed in the Table 1). At the end of the reaction three different diselenides were formed in equal amounts.<sup>14</sup> When a mixture of three seleninic anhydrides was employed there were a very large number of signals in the region of 900-1000 ppm and the exact number of signals could not be ascertained even at higher magnetic field strengths. The reaction mixture produced six different diselenides as predicted. The silicon-29 NMR studies showed no unusual behavior as two and three signals appeared at 26 ppm range in place of one when mixtures of two and three seleninic anhydrides were employed. No additional signals resulted (in silicon-29 NMR) in these mixing experiments. These data suggested that intermediate B, otherwise a symmetrical molecule, now showed the possibility of dissymmetry or various constitutional isomers. This can easily be explained if intermediate B is to form *via* a random associative cyclization/oligomerization of RSeN units. This would allow various structural isomers to coexist ( $R = R^1$  or  $R^2$ ) thereby rendering many signals in the Se-77 analysis.

Further evidence of this hypothesis came from the following isotopic enrichment studies. We prepared N-15 labelled (99% enrichment) hexamethyldisilazane<sup>15</sup> from  $\text{ClSiMe}_3$  and  $^{15}\text{NH}_3$ . When labelled HMDS was treated with BSA the signal at 953 ppm which normally appeared to be a symmetrical species (singlet) now showed three different kind of Se-N coupling patterns ( $s \rightarrow \text{ddd}$ , two  $^1J_{\text{Se-N}}$  97 Hz, 84 and one  $^3J_{\text{Se-N}}$  5 Hz). The signal for the first intermediate showed no change in its appearance indicating no Se-N bond. Similarly Si-29 spectra showed no Si-N coupling as the signal at 26 ppm remained unchanged. This was consistently true in the case of all the seleninic anhydrides. In the carbon spectra one set of signals of the intermediates showed no C-N coupling whereas the other set of peaks (of intermediate B) showed two different C-N couplings which was in support of the other observations. Adding N-15 HMDS to a mixture of two seleninic anhydrides however, further complicated the selenium-77 spectra as a very large number of closely related signals resulted in the region for intermediate B.<sup>16</sup> The Si-29 spectra on the other hand remained unchanged and showed the same two signals around 26 ppm as seen in the earlier mixing experiments. In the N-15 NMR studies the starting material HMDS ( $\delta$   $^{15}\text{N}$  29 ppm) showed distinct  $^1J_{\text{N-H}}$  (62 Hz) but as soon as the seleninic anhydride was added the signal became broad and lost the N-H coupling information. A new signal at 309 ppm grew with respect to time and slowly diminished after reaching a certain concentration level. The chemical shift of 309 ppm is characteristic of an environment for nitrogen as can be found in phosphazanes and phosphocines.<sup>17</sup> A low intensity signal appeared at -2 ppm as well and was identified to be that of  $^{15}\text{N}_2$  which remained constantly low in intensity and diminished upon purging the reaction mixture with argon.

The facts observed thus far are summarized below:

- 1) There is a quantitative reaction between a seleninic anhydride and hexamethyldisilazane:

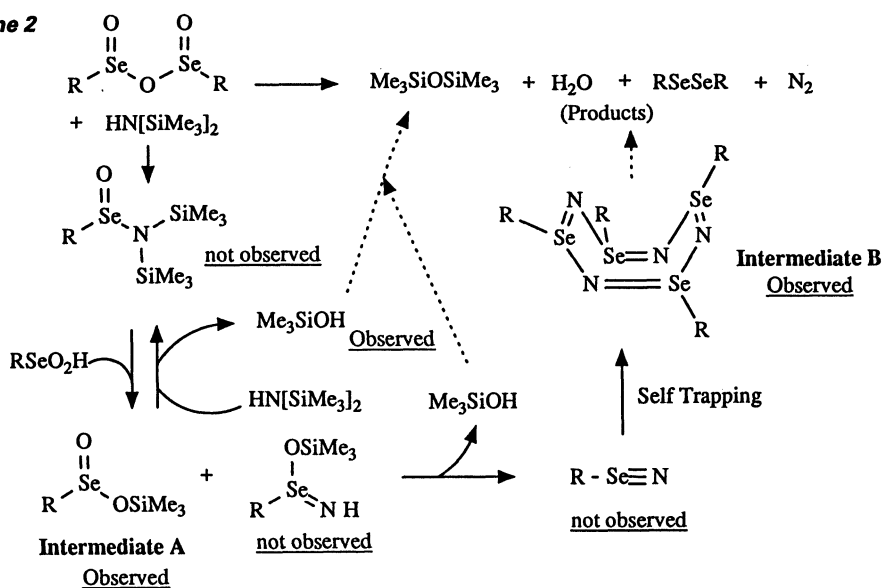


- 2) The nature of the R group has little or no effect on the nature of the reaction and the number of observed intermediates. All the three seleninic anhydrides employed gave comparable results.
- 3) There are two observable intermediates. The first intermediate A (which has comparable chemical shifts to the starting seleninic anhydride) has only one Se and one Si atom and no Si-N or Se-N couplings are observed. The first intermediate thus appeared to be a trimethylsilyl ester of the seleninic acid.<sup>18</sup>
- 4) The rate of appearance of intermediate B is dependent upon the relative ratios of BSA and HMDS used. The larger the amount of HMDS the faster the rate of formation of Intermediate B and faster the rate of disappearance of intermediate A.
- 5) Intermediate B is otherwise a symmetrical molecule with respect to selenium containing RSeN units. It also has more than one Se nucleus and the molecule shows many signals when mixtures of seleninic anhydrides are employed indicating many constitutional isomers.
- 6) A mixture of seleninic anhydrides reacts with HMDS to give a statistical distribution of the corresponding diselenides. (Two seleninic anhydrides give three and three seleninic anhydrides give six diselenides).
- 7) Intermediate B is primarily responsible for the *ortho* oxidation of phenols as it disappears first upon addition of the phenol. Any reactive intermediate for this process should provide a mechanism for 2 e<sup>-</sup> and 2 H<sup>+</sup> oxidation at the *ortho* position of the phenol before the final formation of the iminoquinone is complete.
- 8) In the molecular assembly of intermediate B three different selenium - nitrogen and two carbon - nitrogen bondings were observed and this suggested that a nonequilibrating alternate double/single bond moiety is possible. This fact and the total number of signals observed in the case of mixing experiments eliminates dimeric and trimeric associations of RSeN units.<sup>19</sup>
- 9) The N-15 NMR chemical shifts of the intermediate B indicate a similar environment for the N as in cyclotetraphosphazetetrane and phosphazanes.<sup>17</sup>

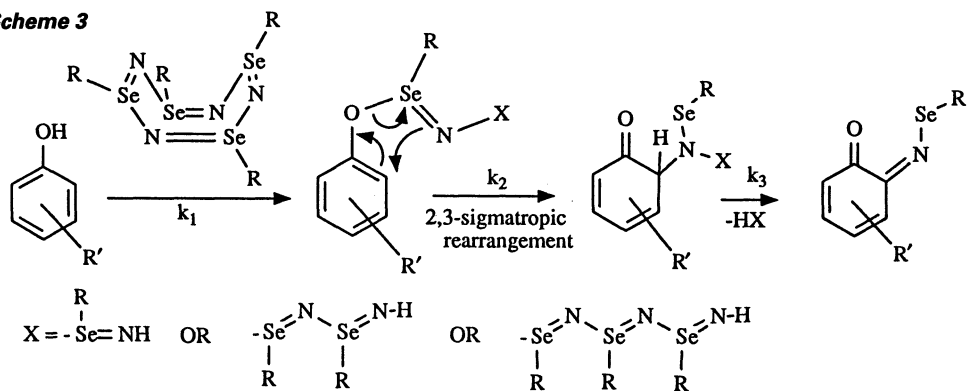
Based on the above findings we now propose a mechanism as depicted in Scheme 2. The participation of the reactive intermediates in the *ortho*-oxidation process of the phenol is illustrated in scheme 3. The moiety X in Scheme 3 could be (RSe=N)<sub>n</sub>RSe=NH [n = 0-2] and would act as a leaving group finally rendering RSeNH<sub>2</sub> which can participate in the formation of the isomeric iminoquinone **9** from **7**. These mechanistic pathways explain all the facts observed thus far.

Having at hand a better understanding of the reaction pathway and the fact that intermediate B shows remarkable potential for *ortho*-oxidation we postulated ligand coupling (scheme 3) as the operating mechanism. We attempted to observe additional entities during the oxidation reaction of the phenol but the reaction was too fast on the NMR time scale for anything to be observed in detectable amounts. We decided to further test the scope of this *ortho*-oxidation process and also establish the nature of mechanism by employing other substrates. When we subjected *p*-anisidine to the reaction mixture of BSA and HMDS in chloroform hoping for *ortho* amination of the anilines,

Scheme 2



Scheme 3



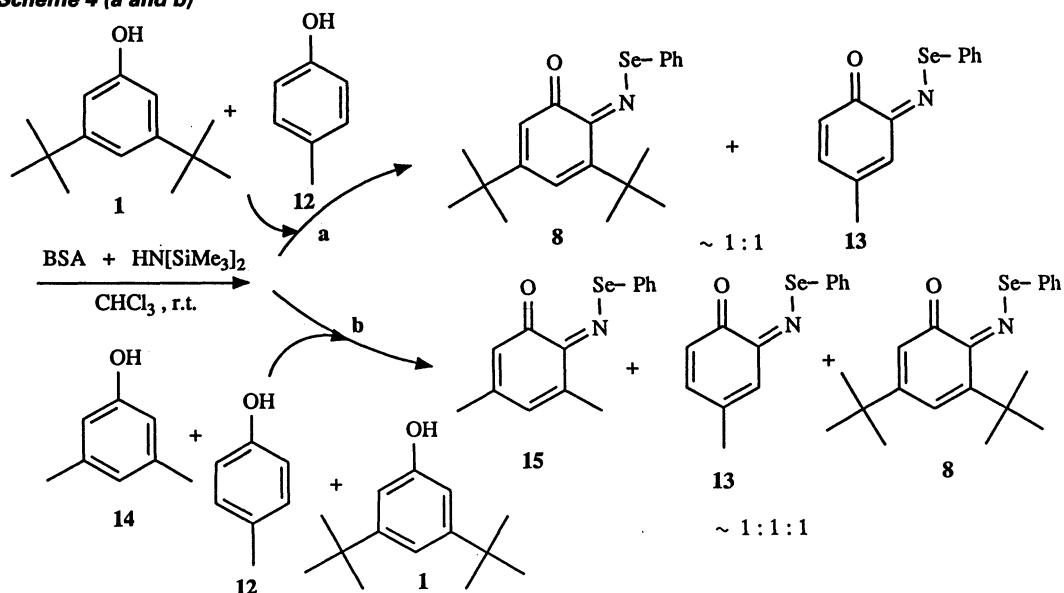
and we observed similar behavior. Deep red coloration took place immediately after the addition of *p*-anisidine just like in the case of various phenols, however, attempts at isolating the adduct failed in our hands. Since diselenides along with the hexamethyldisiloxane are continuously forming during the course of the reaction the product/intermediate separation was always troublesome.

Spectroscopically (Se-77 NMR) we did observe a signal at 764 ppm (which grew at the expense of the signal for the intermediate B) but the adduct was not very stable as it disintegrated into several signals. Various other anilines were tried and they all gave similar results. Electron rich anilines reacted faster than the electron poor aniline (*p*-NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>).

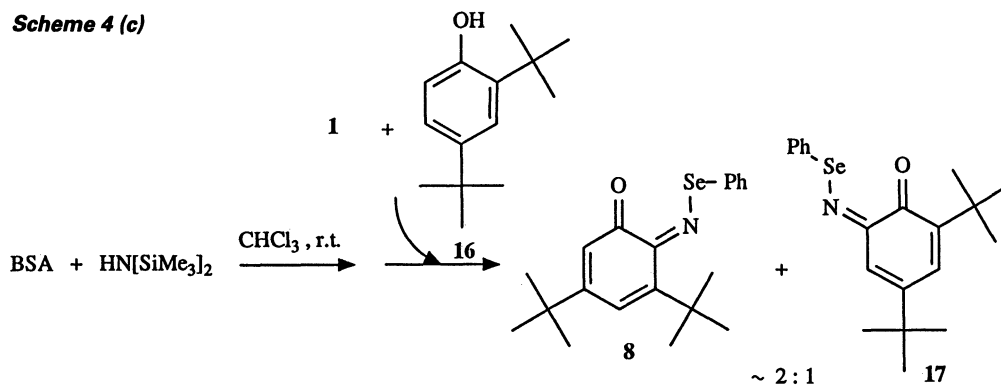
The strongest evidence for the ligand coupling at Se<sup>IV</sup> was obtained when we subjected equimolar mixtures of phenols *viz.* *p*-cresol **12** and 3,5-di-*tert*-butylphenol **1** (in 4 fold excess with respect to BSA) to the same reaction conditions. As shown in scheme 4a, equimolar amounts of the corresponding *ortho*-imino quinones **13** and **8** were obtained in 39% and 40% yields respectively. Similarly, an equimolar mixture of 3,5-di-*tert*-butylphenol **1**, *p*-cresol **12**, and 3,5-dimethylphenol **14**, (in 4 fold excess with respect to BSA) gave the corresponding iminoquinones in equal amounts (28%, 28%, and 26% yields respectively), as exemplified in Scheme 4b. The reaction did not show any steric dependence. In order to further establish the nature of the rate limiting step, we subjected a mixture of 2,4-di-*tert*-butylphenol **16** and 3,5-di-*tert*-butylphenol **1** in equimolar ratio and found

the corresponding iminoquinones **17** and **8** formed in the ratio of ~1:2, in 25% and 48% yields respectively, as illustrated in Scheme 4c. This was in agreement with the calculated values based on the number of *ortho* positions available with the starting phenols. This unequivocally proved that the rate limiting step is the formation of the *O*-seleninyl derivative ( $k_1$ ) and it does not exhibit any steric dependence. The subsequent 2,3-sigmatropic rearrangement ( $k_2$ , ligand coupling) step as well as the following elimination ( $k_3$ ) are too fast on NMR time scale even at  $-20\text{ }^\circ\text{C}$ , as no quaternary carbon centered intermediate was observed by  $^{13}\text{C}$  NMR. When 2,6-di-*tert*-butylphenol **18** was employed in the reaction with BSA and HMDS, the reaction proceeded much slower (by a factor of about 4-5)

Scheme 4 (a and b)

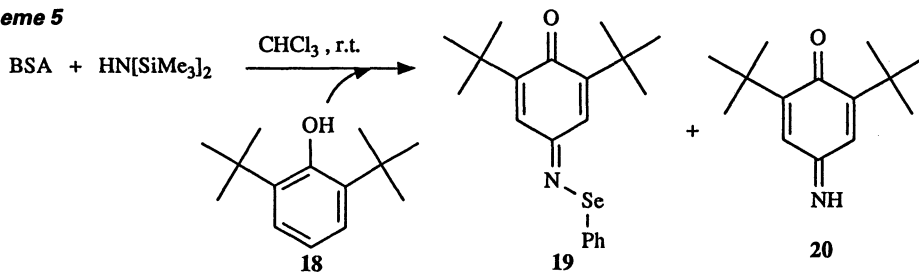


Scheme 4 (c)



compared to the 3,5-di-*tert*-butylphenol and the corresponding 4-phenylselenoaminoquinone **19** was obtained in about 40% yield as shown in scheme 5.

Scheme 5



The present article has summarized the recent work on the mechanistic problem and concluded that ligand coupling on  $\text{Se}^{\text{IV}}$  explains the facility with which such highly hindered compounds can be readily prepared.

#### Acknowledgements

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10. 4 Equivalents of phenol was treated with 1 equivalent of BSA and 6 equivalents of HMDS in  $\text{CHCl}_3$  at r.t. for 2.5 hrs. The reaction gave 91% conversion. When 1 equivalent of phenol was treated with 1 equivalent of BSA and 2 equivalents of HMDS then the iminoquinone formed in 65% yield.
11. The absorption spectra of the diselenides formed during the course of the reaction masked the absorbances of any other entity present in the reaction mixture.
12. The low intensity signals observed in various FAB-MS experiments of BSA and HMDS in  $\text{CHCl}_3$  which appeared at very high m/e values were at 705, 649, 507, 451.
13. Selenium-77 chemical shifts are known to have large variations and thereby are highly dependent on the nature of stereoelectronic environment around the Se and its oxidation state.
14. The relative ratios of all the diselenides formed at the end of the reaction were totally in agreement with the relative stoichiometries of the seleninic anhydrides employed.
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16. Highly diminished S/N ratio and the dynamic range problem made the determination of exact number of signals nearly impossible.
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18. We attempted to synthesize the trimethylsilylester of benzeneseleninic acid by independent route but were unsuccessful, however, we synthesized the triphenylsilylester of the benzeneseleninic acid ( $\text{PhSe(O)OSiPh}_3$ ). The Se-77 chemical shift of this derivative was 1296 ppm.
19. If random association of RSeN units was to produce a 4-membered ring then 4-different Se signals should arise given the possibility of two R groups. Similarly a 6-membered ring would exhibit six signals and an 8-membered ring should provide twelve signals provided additional conformational isomers do not exist.