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Seleno-Michael Reaction of Stable Functionalised Alkyl Selenols: A Versatile Tool for the Synthesis of Acyclic and Cyclic Unsymmetrical Alkyl and Vinyl Selenides

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Abstract. Seleno-Michael additions of stable functionalised primary alkyl selenols to activated alkenes and alkynes are described. In the presence of Al_2O_3, β-hydroxy-, β-amino-, and β-mercapto selenols react smoothly with electron-poor alkenes and alkynes to afford the corresponding unsymmetrical functionalised dialkyl- and alkyl-vinyl-selenides in good yield. The very mild conditions allow a broad range of selenols and Michael acceptors to be converted into the corresponding synthetically valuable seleno-Michael adducts, demonstrating high selectivity and excellent functional group tolerance. Hydroxy- and mercapto-substituted vinyl selenides were efficiently employed for the synthesis of functionalised 1,3-oxaselenolanes, 1,3-thiaselenolanes, and 1,4-thiaselenanes through intramolecular oxa- and thia-Michael additions. Furthermore, a NaH-promoted lactonization enables the synthesis of variously substituted 2-oxo-1,4-oxaselenanes from hydroxy-vinyl-selenides. Evaluation of thiol peroxidase-like properties of novel functionalised organoselenides demonstrated that they possess a remarkable catalytic antioxidant activity.

Keywords: Seleno-Michael; Selenols; Vinyl selenides; dialkyl selenides; antioxidants; Selenium

Introduction

Organoselenium compounds occupy a relevant position in chemical sciences, with broad application in organic synthesis,[1] materials science[2] and polymer chemistry.[3] In addition, selenium-containing organic molecules play an increasingly important role in biology and in medicinal chemistry,[4] since they possess antioxidant,[5] enzyme modulator,[6] anticancer,[7] and cells growth inhibitor[8] activities. Due to their unique properties, in the last decade organoselenides have attracted growing interest among organic chemists, biologists, and medicinal chemists. In this *scenario*, molecular complexity – measured by the extent of bond saturation (fraction of sp^3 hybridized carbons, Fsp^3) and the number of stereogenic centers – is of paramount importance and represents one of the key criteria in order to successfully develop new catalysts and biologically active drug candidates.[9]

However, although several methods for the synthesis of symmetrical dialkyl, diaryl, and divinyl selenides and diselenides have been reported,[10,11] the synthesis of polyfunctionalised unsymmetrical dialkyl and alkyl-vinyl selenides remains a significant challenge. In addition, owing to the use of harsh conditions, a number of synthetic procedures are not tolerant of several functional groups, thus further limiting the diversity of organoselenides available. The development of a new, easy, general, and versatile method to access differently functionalised and substituted dialkyl and alkyl vinyl selenides with high molecular complexity would be, therefore, particularly interesting; enabling to explore new chemical space and enlarge the existing catalysts and drugs libraries.

Among unsymmetrical organoselenides, an interesting class is represented by β-seleno carbonyl compounds, which behave as enone β-anion synthons.[12] The seleno-Michael addition is a versatile tool to access synthetically useful arylseleno carbonyl derivatives. Furthermore, the seleno-Michael reaction is also important for the synthesis of materials and bioactive molecules. For example, this conjugate addition has been applied for the functionalization of selenium containing dynamic polymers.[13] The key step of the stereoselective synthesis of 4'-selenonucleosides with antiviral activity is represented by a seleno-Michael addition.[14] β-Arylseleno carbonyl compounds are commonly prepared by addition of arylselenolates, often generated *in situ* upon treatment of the corresponding diselenides with Zn/$RuCl_3$,[15] MeMgBr,[16] In-Me_3SiCl,[17] or $NaBH_4$,[18,19] to α,β-unsaturated carbonyl compounds. Alternative ways to access β-phenyseleno carbonyl compounds rely on the reactivity of activated alkenes and alkynes with PhSeZnCl[20] or with a phenylselenium borane, such as PhSeBpin.[12,21] Additionally, a very limited number of examples describe the use of benzeneselenol as a Michael donor in conjugate additions to α,β-unsaturated carbonyl compounds.[22] Ceric ammonium nitrate (CAN),[23] alkaloids,[24] and β-cyclodextrins[25] are the most commonly used catalysts or promoters.

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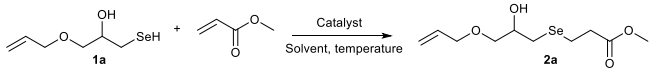
However, while the synthesis and the reactivity of β-arylseleno carbonyl compounds have been extensively studied, to the best of our knowledge β-alkylseleno analogues have never been reported and the reactivity of alkyl selenols with activated alkenes or alkynes remains unexplored. Furthermore, thia-Michael additions of alkyl thiols to electron-poor olefins have been widely studied and applied in organic synthesis.[26] On the other hand, the seleno-Michael reaction of functionalised alkyl selenols has never been described, despite it would represent a powerful tool for the formation of new C-Se bonds.

Recently, we reported a convenient procedure to achieve stable β-hydroxy-, β-amino-, and β-mercapto-alkyl selenols through the ring opening of epoxides, aziridines, and thiiranes with $(Me_3Si)_2Se$.[27] Such alkyl selenols can be easily reacted with electrophiles, such as alkyl halides, strained heterocycles, and acyl chlorides to afford the corresponding functionalised selenides under very mild conditions.[27] To further study the reactivity and the chemical behaviour of alkyl selenols, we wished to investigate whether novel unsymmetrical functionalised dialkyl and alkyl vinyl selenides could be synthesized through a conjugate addition, involving suitable functionalised alkyl selenols and electron poor alkenes and alkynes. In this communication, we report the synthesis and the reactivity of novel functionalised unsymmetrical dialkyl- and alkyl-vinyl-selenides, achieved through an easy, versatile, and mild seleno-Michael addition of β-hydroxy-, β-amino-, and β-mercapto selenols to electron-poor alkenes and alkynes.

Results and Discussion

We commenced our studies by establishing the conditions required to promote the conjugate addition of the β-hydroxy selenol **1a**[27] to methyl acrylate (Table 1). Several reaction conditions and catalysts were investigated, including organic or inorganic bases, Lewis acids, and *on water* conditions. Although the tested inorganic bases were unsuccessful in promoting this reaction (Table 1, entries 1-2), the desired addition product could be achieved in rather good yield by using a slight excess of Et_3N in dichloromethane (entry 3). A comparable yield was obtained when using a large eccess of amine (entry 4).

Table 1: Optimisation of the seleno-Michael addition of β-hydroxy selenol **1a** to methyl acrylate.



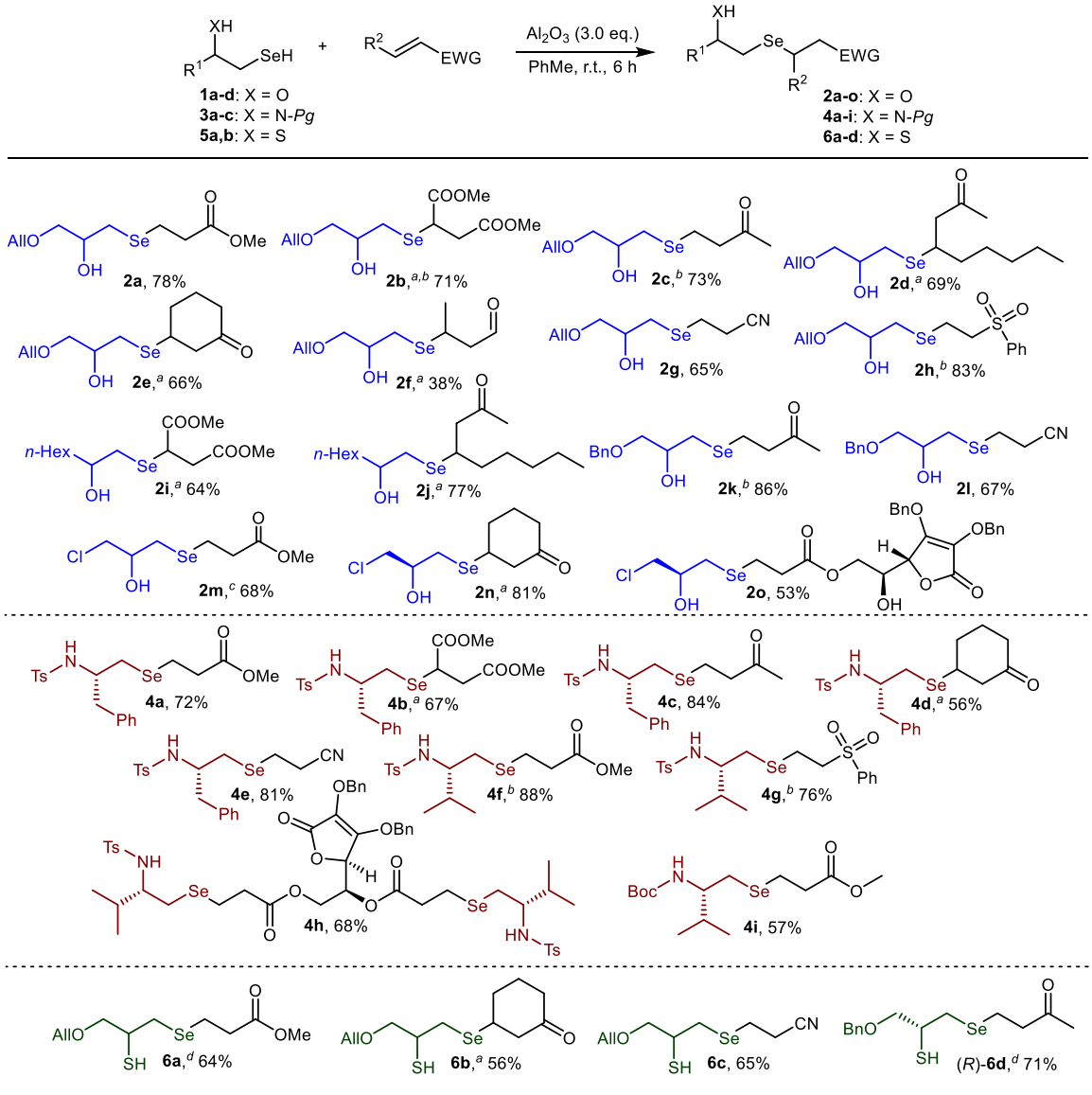
Entry	Catalyst (Equiv.)	Solvent, temp.	Yield (%)	Entry	Catalyst (Equiv.)	Solvent, temp.	Yield (%)
1	Cs_2CO_3 (1.0)	DMF, 0°C to r.t.	26	8	Al_2O_3 (1.0)	PhMe, 70°C	16
2	CsOH (1.0)	THF, 0°C to r.t.	< 5	9	Al_2O_3 (2.0)	PhMe, r.t.	59
3	Et_3N (1.2)	CH_2Cl_2, 0°C to r.t.	61	**10**	**Al_2O_3, (3.0)**	**PhMe, r.t.**	**78[b]**
4	Et_3N (3.0)	CH_2Cl_2, 0°C to r.t.	63	11	Al_2O_3, (3.0)	THF, r.t.	24
5	$BF_3{\cdot}Et_2O$ (1.0)	CH_2Cl_2, r.t.	< 5	12	Al_2O_3, (3.0)	CH_2Cl_2, r.t.	36
6	$FeCl_3$ (0.1)	CH_2Cl_2, r.t.	< 5	13	-	H_2O, r.t.	30
7	Al_2O_3 (1.0)	PhMe, r.t.	43	14	-	H_2O, 100°C	46

[a]Yields referred to isolated product. [b]Use of 4.0 eq. of Al_2O_3 gave comparable yield.

Since Lewis acids are widely used for effecting Michael addition reactions, we reasoned that a seleno-Michael addition also could occur in the presence of a suitable Lewis acid. Although the rather aggressive boron trifluoride diethyl etherate and iron (III) chloride were not effective (Table 1, entries 5-6) and led mainly to the formation of the diselenide arising from the oxidation of **1a**, we were delighted to discover that β-hydroxy selenol **1a** reacted with methyl acrylate in the presence of Al_2O_3 (1.0 eq.) in toluene at room temperature to yield the desired hydroxy-substituted selenide **2a** in 43% yield (Table 1, entry 7). We found that higher reaction temperatures (entry 8) were detrimental to the reaction. Interestingly, significant yields improvements were observed when performing the reaction in the presence of an eccess of Al_2O_3 at room temperature in toluene (entries 9, 10). In our hands, the optimal reaction conditions proved to be the use of 3.0 eq. of Al_2O_3 in toluene at ambient temperature (entry 10), enabling the selective formation of the desired selenide **2a** in good yield, under very mild conditions. Further excess of Al_2O_3 (4.0 eq.) and evaluation of other solvents (entries 11 and 12) gave no yields improvement. Furthermore, the *on water* reaction between hydroxy selenol **1a** and methyl acrylate was also tested.[20,25] Interestingly, under these mild catalyst free conditions **2a** was formed, albeit in lower yields with respect to the use of Al_2O_3/PhMe system (entries 13-14).

Having established optimal conditions for effective seleno-Michael addition of alkyl selenols (Table 1, entry 8), we proceeded to explore the scope of this methodology by using a wide range of electron-deficient olefins and β-functionalised selenols, conveniently achieved through the ring opening reaction of strained heterocycles with $(Me_3Si)_2Se$.[27] Selenium-containing bis-ester **2b** and hydroxy substituted γ-keto-selenide **2c** were efficiently obtained through a clean conjugate addition of **1a** to dimethyl fumarate and methyl vinyl ketone, respectively (Scheme 1). Interestingly, also sterically more demanding Michael acceptors, such as 3-nonen-2-one and 2-cyclohexen-1-one, proved to be reactive under these conditions, allowing to access the functionalised γ-keto-selenides **2d** and **2e**, albeit with a slight reduction in yield. Furthermore, crotonaldehyde, acrylonitrile, and phenyl vinyl sulfone could also be used in this conjugate addition to yield the desired β- seleno- aldehyde **2f**, nitrile **2g**, and sulfone **2h**, respectively (Scheme 1).

Having demonstrated that a variety of electron-deficient alkenes could be employed in this seleno-Michael addition, we therefore explored the scope of this reaction with respect to differently substituted β-hydroxy selenols. The hydroxy substituted selenol **1b** (R^1 = *n*-Hexyl), bearing a saturated alkyl chain could be employed in this procedure (Scheme 1). The reaction of **1b** with dimethyl fumarate and 3-nonen-2-one led to the formation of the functionalised selenium containing bis-ester **2i** and of the hydroxy γ-ketoselenide **2j**, having two linear alkyl substituents (Scheme 1). 1,2-Hydroselenoalcohols bearing useful but labile moieties, such as benzylglycidol- and epichlorohydrin- derivatives **1c** (R^1 = CH_2OBn) and **1d** (R^1 = CH_2Cl), were successfully converted into the corresponding functionalised unsymmetrical selenides **2k**,**l**



[a]Mixture of diastereoisomers was formed (see ESI for details). [b]Reaction carried out using Et_3N in CH_2Cl_2 gave the product in comparable yield. [c]Reaction carried out using Et_3N in CH_2Cl_2 afforded the product in 34% yield and a mixture of side-products was formed. [d]Et_3N/CH_2Cl_2 conditions led to poor seleno-Michael vs thia-Michael selectivity and a mixture of products was formed.

Scheme 1: Scope of the seleno-Michael addition of substituted β-hydroxy-, β-amino-, and β-mercapto- selenols to electron-deficient alkenes.

and **2m**,**n**, by a selective conjugate addition to suitable activated alkenes (Scheme 1).

In order to highlight the potential use of this mild procedure, we applied it to the synthesis of the densely functionalised selenide **2o**, bearing the labile L-ascorbic acid core and the chlorinated side chain. Treatment of enantioenriched 1,2-hydroselenoalcohol (*S*)-**1d** with 6-*O*-L-ascorbyl acrylate 2,3-dibenzyl ether gave **2o** through a clean seleno-Michael reaction.

To further enlarge the scope of this reaction we then focused on β-aminoselenols **3a-c**.[27] A wide variety of substituted enantioenriched *N*-Tosyl and *N*-Boc aminoselenides bearing ester (**4a**,**b**, **4f**, **4i**), keto (**4c**,**d**), cyano (**4e**), and sulfone (**4g**) functionalities were smoothly achieved from the corresponding 1,2-aminoselenols and suitable electron-deficient alkenes. Interestingly, chiral *N*-Tosyl amino-selenide **4h**, containing four controlled stereogenic centers, was efficiently obtained from 1,2-hydroselenoamine **3b** and the natural product-derived 2,3-*O*-dibenzyl-5,6-*O*-L-ascorbyl diacrylate and (Scheme 1).

This methodology was also applied to challenging β-mercaptoselenols **5a-b**, where a competing thio-Michael addition could occur. However, we were pleased to find that, owing to the higher nucleophilicity of selenols with respect to thiols, under the optimised Al_2O_3 mediated conditions the selenol functionality proved to be much more reactive than the thiol group. Therefore, variously substituted mercapto-selenides, bearing ester (**6a**), keto (**6b**,**d**), and cyano (**6c**) moieties were successfully obtained from the corresponding β-mercaptoselenols **5a** and **(*R*)-5b**. Although the formation of the product of double addition could not be completely avoided (5-10% of the double Michael adduct was formed), particularly noteworthy is the possibility to achieve a good selectivity in the seleno-Michael addition with respect to the competing thio-Michael reaction. The presence of a free thiol functionality offers the possibility to further functionalise selenides **6a-d**. To showcase that these class of molecules could be easily functionalised, compound **7** was obtained in good yields by treatment of mercapto-substituted γ-ketoselenide **6d** with

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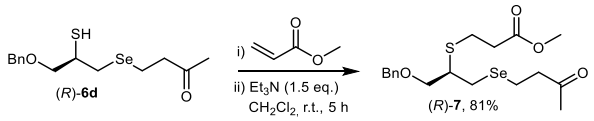
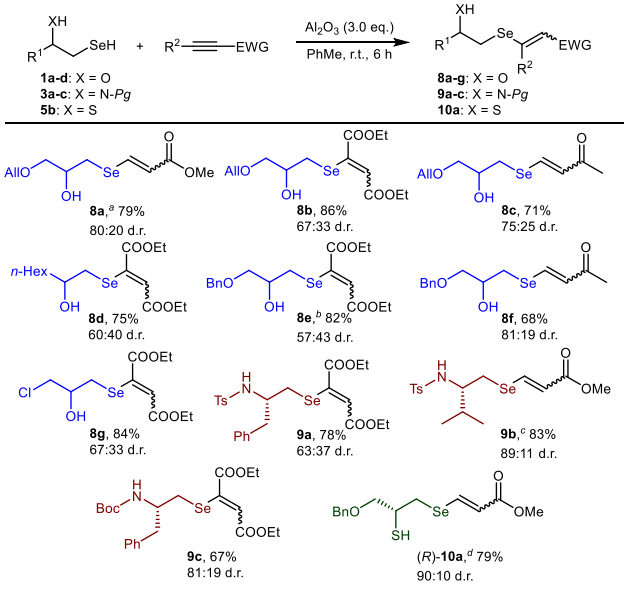
methyl acrylate in the presence of Et_3N (Scheme 2). Notably, this route allows to functionalise the SeH and the SH moieties – often characterized by a similar and competitive reactivity – with two different Michael acceptors.



Scheme 2: Double selective functionalization of β-mercapto selenols with different Michael acceptors.

Having developed a selective and mild procedure[28] to synthesise unsymmetrical dialkyl selenides exploiting the reactivity of selenols with electron-deficient alkenes, we wished to extend the scope to include activated alkynes. This route would allow direct access to novel unsymmetrical functionalised alkyl-vinyl selenides.

Among organoselenium compounds, vinyl selenides are arguably one of the most versatile and interesting classes because of their wide use in stereoselective reactions.[29] However, despite several methods have been developed for their synthesis,[11] the use of transition metals and the harsh conditions are the main drawbacks of the existing methodologies. Therefore, we sought to develop a novel mild procedure to achieve highly functionalised vinyl selenides from alkyl selenols and activated alkynes. Results of this investigation are reported in the Scheme 3.



[a]Reaction carried out using Et_3N in CH_2Cl_2 gave the product in 53% yield and comparable d.r. [b]Reaction carried out using Et_3N in CH_2Cl_2 gave the product in 58% yield and comparable d.r. [c]Reaction carried out using Et_3N in CH_2Cl_2 gave the product in 62% yield and comparable d.r. [d]Et_3N/CH_2Cl_2 conditions led to poor seleno-Michael *vs* thia-Michael selectivity and a mixture of products was formed. d.r. (*Z*/*E* ratio) was determined by ^1H NMR.

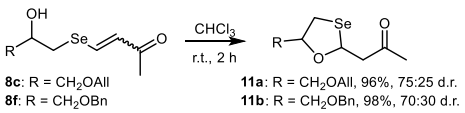
Scheme 3: Scope of seleno-Michael addition of substituted β-hydroxy-, β-amino- and β-mercapto-selenols to electron-deficient alkynes.

We were pleased to find that, under the above reported Al_2O_3-promoted conditions, 1,2-hydroselenoalcohol **1a** reacted smoothly with various activated alkynes, such as methyl propiolate, 3-butyn-2-one, and diethyl acetylenedicarboxylate, to afford the corresponding seleno-Michael products (**8a-c**). Hydroxy substituted alkyl-vinyl selenides bearing ester (**8a**,**b**) and keto (**8c**) functionalities were achieved in good yields and moderate diastereoselectivity (see Scheme 3 and ESI for *Z*/*E* ratio). Differently substituted β-hydroxy selenols (**1b-d**), including the labile epichlorohydrin derivative **1d**, performed well under these conditions, allowing to access a variety of β-hydroxy-alkyl-vinyl selenides bearing different functionalities (**8d-g**).

Furthermore, also chiral *N*-Tosyl or *N*-Boc 1,2-hydroselenoamines **3** and 1,2-mercaptoselenol **5b** were successfully converted into the corresponding functionalised *N*-protected amino- and mercapto-substituted alkyl-vinyl selenides **9a-c** and **10a**, upon treatment with acetylenedicarboxylate and methyl propiolate (Scheme 3). Moderate to good diastereoselectivity was observed.

While the *E*/*Z* configuration of disubstituted selenoalkenes **8a**,**c**,**f**, **9b**, and **10a** could be easily assigned by measuring the ^3J(H,H), the determination of the alkene geometry resulted more challenging for trisubstituted derivatives **8b**,**d**,**e**,**g**, **9a**,**c**. For trisubstituted selenoalkenes the configuration was assigned on the basis of vicinal ^{1}H-^{77}Se coupling constants, ^{77}Se NMR chemical shifts, and nOe spectra (see ESI for details). The typical *transoid* ^3J(H,Se) of *Z* isomers is larger than the *cisoid* ^3J(H,Se) of *E* isomers (Table S2 and Figure S3, ESI).[30] Furthermore, quite huge differences were found about the ^{77}Se NMR chemical shift of *Z* and *E* diastereoisomers of vinyl selenides. The ^{77}Se NMR chemical shift of *Z* diastereoisomers resulted shifted downfield (up to 100 ppm) with respect to the resonance frequency of the ^{77}Se nucleus of *E* diastereoisomers. The presence of 1,5 intramolecular chalcogen bonding interactions (IChBs),[31] involving the Se atom and the carbonyl oxygen, reasonably accounts for the observed deshielding effect (Figure S2 and S4, ESI).[32]

Intriguingly, hydroxy substituted α,β-unsaturated γ-selenoketones **8c**,**f** proved to be rather unstable in slightly acidic solvents, such as chloroform, where an intramolecular oxa-Michael reaction led smoothly to the formation of the corresponding ring closure products **11a**,**b** (Scheme 4). The progress of this mild cyclization reaction could be easily monitored by ^{1}H NMR spectroscopy, using $CDCl_3$ as the solvent (Figure 1). Nonetheless, selenoketones **8c**,**f** demonstrated a high stability in neutral solvents (i.e. diethyl ether or toluene) where no formation of the corresponding 1,3-oxaselenolanes was observed.



Scheme 4: Synthesis of functionalised 1,3-oxaselenolanes **11a,b** from hydroxy-substituted alkyl-vinyl selenides **8c,f**.

Interestingly, the α,β-unsaturated γ-selenoester **8a** did not undergo the expected intramolecular oxa-Michael reaction under these conditions. Attempts to promote the

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ring closure reaction by using acids (Al_2O_3, $BF_3{\cdot}Et_2O$, HCl) or bases (Et_3N, KOH, NaH) were unsuccessful. The same behaviour was observed for the amino substituted analogue **9b**. Contrarily, owing to the strong nucleophile character of the mercapto moiety, α,β-unsaturated γ-selenoester **10a** provided access to disubstituted 1,3-thiaselenolane **12a**, through a facile intramolecular thia-Michael reaction, occurring in the presence of Et_3N (Scheme 5, equation *a*).

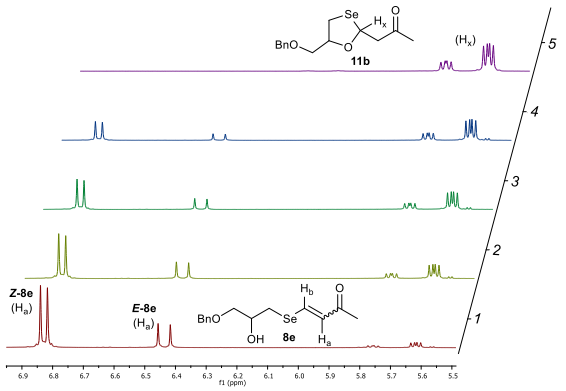
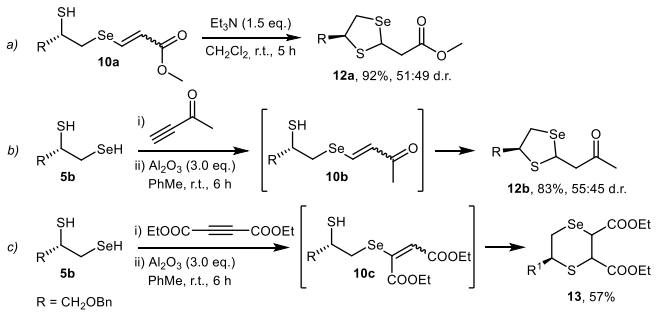


Figure 1: ^1H NMR ($CDCl_3$) monitored intramolecular oxa-Michael ring closure of hydroxy vinyl selenide **8e** giving the 1,3-oxaselenolane **11b**. 1. Reaction time: 5 min (**8e**:**11b** = 90:10); 2. Reaction time: 15 min (**8e**:**11b** = 65:35); 3. Reaction time: 30 min (**8e**:**11b** = 48:52); 4. Reaction time: 60 min (**8e**:**11b** = 30:70); 5. Reaction time: 90 min (**8e**:**11b** < 1:99).

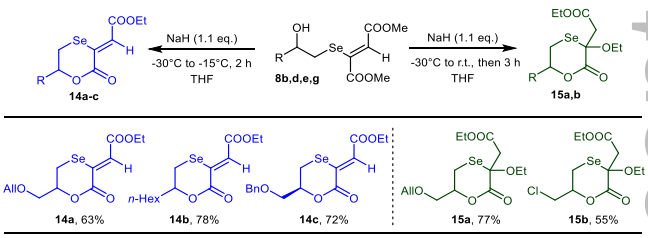


Scheme 5: Synthesis of functionalised 1,3-thiaselenolanes **12a,b** and 1,4-thiaselenanes **13**.

To further explore the versatility of these double hetero-Michael reactions, we considered their application to the synthesis of differently substituted sulfur- and selenium-containing heterocycles of various ring sizes. We found that the reaction of β-mercaptoselenol (*R*)-**5b** with 3-butyn-2-one, led straightforwardly to the disubstituted 1,3-thiaselenolane **12b** in good yield, through a one pot process involving a seleno-Michael and a thia-Michael sequence (Scheme 5, equation *b*). All attempts to isolate the plausible intermediate **10b** were unsuccessful, thus confirming the aforementioned higher reactivity of α,β-unsaturated γ-selenoketones with respect to the corresponding selenoesters. Similarly, the trisubstituted thiaselenane **13** was easily obtained in rather good yield from **5b** and a double activated Michael acceptor, such as the diethyl acetylenedicarboxylate, exploiting the reactivity of the diester intermediate **10c** (Scheme 5, equation *c*).

Prompted by these findings, to further demonstrate the versatility and the synthetic utility of functionalised alkyl vinyl selenides bearing two ester groups, we sought to employ this class of organoselenium compounds for the construction of unsaturated selenium-containing δ-lactones. In addition to their occurrence in various pharmacologically relevant molecules,[33] chalcogen-containing six-membered heterocycles are useful in organic synthesis[34] and in medicinal chemistry.[14,35] Whilst sulfurated derivatives have been widely investigated for their properties, to the best of our knowledge, selenium-containing analogues have received less attention.[36] The paucity of such studies could be ascribed to the lack of methodologies to access these molecules, thus we sought to address this by developing new synthetic routes.

On the basis of our findings about the reactivity of functionalised selenoalkenes, we envisaged hydroxy substituted vinyl selenides as possible precursors of 1,4-oxaselenane derivatives. Therefore, we evaluated whether unsaturated selenium-containing δ-lactone **14a** could be accessed from hydroxy vinyl selenide (*Z*)-**8b** through a base promoted intramolecular lactonization reaction. Although Et_3N and KOH were unsuccessful in promoting the desired cyclisation, we found that (*Z*)-**8b** cyclised in the presence of NaH in THF at low temperature, to yield the desired unsaturated 2-oxo-1,4-oxaselenane **14a** (Scheme 6). Differently substituted and further functionalisable derivatives **14b-c** could be easily achieved under these conditions from vinyl selenides (*Z*)-**8d**,**e** (Scheme 6). Furthermore, the reaction temperature was found to be crucial to isolate α,β-unsaturated derivatives **14**. Indeed, when the reaction of (*Z*)-**8b**,**g** with NaH was allowed to warm to room temperature, we observed exclusive formation of 2-oxo-1,4-oxaselenanes **15a**,**b**. It seems reasonable that compounds **15** can be formed through the oxa-Michael addition of EtO^-, displaced in the NaH promoted cyclisation of vinyl selenides **8**, and α,β-unsaturated lactones **14**.



Scheme 6: Synthesis of functionalised 2-oxo-1,4-oxaselenanes **14** and **15** from hydroxy substituted vinyl selenides

Having disclosed novel procedures for the synthesis of unreported functionalized cyclic and open-chain selenides, we next preliminary evaluated their catalytic antioxidant activity as GPx mimics. Therefore, the thiol peroxidase-like properties of selected compounds were determined by using both the DTT oxidation text[5a,b,37,38] and the GSH/GR coupled assay.[5a,37,38] Results of this investigation are reported in Figures 2 and 3. All the tested compounds exhibited remarkable GPx-like activity. Interestingly, β-seleno nitriles **2g**,**l** and 2-oxo-1,4-oxaselenane **14a** proved to be the more active catalysts according to both tests. The higher GPx-like activity of cyclic selenides with respect to

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their acyclic analogues is in line with results of previous reports.[37b] These findings are summarized in the Table 2 where T_{50} values, determined by DTT test and GSH/GR coupled assay, are reported. Intriguingly, β-hydroxy vinyl selenide **8b** displayed poor catalytic activity with respect to similar saturated derivative. This behaviour might be ascribed to the presence of 1,4 or 1,5 IChB interactions, involving the selenium atom and one of the two carbonyl groups.[5a]

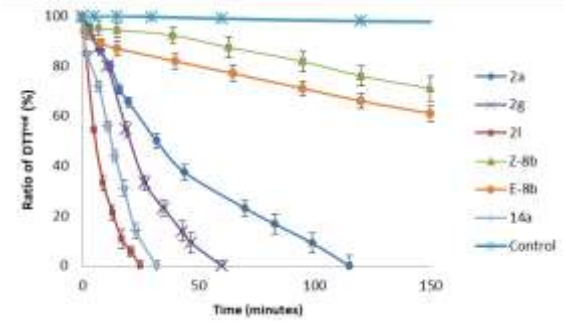

Figure 2: Oxidation of DTT_{red} with H_2O_2 in the presence of Se-containing catalysts (1 mol%). Reaction conditions: $[DTT_{red}]_0$ = 0.14 M, $[H_2O_2]_0$ = 0.14 M, [catalyst] = 0.014 M, CD_3OD (0.6 mL). In the control experiment the reaction was run with no catalyst. The mean ± SD values of three separate experiments are reported.

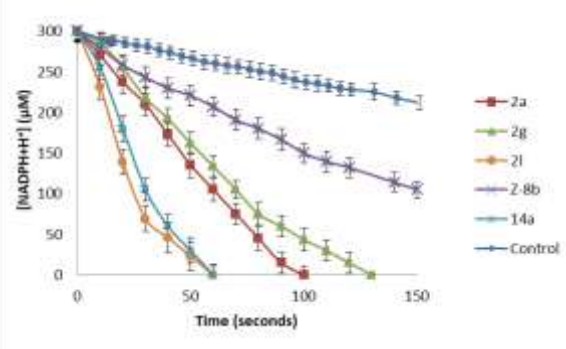

Figure 3: NADPH-coupled GPx assay. Reaction conditions: $[NADPH]_0$ = 0.3 mM, $[GSH]_0$ = 1.0 mM, $[H_2O_2]_0$ = 2.5 mM, [GR] = 4 units per mL, [catalyst] = 0.1 mM in pH 7.4 phosphate buffer at ambient temperature. The mean ± SD values of three separate experiments are reported.

Table 2. Thiol-peroxidase like activity of functionalized organoselenides according DTT and GSH/GR methods

Entry	Compound	DTT (T_{50})[a,b]	GSH/GR (T_{50})[a,c]
1	**2a**	1920 (±187)	46 (±8)
2	**2g**	1380 (±92)	53 (±6)
3	**2l**	390 (±36)	18 (±4)
4	***Z*-8b**	23400 (±1160)	101 (±16)
5	***E*-8b**	21360 (±1082)	88 (±12)
6	**14a**	750 (±78)	25 (±4)

[a]T50 is the time required, in seconds, to reduce the initial thiol concentration with 50% after the addition of H_2O_2; data in parenthesis are the experimental error. [b]DTT oxidation was monitored by the mean of ^{1}H NMR spectroscopy; [c]NADPH consumption was monitored by UV spectroscopy (340 nm).

Conclusion

In conclusion, the seleno-Michael addition of stable β-hydroxy-, β-amino-, and β-mercapto-selenols to electron deficient alkenes and alkynes has been described, unveiling a general, selective, and mild method for the synthesis of novel variously functionalised dialkyl and alkyl-vinyl selenides. The reaction scope was found to be broad, with good functional-group tolerance demonstrated over a range of selenols and electron-deficient alkenes and alkynes. Notably, because of the very mild conditions, the methodology enables the selective functionalization of the selenol moiety in the presence of potentially competitive hydroxy-, amino-, and especially mercapto groups. Furthermore, vinyl selenides bearing hydroxy or the mercapto moieties can be efficiently employed for the synthesis of functionalised five- and six-membered selenium-containing heterocycles. This study can provide an important contribution to the methodologies for the synthesis of densely functionalised acyclic and cyclic organoselenides that, taking into account the growing interest towards organoselenium compounds, will likely find wide application for the synthesis of more complex selenium-containing molecules. Furthermore, we found that the nature of functional groups close to the selenium atom strongly influences the catalytic antioxidant properties of organoselenides, thus opening new possibilities for the synthesis of antioxidants with enhanced activity.

Experimental Section

General. All reactions were carried out in an oven-dried glassware under inert atmosphere (N_2). Solvents were dried using a solvent purification system (Pure-Solv™). All commercial materials were purchased from various commercial sources and used as received, without further purification. Flash column chromatography purifications were performed with Silica gel 60 (230-400 mesh). Thin layer chromatography was performed with TLC plates Silica gel 60 F_{254}, which was visualised under UV light, or by staining with an ethanolic acid solution of *p*-anisaldehyde followed by heating. High resolution mass spectra (HRMS) were recorded by Electrospray Ionization (ESI). GC-MS was performed on a Varian CP 3800/Saturn 2200 instrument.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or toluene-d_8 using Mercury 400, Bruker 400 Ultrashield, and Varian Gemini 200 spectrometers operating at 400 MHz and 200 MHz (for ^{1}H), 100 MHz and 50 MHz (for ^{13}C). ^{77}Se NMR spectra were recorded using Bruker 400 Ultrashield and Varian Gemini 200 spectrometers, operating at 76 MHz and 38 MHz, respectively. NMR signals were referenced to nondeuterated residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H, 77.0 ppm for ^{13}C; Toluene-d_8: 2.09 ppm for ^{1}H, 20.4 ppm for ^{13}C). Diphenyl diselenide $(PhSe)_2$ was used as an external reference for ^{77}Se NMR (δ = 461 ppm). Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz), rounded to the nearest 0.1 Hz. ^{1}H NMR data are reported as follows: chemical shift,

integration, multiplicity (s = singlet, d = doublet, t = triplet, ap d = apparent doublet, m = multiplet, dd = doublet of doublet, bs = broad singlet, bd = broad doublet, ecc.), coupling constant (*J*) or line separation (ls), and assignment. Where reported, NMR assignments are made according to spin systems, using, where appropriate, 2D NMR experiments (COSY, HSQC, HMBC) to assist the assignment. β-Hydroxy-, β-amino-, and β-mercapto-selenols were synthesised from the corresponding epoxides, aziridines, and thiiranes, following a reported procedure.[27] 2,3-*O*-Dibenzyl-6-*O*-L-ascorbyl acrylate and 2,3-*O*-dibenzyl-5,6-*O*-L-ascorbyl diacrylate were prepared according to reported procedures.[28]

General Procedure for the synthesis of functionalised unsymmetrical dialkyl selenides. Neutral Al_2O_3 (61 mg, 0.60 mmol, 3.0 eq.) was added to a stirred solution of the β-functionalised selenol **1**, **3** or **5** (0.20 mmol, 1.0 eq.) and the α,β-unsaturated compound (0.24 mmol, 1.2 eq) in dry toluene (3 mL) at ambient temperature under inert atmosphere (N_2). The reaction mixture was stirred for the required time (see ESI for details), then diluted with Et_2O (5 mL) and filtered through a short pad of Celite. The Celite was washed with Et_2O (2 x 5 mL) and the solvent was removed *in vacuo*. The crude material was subjected to flash column chromatography to afford pure functionalised unsymmetrical selenides.

General Procedure for the synthesis of functionalised unsymmetrical alkyl vinyl selenides. Neutral Al_2O_3 (61 mg, 0.60 mmol, 3.0 eq.) was added to a stirred solution of the β-functionalised-selenol **1**, **3** or **5** (0.20 mmol, 1.0 eq.) and the α,β-unsaturated compound (0.24 mmol, 1.2 eq) in dry toluene (3 mL) at ambient temperature under inert atmosphere (N_2). The reaction mixture was stirred for 6 h, then diluted with Et_2O (5 mL) and filtered through a short pad of Celite. The Celite was washed with Et_2O (2 x 5 mL) and the solvent was removed *in vacuo*. The crude material was subjected to flash column chromatography to afford pure functionalized unsymmetrical alkyl-vinyl selenides.

General procedure for the synthesis of substituted oxaselenane derivatives. To a solution of β-hydroxy vinyl selenide **8b,d,e** (0.5 mmol, 1.0 eq.) in dry THF (5 mL) at -30°C under inert atmosphere (N_2) was portionwise added NaH (0.55 mmol, 1.1 eq.). The reaction mixture was stirred until complete consumption of the substrate (reaction progress monitored by TLC), keeping the reaction temperature below -15°C. Afterwards, saturated *aq*. NH_4Cl (3 mL) was added and the reaction was allowed to warm to room temperature. Then, the mixture was diluted with Et_2O (10 mL) and the organic phase was extracted with Et_2O (2 X 5 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (petroleum ether/ethyl acetate or Et_2O) to yield the desired 2-oxo-1,4-oxaselenane **14**. Compounds **15** were achieved under similar conditions, allowing the reaction mixture to warm to room temperature and then maintained under stirring for 3 h (see ESI for details).

GPx-like activity measurments. Glutathione peroxidase-like activity was evaluated following reported procedures.[5a,b, 37,38]

Full experimental details, products characterization and NMR spectra are reported in the Supplementary Information.

References

[1] a) E. J. Lenardão, C. Santi, L. Sancineto, *New Frontiers in Organoselenium Compounds*, Springer, New York, 2018; b) C. Viglianisi, C. Bonardi, E. Ermini, A. Capperucci, S. Menichetti, D. Tanini, *Synthesis* **2019**, DOI: 10.1055/s-0037-1610354 c) L. Liao, R. Guo, X. Zhao, *Angew. Chem. Int. Ed*. **2017**, *56*, 3201-3205; d) S. A. Shyshkanov, N. V. Orlov, *Chem. Eur. J*. **2016**, *22*, 15458-15467; e) M. E. Jung, F. Perez, C. F. Regan, S. W. Yi, Q. Perron, *Angew. Chem. Int. Ed*. **2013**, *52*, 2060-2062; f) F. Marini, S. Sternativo, *Synlett* **2013**, *24*, 11-19; g) T. Sohn, M. J. Kim, D. Kim, *J. Am. Chem. Soc*. **2010**, *132*, 12226-12227; h) A. J. Mukherjee, S. S. Zade, H. B. Singh, R. B. Sunoj, *Chem. Rev*. **2010**, *110*, 4357-4416.

[2] a) M. Gao, R. Wang, F. Yu, B. Li, L. Chen, *J. Mater. Chem. B*, **2018**, *6*, 6637-6645; b) P. F. Li, T. B. Schon, D. S. Seferos, *Angew. Chem. Int. Ed*. **2015**, *54*, 9361-9366; c) P. Liu, L. Kloo, J. Gardner, *ChemPhotoChem* **2017**, *1*, 363-368.

[3]a) J. Xia, T. Li, C. Lu, H. Xu, *Macromolecules* **2018**, *51*, 7435-7455; b) H. Xu, W. Cao, X. Zhang, *Acc. Chem. Res.* **2013**, *46*, 1647-1658.

[4] a) A. R. Patra, S. S. Roy, A. Basu, A. Bhuniya, A Bhattachariee, S. Hajra, U. H. Sk, R. Baral, S. Bhattacharya, *Sci. Rep.* **2018**, *8*, 2194-2206; b) I. A. Adedara, O. Owoeye, I. O. Awogbindin, B. O. Ajayi, J. B. Roch, E. O. Farombi, *Chem. Biol. Int.* **2018**, *296*, 105-116; c) V. Gandin, P. Khalkar, J. Braude, A. P. Fernandes, *Free Radic. Biol. Med*. **2018**, *127*, 80-97; d) A. Nuthanakanti, M. A. Boerneke, T. Hermann, S. G. Srivatsan, *Angew. Chem. Int. Ed*. **2017**, *56*, 2640-2644; e) S. Kumar, J. Yan, J. Poon, V. P. Singh, X. Lu, M. Karlsson Ott, L Engman, S. Kumar, *Angew. Chem. Int. Ed*. **2016**, *55*, 3729-3733; f) F. Yu, P. Li, G. Li, G. Zhao, T. Chu, K. Han, *J. Am. Chem. Soc*. **2011**, *133*, 11030-11033.

[5] *For a review see*: C. W. Nogueira, G. Zeni J. B. T Rocha, *Chem. Rev*., **2004**, *104*, 6255-6286 and references cited therein. For book capters see: F. V. Singh, T. Wirth, in *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments* (Eds. V. K. Jain, K. I. Priyadarsini), Royal Society of Chemistry, London, **2018**, chapter 3 and references cited therein; L. D. Carrol, M. J. Davies, in *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments* (Eds. V. K. Jain, K. I. Priyadarsini) Royal Society of Chemistry, London, **2018**, chapter 9 and references cited therein. *Inter alia*:

a) D. Tanini, A. Grechi, L. Ricci, S. Dei, E. Teodori, A. Capperucci, *New J. Chem*. **2018**, *42*, 6077-6083; b) D. Tanini, V. D'Esopo, D. Chen, G. Barchielli, A. Capperucci, *Phosphorus Sulfur Silicon Relat. Elem*. **2017**, *192*, 166-168; c) K. P. Bhabak, G. Mugesh, *Acc. Chem. Res*. **2010**, *43*, 1408-1419.

[6] a) A. Angeli, D. Tanini, A. Nocentini, A. Capperucci, M. Ferraroni, P. Gratteri, C.T. Supuran, *Chem. Commun*. **2019**, *55*, 648-651; (b) A. Angeli, D. Tanini, A. Capperucci, C. T. Supuran, *ACS Med. Chem. Lett*. **2017**, *8*, 1213-1217.

[7] a) J. B. T. Rocha, C. S. Oliveir, P. A. Nogara, in *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments* (Eds. V. K. Jain, K. I. Priyadarsini), Royal Society of Chemistry, London, **2018**, chapter 13; b) A. M. Diamond, in *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments* (Eds. V. K. Jain, K. I. Priyadarsini), Royal Society of Chemistry, London, **2018**, chapter 16; c) L. Wang, Z.Yang, J. Fu, H. Yin, K. Xiong, Q. Tan, H. Jin, J. Li, T. Wang, W. Tang, J. Yin, G. Cai, M. Liu, S. Kehr, K. Becker, H. Zeng, *Free Radic. Biol. Med*. **2012**, *52*, 898-908.

[8] a) F. V. Singh, T. Wirth, in *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments* (Eds. V. K. Jain, K. I. Priyadarsini), Royal Society of Chemistry, London, **2018**, chapter 3 and references cited therein; b) F. Nedel, V. F. Campos, D. Alves, A. J. A. McBride, O. A. Dellagostin, T. Collares, L. Savegnago, F. K. Seixas, *Life Sciences*, **2012**, *91*, 345-352.

[9] a) K. Hirata, M. Kotoku, N. Seki, T. Maeba, K. Maeda, S. Hirashima, T. Sakai, S. Obika, A. Hori, Y. Hase, *et al*., *ACS Med. Chem. Lett*., **2016**, *7*, 23-27; b) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem*. **2009**, *52*, 6752-6756; c) P. D. Leeson, B. Springthorpe, *Nature Rev. Drug Discov*. **2007**, *6*, 881-890.

[10] a) G. Mlostoń, A. Capperucci, D. Tanini, R. Hamera-Fałdyga, H. Heimgartner, *Eur. J. Org. Chem*. **2017**, 6831-6839; b) D. Tanini, A. Capperucci, A. Degl'Innocenti, *Eur. J. Org. Chem*. **2015**, 357-369; c) D. Singh, A. M. Deobald, L. R. S. Camargo, G. Tabarelli, O. E. D. Rodrigues, A. L. Braga, *Org. Lett.* **2010**, *12*, 3288-3291; d) A. Krief, W. Dumont, M. Robert, *Chem. Commun.* **2005**, 2167-2168.

[11] a) D. Alves, B. Goldani, E. J. Lenardão, G. Perin, R. F. Schumacher, M. W. Paixão, *Chem. Rec.* **2018**, *18*, 527-542; b) G. Perin, D. Alves, R. G. Jacob, A. M. Barcellos, L. K. Soares, E. J. Lenardão, *ChemistrySelect* **2016**, *2*, 205-258; c) G. Perin, E. J. Lenardão, R. G. Jacob, R. B. Panatieri, *Chem. Rev*. **2009**, *109*, 1277-1301; d) K. Sun, Z. Shi, Z. Liu, B. Luan, J. Zhu, Y, Xue, *Org. Lett*. **2018**, *20*, 6687-6690; e) A. L. Braga, E. F. Alves, C. C. Silveira, L. H. Andrade, *Tetrahedron Lett*. **2000**, *41*, 161-163.

[12] X. Sanz, C. M. Vogels, A. Decken, C. Bo, S. A. Westcott, E. Fernàndez, *Chem. Commun*. **2014**, *50*, 8420-8423.

[13] X. Pan, F. Driessen, X. Zhu, F. E. Du Prez, *ACS Macro Lett*. **2017**, *6*, 89-92.

[14] P. K. Sahu, G. Kim, J. Yu, J. Y. Ahn, J. Song, Y. Choi, X. Jin, J. H. Kim, S. K. Lee, S. Park, L. S. Jeong, *Org. Lett*. **2014**, *16*, 5796-5799.

[15] B. Movassagh, A. Tatar, *Synlett* **2007**, *12*, 1954-1956.

[16] A. Kamimura, H. Mitsudera, Y. Omata, K. Matsuura, M. Shirai, A. Kakehi, *Tetrahedron* **2002**, *58*, 9817-9826.

[17] B. C. Ranu, A. Das, *Adv. Synth. Catal*. **2005**, *347*, 712-714.

[18] G. Padilha, P. T. Birmann, M. Domingues, T. S. Kaufman, L. Savegnago, C. C. Silveira, *Tetrahedron Lett*. **2017**, *58*, 985-990.

[19] M. Yoshimatsu, J. Hasegawa, *J. Chem. Soc., Perkin Trans. 1* **1997**, 211-216.

[20] B. Battistelli, L. Testaferri, M. Tiecco, C. Santi, *Eur. J. Org. Chem*. **2011**, 1848-1851.

[21] M. G. Civit, X. Sanz, C. M. Vogels, C. Bo, S. A. Westcott, E. Fernàndez, *Adv. Synth. Catal*. **2015**, *357*, 3098-3103.

[22] a) D. H. Wadsworth, M. R. Detty, *J. Org. Chem*. **1980**, *45*, 4611-4615; b) M. Miyashita, A. Yoshikoshi, *Synthesis* **1980**, 664-666.

[23] C. M. Chu, S. Gao, M. N. V. Sastry, C. W. Kuo, C. Lu, J. T. Liu, C. F. Yao, *Tetrahedron* **2007**, *63*, 1863-1871.

[24] H. Pluim, H. Wynberg, *Tetrahedron Lett*. **1979**, *14*, 1251-1254.

[25] B. Srinivas, V. P. Kumar, R. Sridhar, V. P. Reddy, Y. V. D. Nageswar, K. R. Rao, *Helv. Chim. Acta* **2009**, *92*, 1080-1084.

[26] *For a recent review see*: P. Wadhwa, A. Kharbanda, A. Sharma, *Asian J. Org. Chem*. **2018**, *7*, 634-661. E. Obijalska, M. Pawelec, G. Mlostoń, A. Capperucci, D. Tanini, H. Heimgartner, *Eur. J. Org. Chem*. **2018**, 3716-3723, and references cited therein.

[27] D. Tanini, C. Tiberi, C. Gellini, P. R. Salvi, A. Capperucci, *Adv, Synth. Catal*. **2018**, *360*, 3367-3375.

[28] Control experiments were carried out by treating β-hydroxy-, β–mercapto-, and β-amino-diselenides with different reducing agents ($NaBH_4$, Rongalite®) to generate the corresponding alkyl selenolates, which were *in situ* reacted with various Michael acceptors (methyl acrylate, methyl fumarate, MVK, phenyl vinyl sulfone, and acetylenedicarboxylate). Under these conditions, complex mixtures of products were formed, thus demonstrating the advantages of this mild novel procedure.

[29] A. V. Martynov, V. A. Potapov, S. V. Amosova, N. A. Makhaeva, I. P. Beletskaya, L. Hevesi, *J. Organomet. Chem*. **2003**, *674*, 101-103. b) C. C. Silveira, P. C. S. Santos, A. L. Braga, *Tetrahedron Lett*. **2002**, *43*, 7517-7520.

[30] a) V. A. Potapov, V. N. Elokhina, L. I. Larina, T. I. Yaroshenko, A. A. Tatarinova, S. V. Amosova, *J. Organomet. Chem*. **2009**, *694*, 3679-3682; b) Y. Y. Rusakov, L. B. Krividin, N. V. Istomina, V. A. Potapov, S. V. Amosova, *Magn. Res. Chem*. **2008**, *46*, 979-985; c) H. Duddeck, *Prog. Nucl. Magn. Reson. Spectrosc*. **1995**, *27*, 1-323.

[31] a) D. J. Pascoe, K. B. Ling, S. L. Cockroft, *J. Am. Chem. Soc*. **2017**, *139*, 15160-15167; b) K. J. Szabo, H. Frisell, L. Engman, M. Piatek, B. Oleksyn, J. Sliwinski, *J. Mol. Struct*. **1998**, *448*, 21-28.

[32] a) K. Selvakumar, H. B. Singh, *Chem. Sci*., **2018**, *9*, 7027-7042; b) M. Iwaoka, S. Tomoda, *J. Am. Chem. Soc*. **1996**, *118*, 8077-8084.

[33] a) J. W. Kim, H. B. Park, B. Y. Chung, *Bull. Korean Chem. Soc.* **2006**, *27*, 1164-1170; b) H. Miyauchi, T. Tanio, N. Ohashi, *Bioorg. Med. Chem. Lett*. **1996**, *6*, 2377-2380.

[34] a) M. J Cook, in *Comprehensive Heterocyclic Chemistry* (Eds. A. R. Katrizky, C. W. Rees), Pergamon Press, Oxford, **1984**, Vol. 3, 943-994; b) J. V. Matlock, T. D. Svejstrup, P. Songara, S. Overington, E. M. McGarrigle, V. K. Aggarwal, *Org. Lett.* **2015**, *17*, 5044-5047 and references cited therein; c) S. J. Gharpure, D. Anuradha, J. V. K. Prasad, P. S. Rao, *Eur. J. Org. Chem*. **2015**, 86-90.

[35] a) K.-K. Tooulia, P. Theodosis-Nobelos, E. A. Rekka, *Arch. Pharm. Chem. Life Sci.* **2015**, *348*, 629-634; b) B. Han, J. L. Liu, Y. Huan, P. Li, Q. Wu, Z. Y. Lin, Z. F. Shen, D. L. Yin, H. H. Huang, *Chin. Chem. Lett.* **2012**, *23*, 297-300.

[36] a) A. Capperucci, C. Salles, S. Scarpelli, D. Tanini, *Phosphorus Sulfur Silicon Relat. Elem.* **2017**, *192*, 172-174; b) S. Menichetti, A. Capperucci, D. Tanini, A. L. Braga, G. V. Botteselle, C. Viglianisi, *Eur. J. Org. Chem*. **2016**, 3097-3102; c) V. A. Potapov, M. V. Musalov, E. V. Abramova, M.V. Musalova, Y. Y. Rusakov, S. V. Amosova, *Chem. Heterocycl. Compd*. **2014**, *49*, 1821-1826.

[37] a) M. Iwaoka, F. Kumakura, *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 1009-1017; b) F. Kumakura, B. Mishra, K. I. Priyadarsini, M. Iwaoka, *Eur. J. Org. Chem*., **2010**, 440-445.

[38] A. Angeli, D. Tanini, T. S. Peat, L. Di Cesare Mannelli, G. Bartolucci, A. Capperucci, C. Ghelardini, C. T. Supuran, F. Carta, *ACS Med. Chem. Lett*. **2017**, *8*, 963-968.

[39] D. Tanini, M. Gori, F. Bicocchi, M. Ambrosi, P. Lo Nostro, A. Capperucci, *Arkivoc, part **ii***, 2017, 407-420.

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FULL PAPER

First seleno-Michael Reaction of Stable Functionalised Alkyl Selenols: A new Tool for the Synthesis of Acyclic and Cyclic Unsymmetrical Alkyl and Vinyl Selenides

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