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Intramolecular Displacement of Phenylselenone by a Hydroxy Group: Stereoselective Synthesis of 2-Substituted Tetrahydrofurans

Lucio Minuti,[†] Anna Barattucci,[#] Paola Maria Bonaccorsi,[#] Maria Luisa Di Gioia,[§] Antonella Leggio,[§] Carlo Siciliano,[§] and Andrea Temperini*[,‡]

Department of Chemistry, University of Perugia, via Elce di Sotto 8, 06123 Perugia, Italy, Department of Chemical Sciences, University of Messina, Viale F. Stagno d'Alcontres 31, 98166 Messina, Italy, Department of Pharmacy and Health Sciences and Nutrition, Multifunctional Building, University of Calabria, 87030 Arcavacata di Rende, Cosenza, Italy, and Department of Chemistry and Technology of Drugs, University of Perugia, via del Liceo 1, 06123 Perugia, Italy

tempa@unipg.it

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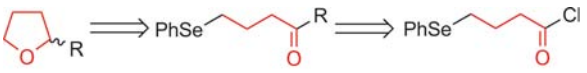
ABSTRACT



R= Alkyl or Aryl

An efficient and stereocontrolled synthesis of 2-substituted tetrahydrofurans has been achieved. The approach employs the asymmetric reduction of γ-phenylseleno ketones obtained by three different procedures that are peculiarly applied to the synthesis of such compounds. Finally, the intramolecular substitution of the phenylselenone residue by the oxygen atom of a hydroxy group gives the tetrahydrofuran ring.

Oxygenated heterocycles, especially tetrahydrofurans (THFs), represent a key structural motif of natural and unnatural products with significant and various biological activities. The substituted THF nucleus is the common structural core of annonaceous acetogenins,[1] lignans,[2] polyether ionophores,[3] and macrolides.[4] Owing to their different bioactivities such as immunosuppressive, antitumor, pesticidal, antiprotozoal, antifeedant, anthelmintic, and antimicrobial agents, considerable effort has been devoted toward the stereoselective synthesis of substituted THFs.[5] Among the number of different approaches that have been devised in order to construct 2-substituted THFs, the cycloetherification reaction plays an important role. Classical approaches have primarily focused on the intramolecular S_N2 reactions between a hydroxy group and a tethered leaving group (e.g., halide, sulfonate, or sulfoxonium),[6] intramolecular oxy-Michael addition reaction mediated by an organocatalyst,[7] hydroalkoxylation/cyclization of alkenols,[8] alkene halo- and selenoetherification,[9] alkene carboetherification,[10] olefin metathesis,[11] and direct C−H arylation/alkylation at α-position of THF.[12]

[†] Department of Chemistry, University of Perugia.
[#] University of Messina.
[§] University of Calabria.
[‡] Department of Chemistry and Technology of Drugs, University of Perugia.

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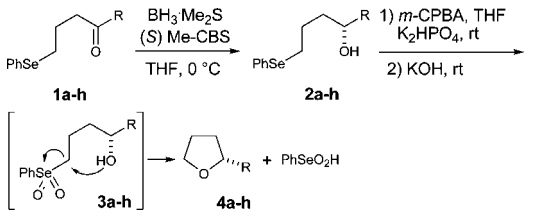
As part of our general interest in the chemistry of organoselenium compounds,[13a] we have recently reported that the phenylselenyl group can be easily and intramolecularly displaced by nitrogen nucleophiles, thus affording substituted 1,3-oxazolin-2-ones[13b] and *N*-azetidines.[13c]

Herein, we report a versatile and stereoselective synthetic route to 2-substituted THFs **4** (Scheme 1).

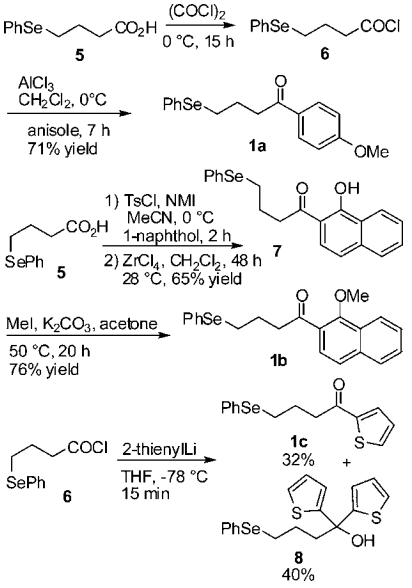
Scheme 1. General Strategy for the Stereospecific Synthesis of 2-Substituted Tetrahydrofurans



Our approach involves the direct intramolecular nucleophilic substitution of the phenylselenone group by the oxygen atom of an alcohol **3**, that is a formal 5-*exo*-tet process. There are only two reports, to date, on the intramolecular nucleophilic deselenenylation reaction for the synthesis of 2-substituted THFs, both of them proceeding *via* a selenonium salt intermediate.[14]

The phenylseleno alcohols **2** are uncommon organoselenium intermediates.[15] We envisaged that they could be easily and enantioselectively prepared by asymmetric CBS-reduction of the corresponding γ-phenylseleno ketones. In our hands, the oxazaborolidine-borane reduction[16] of prochiral ketones **1** gave high level of enantioselectivity in almost all the studied cases. Despite the extensive research effort directed toward the synthesis of α- and β-phenylseleno ketones,[17] the synthesis of γ-phenylseleno ketones **1** remains an unexplored area of research.[18] In this context, we have developed three different strategies for the synthesis of compounds **1**, starting all from 4-(phenylseleno)butanoic acid (**5**) (Scheme 2). Thus, the acid **5** was reacted with oxalyl chloride to lead to

Scheme 2. Preparation of γ-Phenylseleno Ketones **1a**–**c** by Friedel–Crafts Acylation, Fries Rearrangement, and Acylation of 2-Thienyl Lithium, Respectively



the corresponding acyl chloride **6** that was subjected to the Friedel–Crafts acylation reaction with anisole to give ketone **1a** in 71% overall yield. Ketone **1b** was prepared by an unprecedented approach based on the Fries rearrangement of the ester intermediate of **5** to ketone **7** and successive methylation of the free hydroxy group. We explored, also, the quick and direct reaction of an organometallic reagent such as thienyl lithium, with acyl chloride **6** (Scheme 2).[19] As expected, ketone **1c** was obtained in low yield together with the alcohol **8**. Due to the known limitations of the above reaction, we directed our attention to the reactions of **6** with octyl magnesium bromide[20] in the presence of $Fe(acac)_3$ or with lithium dibutylcuprate.[21] Both of these reactions did not give appreciable results. Furthermore, when we reacted (3-fluorophenyl)-(methyl)-copper(I) magnesium bromide, a mixed magnesium cuprate,[22] with compound **6**, the corresponding ketone **1d** was obtained in low yield (30%). Replacement of the methyl group with the thienyl group as a dummy ligand allowed the preparation of the new mixed magnesium cuprate **9d** (R = 3-fluorophenyl) that, reacting with **6**, led to ketone **1d** in 83% yield (Table 1, entry 1). Therefore, various mixed magnesium cuprates **9e**–**h**, capable of selectively transferring the R group to the skeleton of acyl chloride **6**, were employed for the synthesis of ketones **1e**–**h** (Table 1, entries 2–5).

The results reported in Table 1 show that functional group tolerance, good yields, simplicity, and mildness of

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(15) Clive, D. L. J.; Cheng, H. *Chem. Commun.* **2001**, 605.
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(17) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986; Chapter 11.
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(19) Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177.
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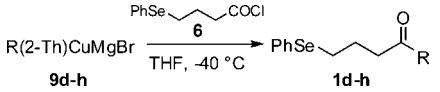
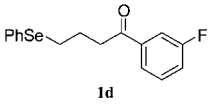
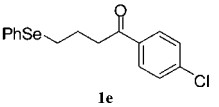
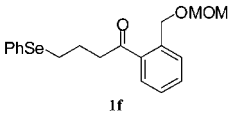
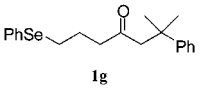
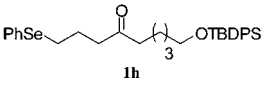
(21) Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5160.
(22) Bergbreiter, D. E.; Killough, J. M. *J. Org. Chem.* **1976**, *41*, 2750.

Table 1. Preparation of Ketones **1d**–**h** by Acylation of Mixed Magnesium Cuprates **9d**–**h** with Acyl Chloride **6**



entry	ketone	time (h)	yield (%)[a]
1	 **1d**	4	83
2	 **1e**	5	78
3	 **1f**	5	74
4	 **1g**	4	76
5	 **1h**	5	77

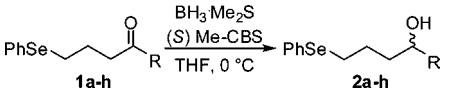
[a] Isolated yield.

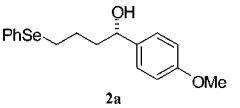
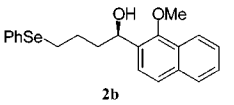
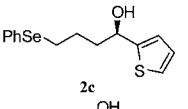
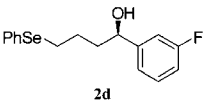
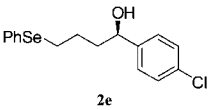
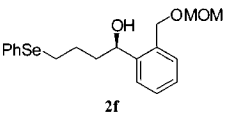
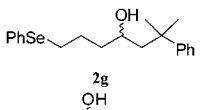
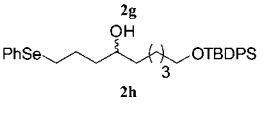
the experimental conditions are valuable characteristics of this novel and alternative organo-copper mediated synthesis of γ-phenylseleno ketones.

On the basis of the above findings we developed the new strategy for accessing a range of 2-substituted THFs **4**, shown in Scheme 1. The enantioselective reduction of ketones **1a**–**h** was achieved *via* the chiral oxazaborolidine-catalyzed Corey procedure to give the enantioenriched γ-phenylseleno alcohols **2a**–**h** in excellent yields (77–90%, Table 2, entries 1–8); in the case of alcohols **2g** and **2h** a poor enantioselectivity was observed (entries 7 and 8). The configuration of the major enantiomer of compounds **2a**–**f** was tentatively assumed according to the mechanism proposed by Corey[16] and others.[23,24] Oxidation of γ-phenylseleno alcohols **2a**–**h** into the corresponding selenones **3a**–**h** was carried out in THF at room temperature with an excess of *m*-chloroperoxybenzoic acid and in the presence of dipotassium hydrogenphosphate, according to our previous report.[13c] The selenone intermediates **3** were not isolated, although their formation could be inferred by thin-layer chromatography (TLC) or clearly established by ^{13}C NMR spectroscopy of the crude reaction mixture.[13b]

Selenones **3a**–**h** underwent cyclization to THFs **4a**–**h** by addition of powdered potassium hydroxide. This cyclization reaction, which represents the key step of the entire process, is a stereospecific intramolecular nucleophilic substitution and occurs easily because of the great leaving ability of the phenylselenonyl group. As shown in

Table 2. Borane (*S*) Me-CBS-Catalyzed Asymmetric Reduction of Ketones **1a**–**h** into Alcohols **2a**–**h**



entry	alcohol	time (h)	yield (%)[a]	ee (%)
1	 **2a**	3[b]	85	67
2	 **2b**	3	77	92
3	 **2c**	10	82	80
4	 **2d**	4	85	91
5	 **2e**	4	86	86
6	 **2f**	12	90	52
7	 **2g**	7	90	30
8	 **2h**	10	82	16

[a] Isolated yield. [b] (*R*) Me-CBS was used.

Table 3, the 2-substituted THFs **4a**–**h** were obtained in good to excellent yields (76–95%) and good enantiomeric ratio (Table 3, entries 1–6), as shown by HPLC analysis on chiral stationary phase. The enantiomeric composition of compounds **4a**–**h** reflected that of the corresponding alcohols **2a**–**h**. It is worth noting that the partial racemization during the cyclization step may be considered to be unlikely in view of the bimolecular nucleophilic substitution character of the reaction involved.

The low levels of enantiomeric ratio observed for products **4g** and **4h** (Table 3, entries 7 and 8) were probably due to the poor enantioselectivity of the reduction step of ketone **1g** and **1h** (Table 2, entries 7 and 8) to alcohols **2g** and **2h**.[24]

Comparison across the data reported in Table 3 indicates that oxidative cyclization of alcohols **2** occurs in good/excellent yields under mild reaction conditions. Along with the different functional groups tolerated in

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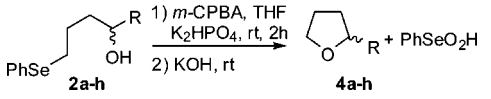
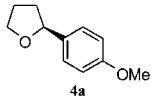
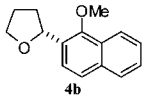
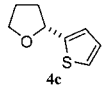
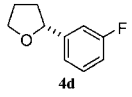
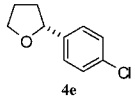
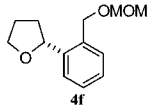
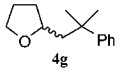
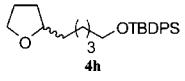
(24) Quallich, G. J.; Woodall, T. M. *Tetrahedron Lett.* **1993**, *34*, 785.
(25) Okada, M.; Kitagawa, O.; Fujita, M.; Taguchi, T. *Tetrahedron* **1996**, *52*, 8135.

Table 3. Oxidative Cyclization of Alcohols **2a**–**h** into Tetrahydrofurans **4a**–**h**



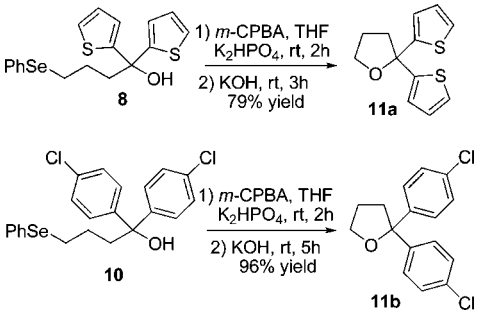
entry	tetrahydrofuran	yield (%)[a]	time (h)	[α]	ee (%)[b]
1	 4a	76	5	-24.8	67
2	 4b	81	4	+28.4	92
3	 4c	80	7	-5.4	80
4	 4d	77	7	+40.4	91
5	 4e	95	4	+39.0	86
6	 4f	76	5	+29.3	52
7	 4g	80	7	-0.5	30
8	 4h	94	22	-2.1	16

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

the alcohol **2**, this makes our method a general valuable synthetic procedure for obtaining chiral 2-substituted THFs. For example, compounds **4a**,[25] **4c**,[26] **4d**,[27] **4e**,[12b] and **4g**[28] have been previously synthesized by different methodologies, but they were obtained in comparable or lower yields and as racemic mixtures.

To further explore the applicability of our methodology, we prepared some 2,2-disubstituted THFs by cyclization of the corresponding tertiary alcohols **8** and **10** (Scheme 3). Although compound **8** was obtained as a byproduct during the preparation of **1c**, the alcohol **10** was easily synthesized in 67% overall yield from the methyl ester derivative of

Scheme 3. Synthesis of 2,2-Disubstituted Tetrahydrofurans



acid **5** with an excess of *p*-chlorophenyl magnesium bromide. Oxidation of these alcohols with *m*-chloroperoxybenzoic acid occurred smoothly at rt in the presence of dipotassium hydrogenphosphate to give the corresponding selenones, which cyclized after the addition of potassium hydroxide to allow the 2,2-disubstituted THFs **11a** and **11b** in 79% and 96% yields, respectively. Compounds **11a**[29] and **11b**[30] were already prepared by different procedures, but in lower yiels (70% and 45%, respectively). It is worth noting, that the phenylseleno moiety introduced at the beginning of our procedure was eliminated as benzeneseleninic acid in the oxidation/cyclization step; the water-soluble potassium benzeneseleninate produced in this step can be separated and the selenium recovered as diphenyl diselenide, thus making the process consistent with atom economy.

In summary, we have formulated a novel, mild stereoselective approach to 2-substituted THFs, starting from phenylseleno ketones **1**. Different and new synthetic strategies for the preparation of the γ-phenylseleno ketones **1** have been also developed. The key step of our procedure is the ring-closure reaction, in which stereospecific intramolecular nucleophilic substitution of the good leaving phenylselenonyl group by the oxygen atom of the alcohol is effected. The present procedure favorably compares with other previously described methods for the preparation of 2-substituted THFs in enantiomeric enriched forms. Our current efforts are directed toward the construction of di- and trisubstituted tetrahydrofurans and substituted tetrahydropyrans.

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Supporting Information Available. Synthetic procedures together with characterization and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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