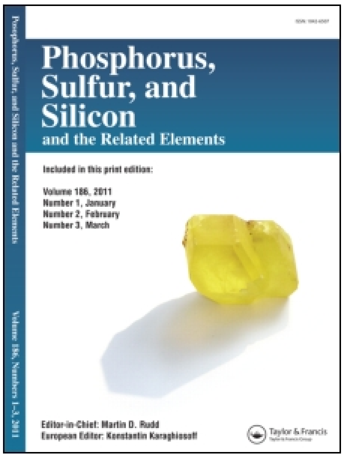

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Catalytic Addition-Elimination Reactions Towards Butenolides

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A wide range of selenium-containing reagents are known to undergo addition – elimination reactions under different reaction conditions. We report on selenium electrophiles, which are regenerated under the reaction conditions employed, and therefore only catalytic amounts of these reagents are necessary.

Keywords Butenolides; diselenides; selenium electrophiles; stereoselective synthesis

INTRODUCTION

For several decades now, selenium reagents have attracted growing interest for their application in organic synthesis.[1,2] Selenium dioxide is a well known and traditionally used oxidizing agent for alkenes, ketones and other substrates, but it was not until 1977 that Umbreit and Sharpless found that only catalytic amounts of selenium dioxide could be used to functionalize alkenes.[3] Phenylseleninic acid (Ph-SeO_2H) has been used as a catalyst for the epoxidation of alkenes and Baeyer-Villiger oxidations. In addition, polystyrene bound arylseleninic acid can be used in catalytic amounts in the oxidation of alkenes, ketones and aromatic systems, which have avoided the contamination of reaction products. It was found that the catalyst is stable to the reaction conditions and can be recycled with no apparent loss of activity.[4] Knochel and coworkers reported the use of organoselenium reagents containing perfluoroalkyl substituents in flourous solvents in similar transformations.[5] The butylselenide pre-catalyst **1** is oxidized to the corresponding selenenic acid under the reaction conditions while the fluorous biphasic catalysis allowed efficient separation of the catalyst

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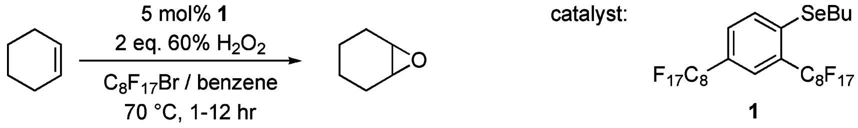
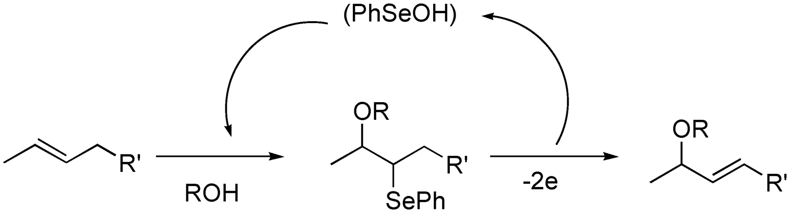
from the reaction mixture. The catalyst could be recycled more than ten times without either decrease in yields or increase in reaction times. A typical epoxidation is shown below.

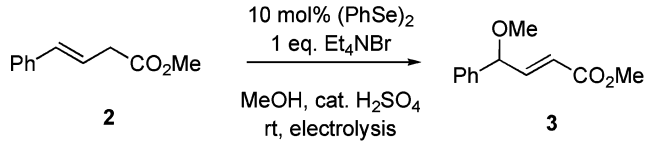


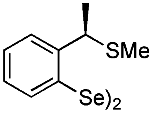
Selenenylation-deselenenylation sequences provide double bond transpositioned allylic alcohols and ethers from alkenes. The sequence involves two steps: Selenenylation with PhSeX (X = Cl, OR, NR_2) followed by oxidation with O_3, $NaIO_4$, or peroxides (H_2O_2, *t*-BuOOH, *m*CPBA) where stoichiometric amounts of PhSeX and large excess of oxidant are normally required. It was found by Torii et al. that this could be achieved in a single step by electrochemical generation of selenium electrophiles from catalytic amounts of diphenyl diselenide.[6] This was achieved without the formation of phenylseleninic acid and selenamide and in the absence of peroxides. Electrochemically generated phenylselenenyl electrophiles react regioselectively with alkenes producing the selenide, followed by electrochemical oxidation to provide the corresponding selenoxide, which instantly undergoes *syn*-elimination to give the desired product.



The selenenylation reagent is regenerated in situ and the transformation is enhanced by the addition of metal salts such as magnesium sulfate. This is increasing the yields of the corresponding products by preventing the reaction to phenylselenenic acid and phenylseleninic acid both by disproportionation and electro-oxidation.

Further developments by Wirth et al. showed that the electrochemical oxyselenenylation-deselenenylation conversion of alkenes into allylic compounds can be successfully achieved with catalytic amounts of diphenyl diselenide (10 mol%) or other enantiomerically pure diselenides using acceptor substituted alkenes such as **2** as substrates.[7] Tetraethylammonium bromide was employed in the reaction to act as both, a redox catalyst and an electrolyte. The reaction is initiated by the anodic oxidation of bromide to bromine, which reacts with the diselenide to form the corresponding arylselenenyl bromide. After addition to the alkene and formation of the selenide, a second equivalent of bromine forms an unstable tetravalent selenium derivative, which acts as a good leaving group thus generating the elimination product **3**. Compound **3** has been obtained with up to 66% *ee* with 10 mol% of diselenide **4** in place of diphenyl diselenide in this reaction.





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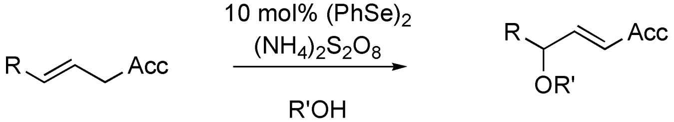
The reaction sequence developed by Tomoada et al. employs nitrogen-containing enantiomerically pure selenium reagents as catalysts in the presence of copper(II) nitrate for the conversion of alkenes into the allylic compounds.[8] After screening a range of oxidizing agents, it was found that sodium persulfate was best for the catalytic reaction. Higher conversions were observed using 3Å molecular sieves, showing that the removal of water is essential for the reaction to proceed. Still the reaction is sluggish and turnover numbers are low.

This prompted work by Tiecco et al. to convert α,β-unsaturated esters, amides, and nitriles into α-alkoxy or α-hydroxy derivatives.[9] They developed a multistep one-pot synthesis using excess ammonium persulfate and using only catalytic amounts of diphenyl diselenide. They have shown that the intermediate alkylphenyl selenides reacts with the persulfates regioselectively towards the elimination products **5**, which were obtained in good yields (23–90%) in just a few hours. An electron-withdrawing group in the allylic position is essential for the success of the reaction as simple unsubstituted alkenes gave rise to product mixtures.



5 (Acc: CO_2Me, CN, $CONMe_2$)
(R: H, Me, Et, Ph, R': H, Me)

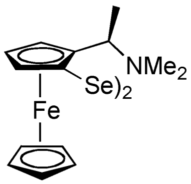
Tiecco et al. also carried out intermolecular versions of this catalytic oxidation to produce butenolides, which are obtained from the reaction of the easily available β,γ-unsaturated acids with catalytic amounts of diphenyl diselenide and an excess of ammonium persulfate in acetonitrile.[10] The carboxy group is found to act as both an internal nucleophile and as an electron withdrawing group in the γ position and again produces good yields in relatively short reaction times. It was also observed in some cases that better yields were obtained with the catalytic reaction compared to using stoichiometric amounts of diphenyl diselenide.

Tiecco and coworkers has taken this one step further and utilizes the previous reaction conditions to convert alkenols to the corresponding 2,5-dihydrofurans.[11] Excellent yields were obtained (90–96%) with traces of a side product. The cyclization - elimination process gives rise to two stereoisomeric of the 2,5-dihydrofurans in good yields, where the selectivity reflects the steric demands in the approach of the electrophile to the π-bond. *Erythro*-unsaturated alcohols yield *trans*-2,5-dihydrofurans whereas the *threo*-unsaturated alcohols gave the *cis*-products. The observed stereoselecitvities of the process imply that only the major isomer of the intermediate undergoes elimination to afford the corresponding 2,5-dihydrofurans. When ammonium persulfate was reacted with the major isomer of the intermediate the desired product was quantitatively transformed, where as the minor isomer gave unidentified products, showing the *cis* relationship renders the approach of the persulfate anion to the selenium atom more difficult.

Tomoda et al. reported the first catalytic asymmetric conversion of *trans*-β-methyl styrene into optically active allylic ethers using diaryl diselenides with a chiral pyrrolidine moiety in the *ortho*-position.[12] Yields of 24% and enantioselectivities of up to 32% *ee* were observed using previous literature methods and with copper(II) nitrate. The moderate asymmetric induction is believed to be due the strong interaction between the electrophilic selenium atom and the tertiary nitrogen of the chiral pyrrolidine moiety.

The highest diastereoselectivities (96% *de*) of asymmetric methoxyselenenylation of alkenes together with excellent chemical yields (99%) were achieved using ferrocenyl selenium triflates.[13] Diselenide **6** is the precursor for the electrophile and when applied to a range of alkenes all resulted in high yields (96–99%) and moderate to high diastereoselectivities (15–96%). It was observed that sterically large groups in the alkene are necessary to achieve high facial selectivity.

In 1998, Wirth and coworkers used peroxydisulfates for the generation of the nitrogen containing selenium electrophile for the catalytic oxyselenenylation-elimination reaction with *trans*-β methylstyrene.[14] It is known that metal ions can accelerate the decomposition of peroxo disulfates and varying the metal salts was found to have a strong influence on the stereoselectivity with nickel



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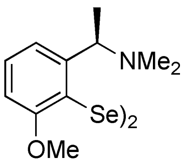

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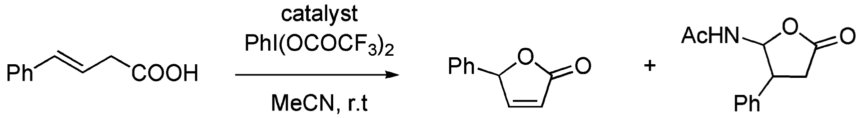
nitrate being the most effective salt with ee's of up to 71% and when diselenide **7** was used enantioselectivities of up to 75% was observed. These are the highest enantioselecitivities obtained for the catalytic oxyselenenylation-elimination reaction so far obtained, but a major drawback was again the low turnover number.

RESULTS AND DISCUSSION

In recent work on the cyclization of alkenoic acids **8** into the corresponding butenolides **9**, we found that acetonitrile, 5 mol% diphenyl diselenide as a catalyst and bis(trifluoroacetoxy)iodobenzene as the oxidant were the optimum conditions for this reaction procedure.[15] Lower catalytic loading resulted in the rearranged products **10** because the hypervalent iodine reagent then directly reacts with the substrate.



8 **9** **10**

Full conversion to the products was observed only with diphenyl diselenide. Diphenyl disulfide showed less reactivity, and diphenyl ditelluride reacted even slower, as well. This lower reactivity is then reflected in the increased amount of rearranged product **10**, which results from the direct reaction of alkene **8** with the hypervalent iodine oxidant. If performed in acetonitrile, the capture of the intermediate phenonium ion by acetonitrile and subsequent hydrolysis led to the formation of the by-product **10**. A range of other dichalcogen catalysts was also tested and the results are summarized in Table I.

From the results in Table I, it can be clearly seen that diselenides are the better catalysts, where diphenyl diselenide having superior yields to

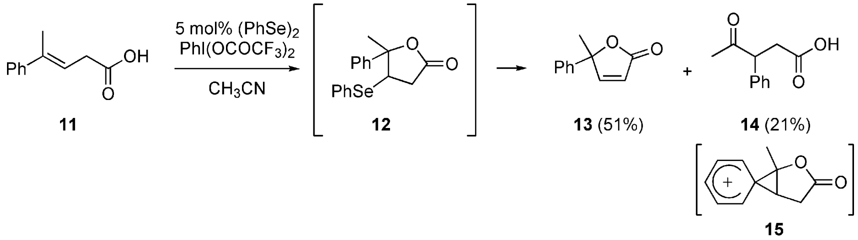
TABLE I Different Dichalcogen Catalysts for the Addition / Elimination Sequence

Catalyst	**13 : 14** (Ratio)	Yield (%)
$(PhSe)_2$	100:0	70
$(MeSe)_2$	100:0	56
$(PhS)_2$	25:75[a]	—
$(MeS)_2$	25:75[a]	—
$(PhTe)_2$	28:72[a]	—

[a]Determined by NMR.

dimethyl diselenide. The other results indicate that the other catalysts are not as active as the diselenides and give mainly the rearranged product that correlate with the results of using lower catalytic loadings with diphenyl diselenide or no catalyst at all.

For the investigation of trisubstituted alkenes in such cyclization reactions, (*E*)-4-phenylpent-3-enoic acid **11** was synthesized. The cyclization resulted in a mixture of products and compounds **13** and **14** were observed.



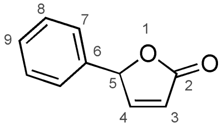
After the initial selenolactonization to **12**, the elimination to **13** occurred similar to disubstituted alkene substrates. 4-Oxo-3-phenylpentanoic acid **14** was found as a by-product, but without the diselenide catalyst, **14** was the only product being formed. The reaction of bis(trifluoroacetoxy)iodobenzene with **11** leads, after cyclization, to a phenyl migration via phenonium ion **15** and reaction with trifluoroacetate or water and subsequent ring-opening of the ketal results in the formation of **14**. Compound **12** was also synthesized independently to investigate its further oxidation. The elimination product **13** (86% yield) was the only product observed and no rearranged product **14** was detected. The rearrangement to **14** therefore occurs only via the direct reaction of **11** with bis(trifluoroacetoxy)iodobenzene.

EXPERIMENTAL

General

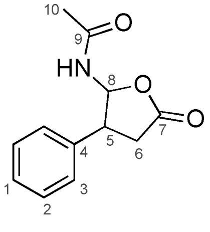
^{1}H and ^{13}C NMR experiments were carried out on a Bruker 400-DPX spectrometer. IR measurements were taken using a Perkin-Elmer 1600 FTIR spectrometer as a liquid film. Low-resolution mass spectrometry was carried out using a Varian Saturn 2 GC-MS. Flash chromatography was completed using Fisher Silica Gel (35–70 mesh). Preparative thin layer chromatography was carried out using Merck silica gel 60 F254 on glass plates. All solvents used were dried and purified by standard methods. Reactions requiring the exclusion of air were carried out under an atmosphere of argon in oven-dried glassware.

5-Phenylfuran-2(5H)-one (9)[16]



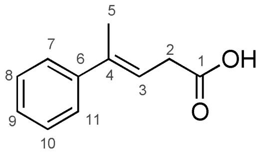
Colorless oil, (24 mg, 70%); ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.53$ (1H, dd, J 5.5, 1.6 Hz, H-4), 7.40–7.35 (3H, m, H-7,9), 7.30–7.25 (2H, m, H-8), 6.23 (1H, dd, J 5.5, 2.0 Hz, H-5), 6.01 (1H, dd, J 2.0, 1.6 Hz, H-3) ppm; ^{13}C NMR (63 MHz, CDCl$_3$): $\delta = 173.1$ (C-2), 155.9 (C-4), 134.3 (C-6), 129.4 (C-9), 129.2 (2C, C-8), 126.5 (2C, C-7), 120.1 (C-3), 84.4 (C-5) ppm.

N-(5-Oxo-3-phenyltetrahydrofuran-2-yl)ethanamide (10)



Colorless oil, (29 mg, 28%); IR (film): $\nu_{\max} = 3299$, 1782, 1678, 1541, 1372, 1260, 1166, 943, 826, 732, 698 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.12$–7. 38 (5H, m, H-1,2,3), 6.15 (1H, dd, J 7.7, 1.4 Hz, H-8), 3.55 (1H, q, J 9.1 Hz, H-5), 3.00 (1H, dd, J 8.8, 17.6 Hz, H-6a), 2.70 (1H, dd, J 10.7, 17.6 Hz, H-6b), 1.95 (3H, s, H-10) ppm; ^{13}C NMR (63 MHz, CDCl$_3$): $\delta = 174.3$ (C-7), 171.4 (C-9), 136.9 (C-4), 129.3 (2C, C-2), 128.2 (C-1), 127.1 (2C, C-3), 86.1 (C-8), 46.9 (C-5), 37.2 (C-6), 23.2 (C-10) ppm; MS: *m*/*z*(%): 160 (M^+100), 178 (58), 201 (70), 220 (18); HRMS $C_{12}H_{14}NO_3$: found 220.0979, calcd. 220.0974.

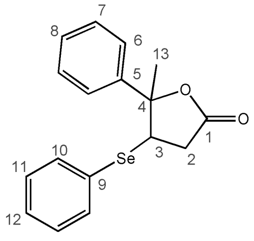
(*E*)-4-Phenylpent-3-enoic acid (11)[17]



2-Phenylpropanal (10 mmol, 1.34 g) and malonic acid (10 mmol, 1.04 g) was mixed thoroughly with chromatography grade silica (200 mesh, 1 g) and the resulting powder in a microwave tube was subjected to microwave irradiation (300 W, 50°C, 10 min). The reaction mixture was allowed to cool to room temperature and extracted with dichloromethane (30 mL). The solvent was removed under reduced pressure the compound was purified by flash chromatography eluting with petroleum ether:ethyl acetate:acetic acid (90:8:2).[18]

White solid (689 mg, 41%); m.p. = 56–58°C; IR (film): $\nu_{\max} = 3583$, 3055, 2360, 2341, 1699, 1444, 1392, 1287, 939, 818, 748, 696, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.41–7.45$ (2H, m, H-7,11), 7.32–7.37 (2H, m, H-8, 10), 7.26–7.29 (1H, m, H-9), 5.96 (1H, td, *J* 7.0, 1.4 Hz, H-3), 3.34 (2H, d, J 7.2 Hz, H-2), 2.13 (3H, s, H-5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 178.2$ (C-1), 142.9 (C-6), 138.7 (C-4), 128.8 (C-8, 10), 128.3 (C-9), 125.8 (C-7, 11), 118.4 (C-3), 34.2 (C-2), 16.3 (C-5) ppm; MS: *m*/*z*(%): 176 (M^+44), 131 (100), 91 (38); HRMS $C_{11}H_{12}O_2$: found 176.0830, calcd. 176.0837.

Dihydro-5-methyl-5-phenyl-4-(phenylselenyl)furan-2(3H)-one (12)



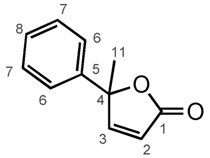
To a solution of diselenide (0.6 mmol) in acetonitrile (10 mL) (*E*)-4-phenylbut-3-enoic acid (1.2 mmol) was added, followed by bis(trifluoroacetoxy)iodobenzene (0.6 mmol) and the mixture stirred under argon at room temperature until TLC showed no remaining starting material. The solvent was then evaporated under reduced pressure and the residue was purified immediately by flash column chromatography eluting with ethyl acetate : light petroleum (2:8) to yield the addition products.

IR (film): $\nu_{max} = 3016, 2918, 2860, 1608, 1472, 1375, 1037, 835, 687$ cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.37$–7.43 (4H, m, H-Ar), 7.15–7.30 (6H, m, H-Ar), 3.95 (1H, t, *J* 7.5 Hz, H-3), 2.85 (1H, dd, *J* 18.0, 7.8 Hz, H-2a), 2.70 (1H, dd, *J* 18.0, 7.3 Hz, H-2b) ppm; ^{13}C NMR (63 MHz, CDCl$_3$): $\delta = 174.2$ (C-1), 143.2 (C-5), 134.9 (2C, C-10), 129.5 (2C, C-11), 128.7 (2C, C-7), 128.5 (C-12), 128.1 (C-8), 127.7 (C-9) 124.3 (2C, C-6), 89.0 (C-4), 48.2 (C-3), 37.8 (C-2), 25.7 (C-13) ppm; MS: *m/z*(%): 332 (M$^+$, 8), 314 (20), 234 (10), 184 (26), 159 (56), 131 (100), 103 (35), 91 (9), 77 (70); HRMS $C_{17}H_{16}O_2Se$: found 332.0314, calcd. 332.0316.

General Procedure for the Catalytic Reaction

To a solution of diphenyl diselenide (5 mol%, 3.4 mg, 0.01 mmol) in acetonitrile (3 mL) was added the β,γ-unsaturated acid (0.22 mmol), followed by bis(trifluoroacetoxy)iodobenzene (100 mg, 0.23 mmol) and the mixture stirred under argon at room temperature until TLC showed no remaining starting material. The solvent was then evaporated under reduced pressure and the residue was purified immediately by flash column chromatography eluting with ethyl acetate : light petroleum (2:8) to yield the cyclization products.

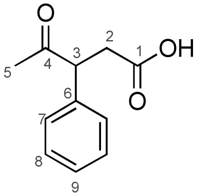
5-Methyl-5-phenylfuran-2(5H)-one (13)[19]



^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.57$ (1H, d, *J* 5.5 Hz, H-3), 7.20-7.40 (5H, m, H-6,7,8), 5.98 (1H, d, *J* 5.5 Hz, H-2), 1.78 (3H, s, H-11) ppm; ^{13}C NMR (63 MHz, CDCl$_3$): $\delta = 172.4$ (C-1), 160.4 (C-3), 139.3 (C-5), 128.9 (2C, C-7), 128.4 (C-8), 124.8 (2C, C-6), 119.4 (C-2), 88.9 (C-4), 26.4 (C-11) ppm.

4-Oxo-3-phenylpentanoic acid (14)[20]

^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.20$–7.40 (5H, m, H-7,8,9), 4.10 (1H, dd, *J* 9.8, 4.7 Hz, H-3), 3.20 (1H, dd, *J* 17.4, 9.9 Hz, H-2a), 2.50 (1H,



dd, *J* 17.4, 4.7 Hz, H-2b), 2.05 (3H, s, H-5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 206.8$ (C-4), 177.8 (C-1), 142.9 (C-6), 128.9 (2C, C-7), 127.9 (2C, C-8), 127.3 (C-9), 54.6 (C-3), 36.7 (C-5), 28.8 (C-2) ppm.

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