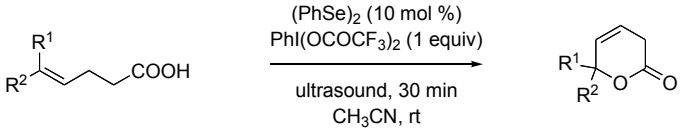
Introduction:

Organoselenium chemistry has been developed into an important tool in synthetic and natural product chemistry. Several organoselenium reagents have been employed in various useful synthetic transformations such as selenenylations, selenocyclizations, selenoxide eliminations and 2,3-sigmatropic rearrangements. Recently, organoselenium reagents have been used catalytically in various synthetic transformations such as oxidation of alcohols, olefins and carbonyl compounds, elimination reactions, Diels-Alder reactions, Baylis-Hillman and radical chain reactions.

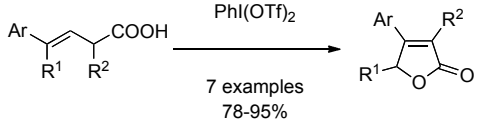
Results and Discussions:

Our target was to develop the selenium-catalyzed cyclization reactions. Initially, we emphasized on the synthesis of various olefins containing carboxylic groups as an internal nucleophile. The stereoselective selenocyclization reactions of these scaffolds are known by various chiral selenium electrophiles used in stoichiometric amounts. We want to achieve the selenium-catalyzed cyclization of olefins having internal nucleophilic center based on selenenylation followed by an oxidative elimination. In order to progress our project, we have synthesized a series of various γ,δ-unsaturated acids by two different synthetic approaches in good to excellent yields. Further, we emphasized on the cyclization of these acids using a catalytic amount diphenyl diselenide and stoichiometric amounts of hypervalent iodine reagents. Initially, we optimized the reaction conditions for the cyclization of 5,5-diphenylpent-4-enoic acid into 6,6-diphenyl-3,6-dihydro-2*H*-pyran-2-one using different solvents, hypervalent iodine reagents and different amount of diphenyl diselenide at room temperature. Finally, the best result was obtained using 10-mol% of diphenyl diselenide, one equivalent of [(trifluoroacetoxy)iodo]benzene in acetonitrile at room temperature under inert atmosphere. After obtaining the best reaction condition, we synthesized a series of cyclized products in up to 87% yield (Scheme 1). 2*H*-Pyran-2-one systems are important synthetic intermediates for the synthesis of several biologically important scaffolds and common structural motifs found in various natural products. The reaction tolerated various electron withdrawing and donating functionalities in the aromatic rings.



Scheme 1.

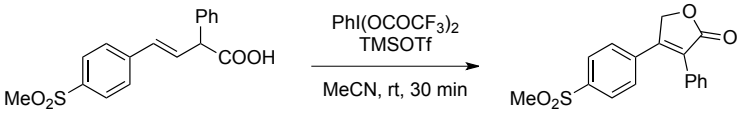
After that the stereoselective synthesis of 5-methyl-5-phenylfuran-2(5*H*)-one has been achieved in 57% yield with 39% *ee* by 1,2-bis(2-(1-(methoxymethoxy)propyl)phenyl)diselane catalyzed cyclization of 4-phenylpentenoic acid. During the progress of these reactions, we discovered a novel oxidative rearrangement of 4-arylbut-3-enoic acids to 4-arylfuran-2(5*H*)-ones mediated by hypervalent iodine compounds in good to excellent yields under mild reaction conditions as shown in Scheme 2. Optimal reagents reaction conditions for this reaction were established using 4,4-diphenylbut-3-enoic acid as model substrate. Different hypervalent iodine reagents, solvents and Lewis acids were optimized and the best result was obtained by using the combination of bis(trifluoroacetoxy)iodobenzene and TMSOTf in acetonitrile at room temperature. With these optimized reaction conditions, a series of various 4-arylbut-3-enoic acids were rearranged to yield the 4-arylfuranones in 78–95% yields (Scheme 2).



Scheme 2.

The oxidative rearrangement is proceeding smoothly with different substrates having both mono- and disubstitution at C-4 position. The course of reaction was different with (*E*)- and (*Z*)-isomers of substrates. The rearrangement reaction was working nicely with (*E*)-4-phenylbut-3-enoic acid and corresponding furanone was isolated in 89% yield. Interestingly, with (*Z*)-4-phenylbut-3-enoic acid only the cyclization product without rearrangement was isolated in 81% yield. The efforts were also made for different ring sizes. The mechanism of this transformation was also studied in detail by computational investigations of possible intermediates.

Furanone scaffolds are basic structural motifs found in various naturally occurring biologically active compounds. Synthetic furanones with interesting pharmacological and pharmacokinetic properties have been reported. For example, the furanone derivative Rofecoxib is known as a selective COX-2 inhibitor. Rofecoxib was synthesized in a straightforward manner from the corresponding acid in 83% yield.



Rofecoxib

Scheme 3.

We have developed an alternative approach for the synthesis of 2-arylbenzofurans and naphthofurans by oxidative cyclization of *o*-hydroxystilbenes using [bis(acetoxy)iodo]benzene as oxidant. Benzofuran scaffolds are basic structural motifs found in various naturally occurring biologically active compounds. Initially, different solvents and hypervalent iodine reagents were employed to optimize the reaction conditions. The best result was obtained with [bis(acetoxy)iodo]benzene in acetonitrile at room temperature. After getting the best reaction conditions, a series of 2-hydroxystilbenes were successfully cyclized to yield the 2-arylbenzofurans in 68-87% yields (Scheme 4).

Scheme 4.

The cyclization reactions were working smoothly with substrates having both electron donating and withdrawn groups bearing aromatic substituents and the products were isolated in good to excellent yields. It was also observed that the products were obtained in higher yields when electron-donating groups bearing aromatic substituents were used in starting materials. Further, the (E)-2-styrylnaphthols were cyclized to 2-naphthofurans by using one equivalent of [bis(acetoxy)iodo]benzene in 88-95% yields under same reaction conditions.

The selenenylation of styrene was achieved up to 88% diasteremric excess by chiral selenium electrophile 1,2-bis(2-(1-(methoxymethoxy)propyl)phenyl)diselane using silver tris(perfluoroalkyl)trifluorophosphate (AgFAP) as new counterion.

Furthermore, we have demonstrated the iodine catalyzed addition reactions of different styrene systems with diphenyldiselenide in good yields. The strength of this reaction is that the styrenes are using as nucleophile in these reactions.

Summary:

1. We have established a new approach for the facile synthesis of different six-membered lactones from γ,δ-unsaturated carboxylic acids using catalytic amounts of diphenyl diselenide. This approach to synthesize these scaffolds is very simple, economical, and metal-free.
2. We have developed an efficient novel oxidative rearrangement leading to highly substituted furanone derivatives and investigated the mechanism of this transformation in detail.
3. We have demonstrated an alternative approach for the synthesis of 2-arylbenzofurans and naphthofurans by oxidative cyclization of *o*-hydroxy stilbenes using [bis(acetoxy)iodo]benzene as oxidant.
4. The stereoselective synthesis of 5-methyl-5-phenylfuran-2(5*H*)-one has been achieved in 39% *ee* by using 1,2-bis(2-(1-(methoxymethoxy)propyl)phenyl)diselane as chiral selenium catalyst.
5. We have achieved the selenenylation of styrene up to 88% diasteremric excess by chiral selenium electrophile 1,2-bis(2-(1-(methoxymethoxy)propyl)phenyl)diselane using silver tris(perfluoroalkyl)trifluorophosphate (AgFAP) as new counterion.

Research Publications:

1- Selenium-Catalyzed Regioselective Cyclization of Unsaturated Carboxylic Acids Using Hypervalent Iodine Oxidants
Singh, F. V.; Wirth, T. *Org. Lett.* **2011**, *13*, 6504.

2- Selenium Compounds as Ligands and Catalysts: *Organoselenium Chemistry*
Singh, F. V.; Wirth, T. Ed.: T. Wirth, Wiley-VCH, **2011**, 321-360.

3- Hypervalent Iodine(III) Mediated Cyclization of *ortho*-Stillbenes into Benzofurans
Singh, F. V.; Wirth, T. *Synthesis* **2012**, *44*, 1171.

4- Stereoselective reactions of organoselenium reagents including catalysis
Singh, F. V.; Wirth, T. in Patai Series: *Organic Selenium and Tellurium Compounds*, Vol. 3, Ed.: Z. Rappoport, John Wiley & Sons, **2012**, 303-355.

5- Novel Oxidative Rearrangements Using Hypervalent Iodine Reagents
Singh, F. V.; Rehbein, J.; Wirth, T. *Angew. Chem. Int. Ed.* (Submitted).

6- Iodine-Mediated Addition Reactions of Alkenes with Diselenide Using Styrenes as Nucleophile
Gabriele E.; **Singh, F. V.**; Wirth, T. *Tetrahedron* (Submitted).