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# PhSeBr mediated hydroxylative oxidative dearomatization of naphthols – an open air facile one-pot synthesis of ketols†

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A new methodology for oxidative-dearomatization of planar phenols is described. An economic, viable one-pot metal free protocol for direct conversion of naphthols to α-ketols is reported. Naphthols were found to undergo facile unprecedented oxidative dearomatization with regioselective hydroxylation with phenyl selenyl bromide in open air conditions. Quaternary stereocenters were developed along with formation of sterically demanding α- and γ-ketols with high yields. Functional group tolerance like esters is revealed. A thorough study of the stereoelectronic demands of the unusual oxy-selenium reactive intermediate involved in dearomatization of 1- and 2-naphthols is carried out. 4-Hydroxy cyclohexadieneone and cyclohexadieneone aryl ethers were generated from dialkyl-phenols under similar reaction conditions providing direct evidence of the mechanical postulate. The first instance of the phenoxy–selenium interaction leading to facile dearomatization of arenes is highlighted in this manuscript.

Controlled generation of well-functionalized three-dimensional structures from simple planar aromatics allows a fast access to solve molecular intricacy at higher levels. Dearomatization of abundant arenes is thus considered to be the shortest and most powerful approach towards this goal.[1]

In the recent years, there has been continued interest in accomplishing oxidative and alkylative dearomatization reactions *via* metal–arene complexation,[2] hypervalent iodine mediated oxidation[3] and reductive alkylation under Birch conditions[4] where a stoichiometric amount of metal reagent or oxidant, in general is required. Transition-metal catalyzed dearomatization[5] of aromatic compounds has also been observed to make significant progress in recent years. The hypervalent iodine compounds have been a keen point of sufficient attention due to their chemoselective oxidising properties and also being environmentally acceptable. There have been limited eye-catching reports on this reaction, Krohn reported a zirconium catalysed TBHP mediated oxidation of naphthols to such ketols.[6] Quideau and coworkers came up with an asymmetric version of this transformation employing *in situ* generated iodanes from chiral iodoarenes and *m*-CPBA as a co-catalyst.[7] Several asymmetric approaches have been developed using chiral iodine complexes,[8] interestingly metal carbonyls have also been extensively used in this transformation.[9] Fewer attempts on organocatalytic transformations have also been fairly accomplished.[10] A closer study on the natural product reports, upholds an impression that only phenyl iodobenzene diacetate (PIDA) has been effectively utilized as an effective dearomatization reagent in wide scale natural product syntheses.[11] Some catalytic processes are also attempted with moderate results and fewer substrate scope.[12] Hypervalent iodine complexes are synthesised under rigorous conditions in presence of drastic oxidising agents like sulphuric acid and potassium bromate. Again, the utmost significance of these complexes in dearomatisation reaction and drawbacks like not being generalizable, scalable, non-economic and creating metal-free environment associated with all such processes has put us an urge for exploring newer simplified pathways of this reaction. Undoubtedly, the chemist community has no generalised & judicious alternative to dearomatisation till now.

Parallely, during one of our endeavours towards natural products like lacinilene C(A), lacinilene D(B), and cyclosordurine D(C)[6] encompassing a α-ketol framework, it was surprisingly felt that scanty direct protocols are available for transformation of alkyl-naphthones to α-ketols[13] which certainly act as important precursors in modern organic synthesis (Fig. 1).

An oxidative dearomatization protocol employing diphenylseleninic anhydride acted as a key step in the total synthesis

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, spectral data for all compounds, including copies of $^{1}H$, $^{13}C$, NMR spectra. See DOI: 10.1039/c6ra00036c

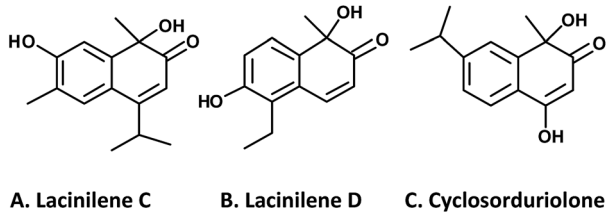



Fig. 1 Biologically active α-ketol natural products.

of lacinilene methyl ether (LCME).[14] Facile generation of α-ketols from planar alkyl napthols is a challenging task. Also scanty protocols have been reported in literature for the direct one-pot benzylic C–H activation of the α-H of a naphthoquinone to corresponding hydroxy, delivering such ketols. Cyclic diketone like 1,2-napthoquinones act as a versatile starting templates for numerous organic transformations, which makes this attempt an attractive one for the chemist community (Fig. 2).

An extensive literature survey fetched us with an important report from Barton *et al.*[15] where benzeneseleninic anhydride has been successfully employed in transforming phenol to *ortho*-hydroxy dieneones. Meyer's *et al.*[14] has also referred to this protocol in the synthesis of lacinilene methyl ether. Sir D. H. R. Barton's report of benzene seleninic anhydride being used as a useful protocol for regioselective *ortho*-hydroxylative dearomatization of phenols, though the yields were not satisfactory in most of the substrates. The report also conveys an important information on the mechanistic articulation where the author has pointed out that the oxidative dearomatization using benzeneseleninic anhydride may proceed in a variety of ways which seem indistinct. One of the plausible mechanisms involve a phenoxy–seleno reactive intermediate (A). In all cases diphenyl diselenide was found to be a major byproduct.[15] Selenium exhibiting both electrophilic and nucleophilic tendencies and associated inconsistencies in the mechanisms in oxidative dearomatization with selenium reagents prescribed till now acted as an addendum to study its application in these reactions. This manuscript was a lucrative source which led us to look into the selenium mediated dearomatization reaction with a new ideology.

(a) Zr catalysed hydroxylative dearomatisation of naphthols (previous work).[6]

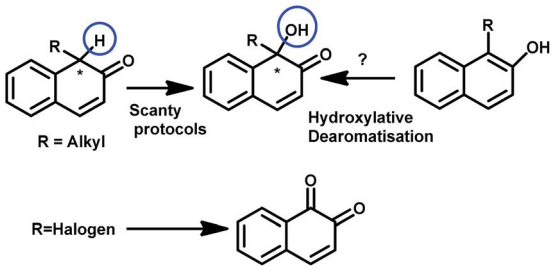
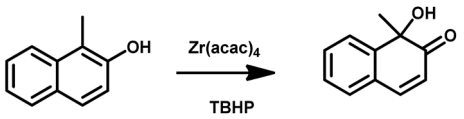
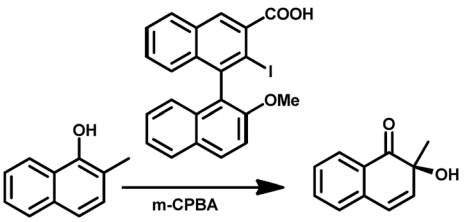


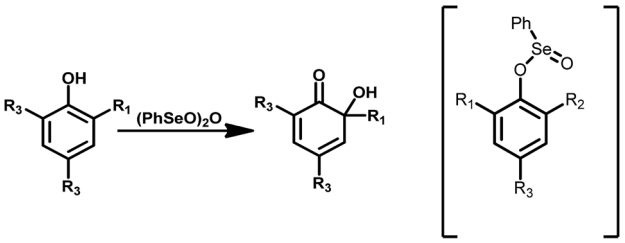

Fig. 2 Scanty Protocols.




(b) Asymmetric induction by *in situ* generated chiral benziodoxolone reagent (previous work).[7]

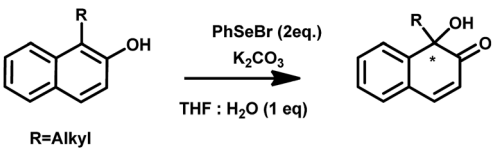



(c) Sir D. H. R. Barton's report – oxidation of phenols to *o*-hydroxy-dienones with benzeneseleninic anhydride.[15]

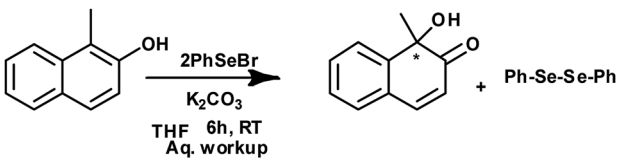



To our information, no other elegant protocol is reported in literature for such straightforward regioselective hydroxylation of naphthols encompassing a dearomatization reaction.

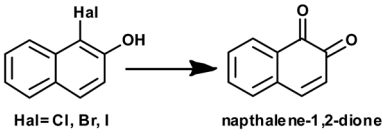
(d) This work:




Herein, we report a viable, economic and high yielding protocol of oxidation of alkyl-naphthols to benzylic α-ketols employing phenyl selenium bromide. 1,2-Naphthoquinones are




Scheme 1




Scheme 2

synthesized from halogenated naphthols (Scheme 2). The reaction is an open air transformation.

In an initial attempt, the envisioned oxidative dearomatization of 1-methylnapthalene-2-ol [$S_3$] was investigated with phenyl selenyl bromide and potassium carbonate as a base and THF as a solvent in open air atmosphere, which delivered 1-hydroxy-1-methylnaphthalen-2(1*H*)-one (1(c)) in fair yields only after execution of an aqueous workup (Scheme 1).

The reaction required 2 equivalents of PhSeBr for completion, however use of 1 equivalent did not pose any retarding effect on the reaction rate but only retaining of the substrate which claimed for a unimolecular rate of reaction w.r.t to PhSeBr, however the addition of two equivalents resulted into complete consumption of the substrate (Table 1).

In our case, though it was apprehended that the transformation happened to be after addition of water, but to our surprise no reaction occurred in THF : $H_2O$ (10 : 1). A thorough study of equivalents of water used in combination with THF as solvent is given below, (Table 2) presence of one equivalent of water completed the reaction whereas increase in amounts retarded the reaction or no reaction at all.

This observation pointed towards a reactive intermediate which was only stable in minimal amounts of water. Combination of different bases and solvents suggested $K_2CO_3$ and THF to be the best combination (Table 3).

Exposure of a wide range of 2-alkyl-naphthols to similar reaction conditions delivered α-ketols in appreciable yields in every case with concomitant formation of PhSe–SePh as a by-product which was again found to be a similar observation as reported by Barton *et al.*[15] Functional group tolerance with esters is depicted ($S_8$, $S_9$, Table 4). More electron donating alkyl groups delivered better yields providing a sensible evidence of more stable oxy-seleno reactive intermediate being involved in this reaction. The diphenyl-diselinide can be easily converted to PhSeBr employing a simple bromination in THF and thus the reagent can be reused and thus use of two equivalents initially can be partially compensated.

Table 1 Equivalents of PhSeBr required for substrate completion

| Sl no. | PhSeBr (no. of equivalents used) | Substrate consumed (in%) |
|---|---|---|
| 1 | 1 | 50 |
| 2 | 1.25 | 60 |
| 3 | 1.5 | 75 |
| 4 | 1.75 | 80 |
| 5 | 2 | 100 |

Table 3 Optimization of reaction conditions

| Sl no. | Solvent | Base | Yield (%) |
|---|---|---|---|
| 1 | THF/MeOH | Py | 60 |
| 2 | MeOH | $NEt_3$ | 55 |
| 3 | THF/dioxane | MeONa | 20 |
| 4 | THF/MeOH | KOH | 60 |
| 5 | DCM | $K_2CO_3$ | 65 |
| 6 | DMF | MeONa | 30 |
| 7 | THF | $Na_2CO_3$ | 55 |
| 8 | DMSO | $K_2CO_3$ | 60 |
| 9 | $Et_2O$ | $K_2CO_3$ | 50 |
| 10 | THF | $Cs_2CO_3$ | 75 |
| **11** | **THF** | **$K_2CO_3$** | **95** |
| 12 | THF | $KOBu^t$ | 80 |
| 13 | $Et_2O$ | $KOBu^t$ | 72 |
| 14 | THF | DBU | 40 |
| 15 | $H_2O$ | $K_2CO_3$ | No reaction |
| 16 | $H_2O$ | $Cs_2CO_3$ | No reaction |
| 17 | THF : $H_2O$ (1 : 1) | $K_2CO_3$ | No reaction |
| 18 | THF : $H_2O$ (10 : 1) | Py | No reaction |
| 19 | MeOH : $H_2O$ | $K_2CO_3$ | No reaction |

Interestingly, 1-halo-2-naphthols (Br, Cl, I) (Table 4-$S_{10}$, $S_{11}$) delivered napthoquinones 1(j) in appreciable yields [Table 4].

Dearomatization of 1-naphthol derivatives have been rare encounters to the best of our knowledge.[7] Suitably substituted α-naphthols also delivered the γ-ketols in moderate to good yields respectively ($S_{13}$, $S_{14}$). Thus the reported protocol unambiguously presents a successful strategy towards open air dearomatization of substituted planar 1-naphthol rings into γ-ketols making them viable for further significant transformations at ease.

Barton *et al.*[15] reported an involvement of a reactive intermediate (A) during the benzeneseleninic anhydride oxidations for effective *ortho*-hydroxylation in the phenolate anions. In our case, no chances of seleno-oxidation was prevalent in the employed reaction conditions which might deliver the *ortho*-hydroxylated products. Thus, the intermediate as proposed by Barton *et al.* seems implausible in our case, rather we do propose an oxy-seleno naphthol reactive intermediate (B) being operative with the alkyl napthaloate anion and which exhibits a persistence deep red coloration during the reaction condition and decolourises slowly or immediately after addition of water, breaking the oxy-selenium bond. As an additional evidence, we

Table 2 Amount of water required for substrate completion

| Sl no. | Amount of alkyl naphthol (mmol) | Amount of THF solvent (ml) | Water added (mmol) | Time required for completion | Percentage yield |
|---|---|---|---|---|---|
| 1 | 0.12 | 3 | 0.2 | 8 h | 85% |
| 2 | 0.12 | 3 | 0.4 | 8 h | 75% |
| 3 | 0.12 | 3 | 0.6 | 10 h | 65% |
| 4 | 0.12 | 3 | 0.8 | 18 h | 60% |
| 5 | 0.12 | 3 | 1.0 | No reaction | — |
| 6 | 0.12 | 3 | 1.2 | No reaction | — |

Table 4 Dearomatization on substituted naphthols

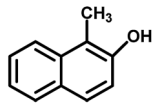
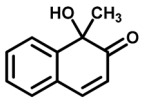
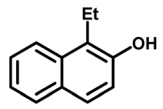
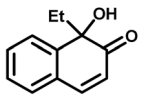
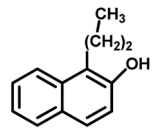
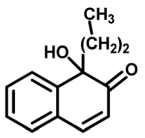
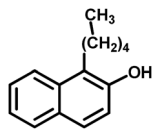
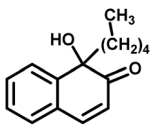
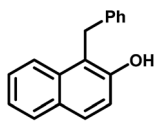
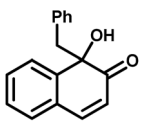
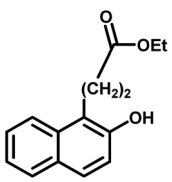
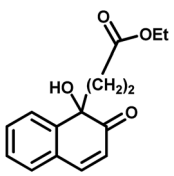
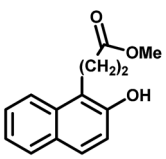
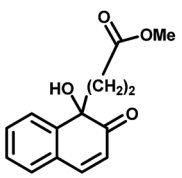
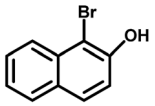
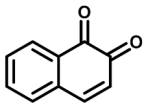
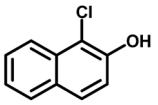
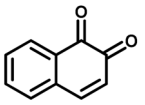
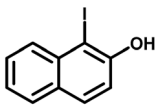
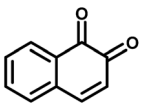
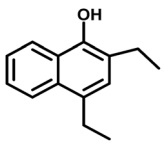
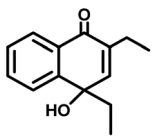
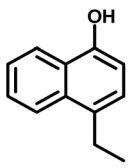
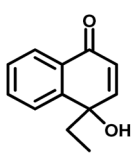
| Entry | Substrates | Products | Yields |
|---|---|---|---|
| (i) |  |  | 97% |
| | $S_3$ [16] | 1(c) [17] | |
| (ii) |  |  | 87% |
| | $S_4$ [18] | 1(d) [19] | |
| (iii) |  |  | 91% |
| | $S_5$ [20] | 1(e) | |
| (iv) |  |  | 98% |
| | $S_6$ [20] | 1(f) | |
| (v) |  |  | 80% |
| | $S_7$ [21] | 1(g) | |
| (vi) |  |  | 67% |
| | $S_8$ [22] | 1(h) | |
| (vii) |  |  | 73% |
| | $S_9$ | 1(i) | |

Table 4 (*Contd.*)

| Entry | Substrates | Products | Yields |
|---|---|---|---|
| (viii) |  |  | 80% |
| | $S_{10}$ | 1(j) [19] | |
| (ix) |  |  | 60% |
| | $S_{11}$ [23] | 1(j) | |
| (x) |  |  | 50% |
| | $S_{12}$ [24] | 1(j) | |
| (xi) |  |  | 77% |
| | $S_{13}$ | 1(k) | |
| (xii) |  |  | 65% |
| | $S_{14}$ | 1(l) | |

have taken a UV-data of the colored intermediate which exhibits a hypsochromic shift as expected due to losing of partial aromaticity, attesting our postulate (Fig. 3).

Though C–Se bond formation is a favorable situation with comparable electronegativity of (2.5 and 2.55) for C & Se respectively, but nucleophilic substitution at quaternary benzylic position in intermediate (C) delivering the ketol seems insensible.

Exposing the reaction mixtures to $^{1}H$, $^{13}C$ and $^{77}Se$ NMR clearly demonstrated the presence of the oxy-seleno intermediate. Running crude NMR experiments with the reaction mixtures clearly depicted a C=O at 206 ppm, C–O at 145 ppm

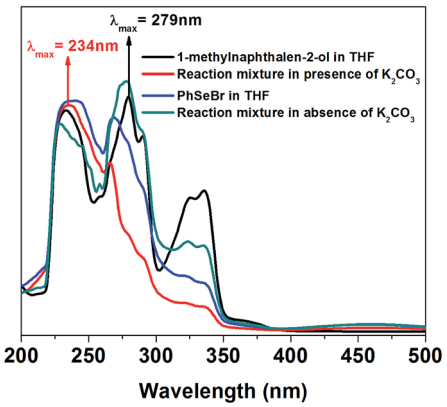



Fig. 3 Ultra-violet spectra of the reaction mixture [1-methylnaphthalen-2-ol, PhSeBr & $K_2CO_3$ (as base)].

and C–OH at 68 ppm in the $^{13}C$ NMR spectrum which concluded for the presence of both ketol & naphthols in the reaction mixture. The clear notations of 1116 ppm in $^{77}Se$ NMR also confirmed the presence of the designated intermediate, the standards being $\delta = 425$ and 870 for PhSe–SePh and PhSeBr respectively.[25] (Fig. 4) it is clearly noticeable that the newly generated olefinic and aromatic signals of the reactive intermediate B [Fig. 4(d)] start disappearing with emergence of new olefinic signals of the ketol on addition of catalytic amounts of water [Fig. 4(c)].

We conclude that a nucleophilic attack at the aromatic carbon by a water molecule with the concomitant migration of the double bond in the reactive intermediate (B) delivered the ketols as the major product (Scheme 3).

The leaving phenyl selenide anion reacts with another molecule of the oxy-seleno-napthoxy intermediate to deliver diphenyldiselenide thus regenerating the naphthol. Specifically, one equivalent of PhSeBr is required for complete generation of the phenoxy–seleno intermediate.

IR spectra of the crude reaction mixture shows a notable decrease in intensity of the naphthol O–H stretching frequencies at 3000 $cm^{-1}$ which clearly puts forward an additional evidence towards the formation of the emphasized oxy-seleno reactive intermediate. The reaction was repeated with 1-ethyl-2-naphthol, and in both cases ended up with the ketols. Barton *et al.*[15] reported equivalent chances of benzeneseleninic anhydride acting as electrophilic oxidant rather than only formation of the reactive intermediate (A), which confirms the above prediction and provides a significant evidence of the possible involvement of the intermediate (B) in the dearomatization reaction with similar selenium reagents. Replacement of PhSeBr with PhSeCl exhibited notable reduced yields and reaction rates.

Reaction of unsubstituted naphthols delivered bromonaphthols as a prime product which is expected to be a kinetic outcome where bromide ion acts a nucleophile. Attempting a more insight to the reaction, (*E*)-ethyl 3-(2-hydroxynaphthalen-1-yl)acrylate ($S_{15}$) was treated in the same reaction conditions. Direct exposure to column chromatography without any aqueous work delivered stereoselective (*E*)-

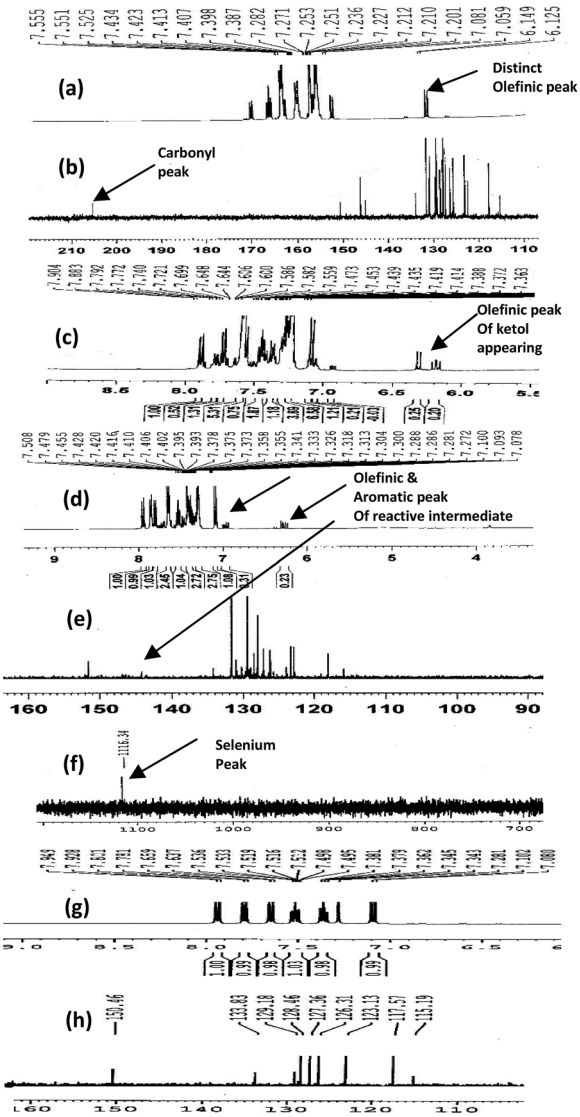


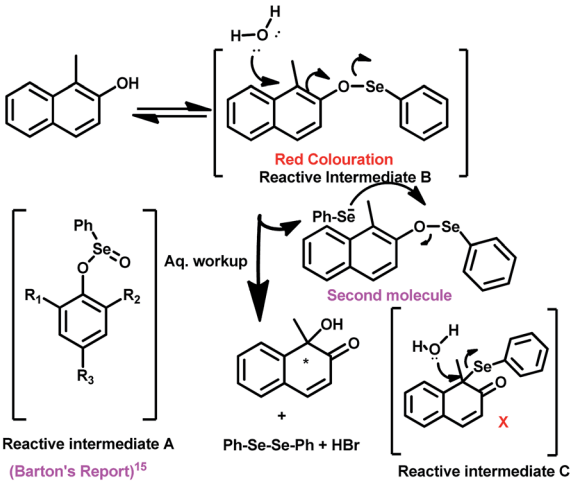

Fig. 4 (a) $^1H$ NMR of reaction mixture (1-methylnaphthalen-2-ol, PhSeBr) with $K_2CO_3$ after addition of water (1 equiv.) (b) corresponding $^{13}C$ NMR (c) $^1H$ NMR of reaction mixture after addition of catalytic amount of water & methanol, olefinic peaks of the ketol start appearing (d) $^1H$ NMR of reaction mixture before addition of water (e) corresponding $^{13}C$ NMR (f) $^{77}Se$ NMR of the reaction mixture before addition of water (g) $^1H$ NMR of 1-methyl-2-naphthol (h) corresponding $^{13}C$ NMR.

ethyl-2-bromo-3-(2-hydroxynaphthalen-1-yl)acrylate [as per NOE studies] further proving the oxidative dearomatization mechanism being involved in the reaction. Thus, this strategy also puts forward an easy approach for efficient vinylic bromination which can be utilised in broader directions (Scheme 4).

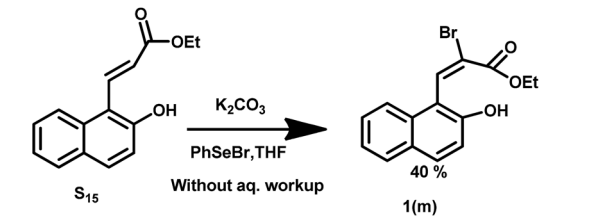
Further affirmation of the mechanistic postulate turned up when 2,6-dialkylphenol were found to deliver cyclohexadieneone aryl and bi-aryl ether under same reaction conditions. The formation of this ethers provided a clear evidence in support of the prevalence of the phenoxy–seleno intermediate (F).

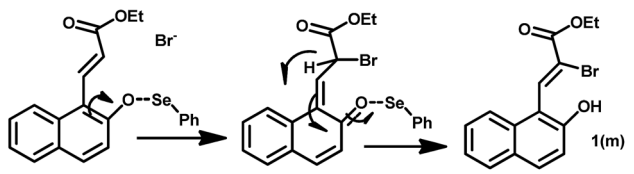
Notable changes were observed, when 2,4,6-trimethyl-phenol was exposed to similar experimental conditions, $^{13}C$ NMR of




Scheme 3




Scheme 4

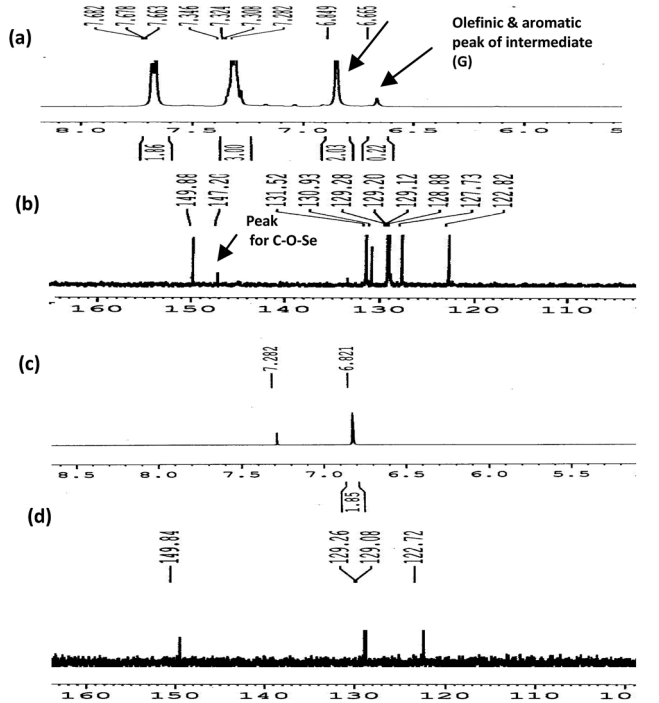
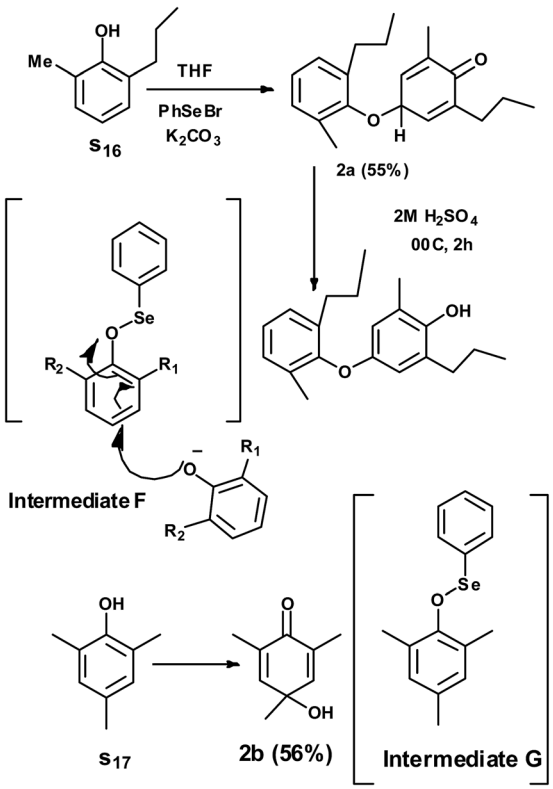



Fig. 5 *In situ* NMR studies with 2,4,6-trimethyl phenol ($S_{17}$) (a) $^{1}$H NMR of reaction mixture before addition of water (b) corresponding $^{13}$C NMR (c) $^{1}$H NMR of 2,4,6-trimethyl phenol (d) corresponding $^{13}$C NMR [full spectra are available in the ESI†].

crude reaction mixture cleanly indicate the presence of two aromatic phenoxy C-13 signal at 149.88 and 147.20 pointing out towards the phenol and phenoxy–selenium intermediate [G] respectively. The growing signal at 147.20 ppm exhibited a notable increase with time and completely vanished on addition of water delivering the 4-hydroxy-2,4,6-trimethyl cyclohexenedieneone as the sole product (Fig. 5).

In this case the biaryl ether formation is restricted due to an existent steric crowding at the *para* position. Diphenyl diselenide was the prime by-product in all observations (Scheme 5).

In order to see which intermediate was exhibited enhanced susceptibility towards nucleophilic addition of $H_2O$ to form the desired product, we have optimized both the intermediates "B" and "C" using B3LYP/6-311+G(d,p)[26] level of theory using G09w program[27] (Fig. 5) depicts the optimized geometries of reactive intermediate "B" and (Fig. 6) depicts the optimization of reactive intermediate C. Frequency calculation is also performed in the same level and basis set to make sure that these structures are on the minima of the potential energy surface. We have found that both the intermediates are in ground state due to the




Scheme 5

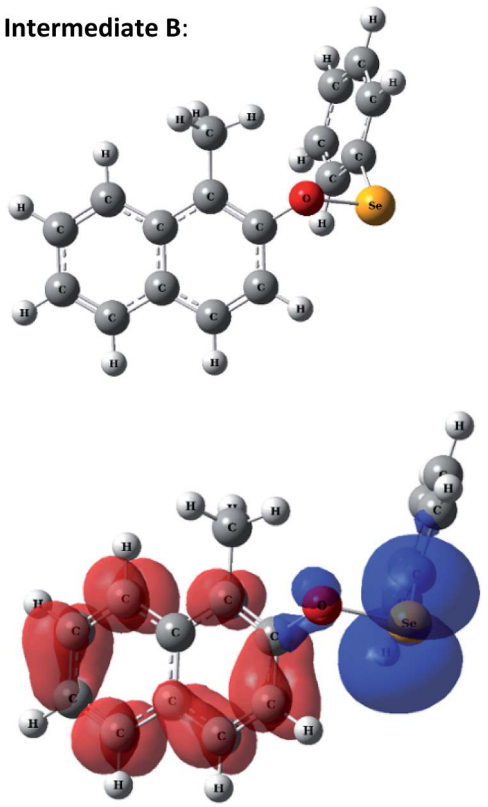



Fig. 6 Optimized geometry of intermediate B with electrophilic and nucleophilic regions (red: electrophilic; blue: nucleophilic).

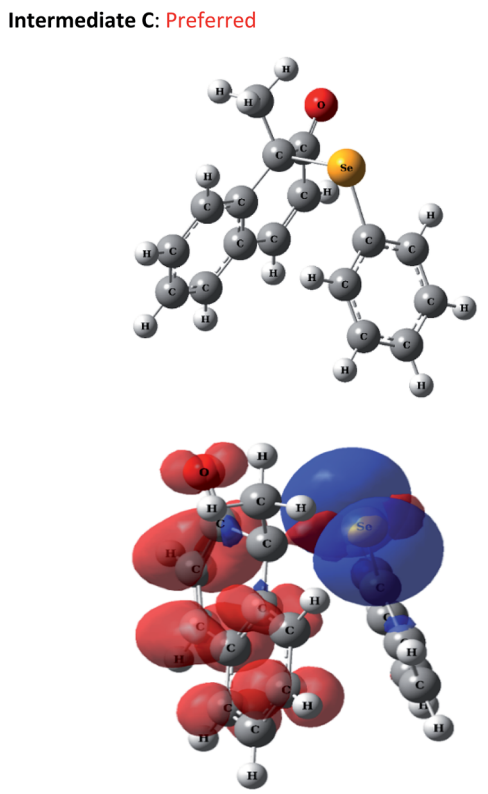



Fig. 7 Optimized geometry of intermediate C with electrophilic and nucleophilic regions (red: electrophilic; blue: nucleophilic).

absence of any negative frequency in the vibration level. Further energy calculation have enabled us to conclude that reactive intermediate B is 3.2 kcal $mol^{-1}$ less stable than C. We have also calculated the hardness which is a conceptual density functional theory (CDFT)[28] based global reactivity descriptor of reactive intermediate B and C from the frontier molecular orbitals to confirm the stability of both the intermediate. The hardness value also reveals that reactive intermediate B is less stable than C. In other sense we can say that intermediate B is more reactive than intermediate C.

To investigate the reactive sites of the intermediates in detail we have calculated another CDFT based reactivity descriptor called dual descriptor.[29] From this descriptor we can easily identify the electrophilic and nucleophilic regions inside the molecule at the same time. Fig. 5 tells us about the reactive sites of reactive intermediate B. In this figure red colored region indicates the electrophilic regions whereas blue corresponds nucleophilic regions. If we look at the dual descriptor of reactive intermediate B we have found that the quarternary C-center (attached to Me) belongs to electrophilic region which suggest that nucleophilic attack of $H_2O$ is possible in this center to form the desired product. But in the case of isomer C, we could not find any nucleophilic/electrophilic region on the same carbon center. This observation clearly demonstrates that intermediate B is more susceptible for nucleophilic addition of $H_2O$ as compared to intermediate C. These findings nicely correlate with the experimental findings (Fig. 7).

## Conclusions

There have been very limited reports in the literature available for these transformations. Either transition metal or hypervalent iodine along with peroxyacids have been used in wider scales. In case of benzeneseleninic anhydride oxidations, the yields are unsatisfactory along with indistinct mechanisms being postulated. In this report, though two equivalents of PhSeBr is consumed for completion of the reaction, the overall importance of this reaction and the distinct presence of an phenoxy–seleno intermediate in the reaction medium encompassing an oxidative dearomatization of naphthol core creates an uniqueness of this unprecedented synthetic methodology. In summary, an easy, viable, economic metal-free protocol for one-pot synthesis of α-ketols from alkyl substituted naphthols is achieved. Halogenated 2-naphthols delivered naphthoquinones whereas the alkyl-1-naphthols delivered γ-ketols in good yields. The understanding of selenium mediated dearomatizations has been put up to an advanced step which had remained dormant for the last two decades. A fair functional group tolerance is also exhibited. No inert atmosphere is required for this reaction, as it can be carried out in open sample vials. Thus the strategy outweighs the present available strategies with respect to its easy availability, reaction conditions and economy. The methodology also provides a facile access to quaternary benzylic stereocentres with the formation of ketols which can be facile entry points to solve three dimensional molecular complexities. The NMR studies of crude reaction mixtures unambiguously

prove the presence of a phenoxy–seleno intermediate (B). The formation of cyclohexadienyl aryl ethers and hydroxylcyclohexadieneone from 2,6-dialkyl phenol and 2,4,6-trialkyl phenol further attest to this manifestation. Theoretical interpretation also correlate well with the experimental findings. The developed protocol can be one of the most facile accessible entry points to three dimensional molecular complexities from abundant and cheap planar naphthols for developing sterically demanding benzylic alcohols. The asymmetric variant of this methodology would be reported soon.

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