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Green solvents in organoselenium chemistry

--Manuscript Draft--

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Abstract:	Organoselenium chemistry involve unique methods for the preparation of reaction intermediates and biologically-relevant compounds. However, common methods frequently have drawbacks such as the use of halogenated volatile solvents, expensive catalysts systems and sophisticated experimental fittings. Therefore, sustainable organoselenium chemistry is developing. Here we review green solvent alternatives in organoselenium chemistry. We present the application of the ionic liquids and deep eutectic solvents in the synthesis of seleno-functionalized molecules under mild reaction conditions; the application of polyethylene glycol, glycerol and ethanol as a solvents; and organoselenium compounds as a starting materials for the preparation of ionic liquids.	
Suggested Reviewers:	<p>Claudio Santi, PhD Associate Professor, Universita degli Studi di Perugia claudio.santi@unipg.it Claudio Santi is an international expert in the organoselenium chemistry with rich experience in the application of the selenium catalyst as green reagents.</p> <p>Antonio Luiz Braga, PhD Universidade do Estado de Santa Catarina braga.antonio@ufsc.br Antonio Luiz Braga is international expert in the green organoselenium chemistry.</p>	
Response to Reviewers:	<p>Dear Prof. Robert Didier, Please consider our revised review entitled "The origin and current trends of the green organoselenium chemistry" for the publication in Environmental Chemistry Letters. I appreciate the interest that the editor and reviewers have taken in our manuscript and the constructive criticism they have given – all suggested changes clearly improved our manuscript. I am also including a point-by-point response to the reviewers in addition to the changes described in the manuscript. Answer on reviewers' comments:</p>	

Reviewer #1: The review article entitle The origin and current trends of the green organoselenium chemistry was carefully reviewed.
The presentation is poor and normal, I could not find extensive work in the review paper.
And also recent references are not considered. In each table proper references are missing.

Answer: A new literature survey which covers available literature from 2017 and 2018 is added in a review (all changes are highlighted yellow in the text). In addition, we have added proper references in all Schemes.

Reviewer #2: Dear Author,
it is a good work where, you prepered a series of PtnOm/CeO2 catalyts with n =1-4 and tested them in the CO oxidation reaction, and it was found that all catalyts provide full CO conversion at temperature above 180°C combining with a great thermostability.
But you used only one test to confirm the oxidation reaction and not use any tools to confirm the structure of a series of PtnOm/CeO2 catalyts with n =1-4 prepered, such as raman, FTIR, XRD and others.
I think this work need more measurements.

Answer: Our review is dealing with the application of the alternative solvents in the organoselenium area, so, as you can see, this comment is not related to our review and it is probably some technical error which happened during submission process.

Editorial remark: You are suggested to include a review of literature available for 2017 and 2018.

Answer: We have included literature data for 2017 and 2018 into text of a review (all changes are highlighted yellow).

With this revision, we have responded to all the comments made by Editor and Reviewers. We believe that revised review will now be acceptable for publication in Environmental Chemistry Letters.

Sincerely,
Marina Kostic

Corresponding author

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Green solvents in organoselenium chemistry

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Abstract

Organoselenium chemistry involve unique methods for the preparation of reaction intermediates and biologically-relevant compounds. However, common methods frequently have drawbacks such as the use of halogenated volatile solvents, expensive catalysts systems and sophisticated experimental fittings. Therefore, sustainable organoselenium chemistry is developing. Here we review green solvent alternatives in organoselenium chemistry. We present the application of the ionic liquids and deep eutectic solvents in the synthesis of seleno-functionalized molecules under mild reaction conditions; the application of polyethylene glycol, glycerol and ethanol as a solvents; and organoselenium compounds as a starting materials for the preparation of ionic liquids.

Keywords: green chemistry, ionic liquids, selenium.

1. Introduction

The increasing demands for meeting the criteria of the sustainable chemistry brought the need for reducing or completely eliminating the use of volatile and flammable organic compounds. Therefore, recently a number of different reaction media have been proposed as an alternative to the traditional volatile organic compounds (VOC). Among them, the ionic liquids (IL) and their

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4 analogues deep eutectic solvents (DES), as well as some bio-derived solvents have emerged as
5 promising choice due to the unique chemical and physical properties, recyclability, non-
6 flammability and eco-friendly nature (Sharifi et al. 2014, Azizi et al., 2016, Moura et al. 2017,
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8 Hu et al. 2018, Lu et al. 2018).
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12 The ionic liquids are salts in liquid state, composed solely of ions which are weakly coordinated
13 (**Figure 1**). An almost unlimited number of cation-anion combinations have led to the rapid
14 progress in the field of their design and synthesis. Since the basic physiochemical properties of
15 ionic liquids depend on both nature of cation and anion, the proper combination of the ionic-pair
16 elements has allowed synthetic chemists to create ionic liquids for very specific applications in
17 different domains of science. At the same time, this was one of the main reasons for their
18 extensive use as solvents and/or catalysts systems (Welton 1999).
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26 Similar effect in the regulation of desired features of nonconventional solvents can be achieved
27 by the combination of different ratios of quaternary ammonium salts and some of the hydrogen
28 bond donor molecules (urea, glycerol or oxalic acid, **Figure 1**). The binary mixtures formed in
29 this way are known as deep eutectic solvents (DEP) (Smith et al. 2014). Although they present
30 ionic liquid analogues and have some features in common; still, DEP are cheaper, easier for
31 synthesis and in some cases, biodegradable.
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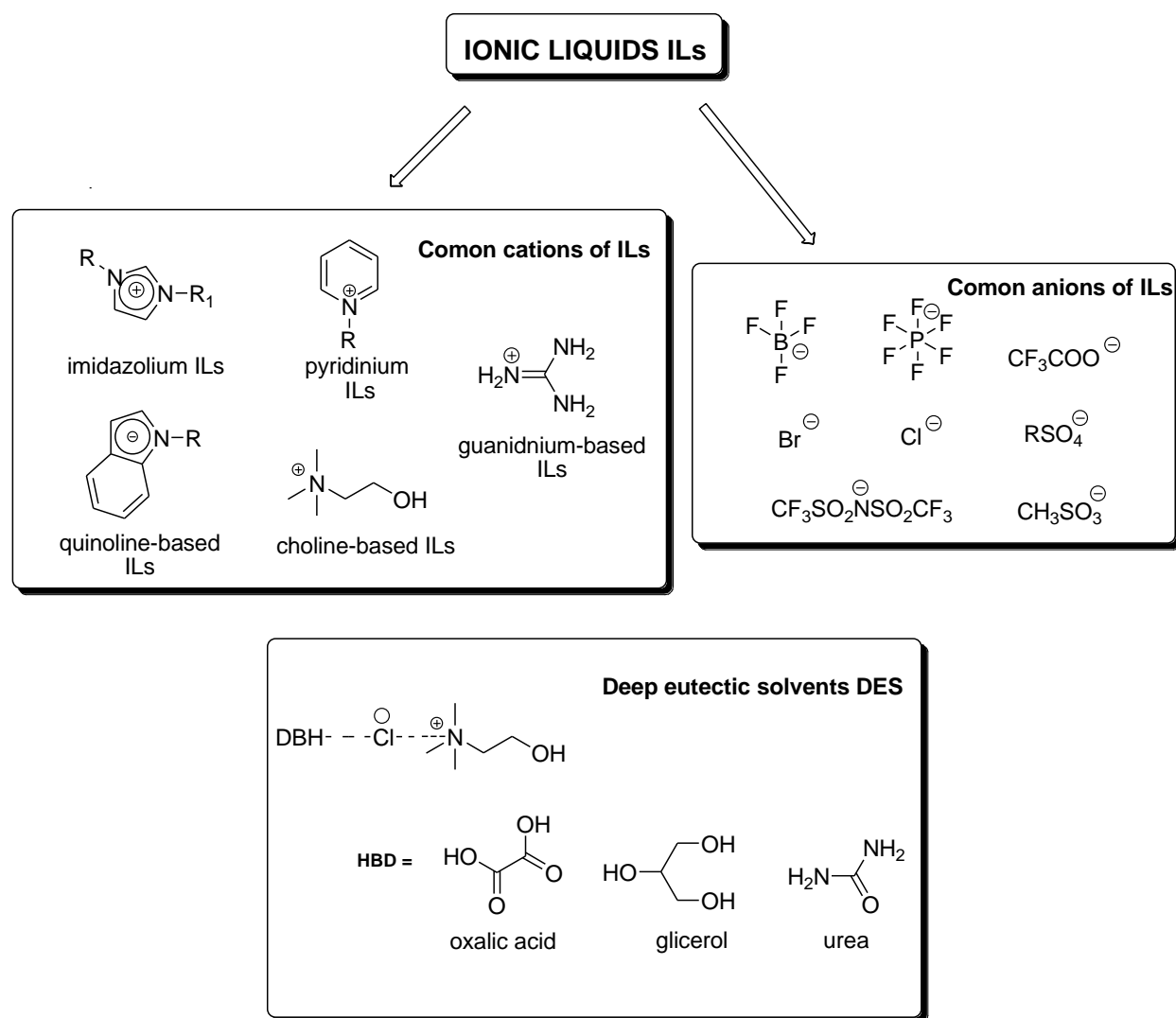
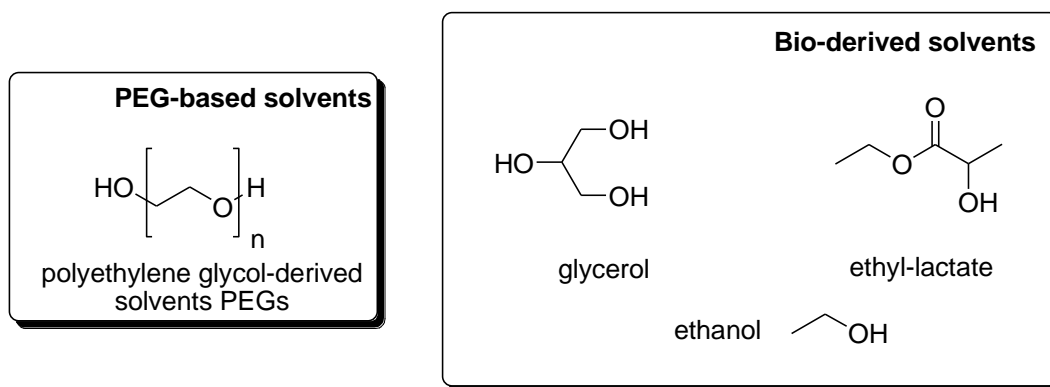


Figure 1. The examples of the ionic liquids (IL) and deep eutectic solvents (DES)

The years of research experience in using these systems in organic synthesis have revealed some of their disadvantages, such as toxicity, the presence of impurities and high cost of preparation; or, in the case of deep eutectic solvents - limited application in electrochemistry and low reaction rates due to the high viscosity of these binary mixtures. Taking all this into consideration, it becomes clear that there is no ideal green substitute for traditional solvents. However, this is still driving force for the tireless world of chemical science and industry to make additional efforts and keep the search for improved variants and better solution for practical application in this field.

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4 Recently, liquid polymers such as poly(ethylene glycols) PEGs and some bio-derived
5 compounds (glycerol, ethyl lactate) have emerged as green alternatives for circumventing
6 problems connected with the use of common organic solvents (**Figure 2**) (Kerton and Marriot
7 2013; Reichardt and Welton 2010). Due to the high dissolution capacity for different types of
8 organic compounds, significant phase extraction potential, non-toxic nature and most important -
9 biodegradable abilities, these types of solvents have found intensive application in the area of
10 medicinal chemistry. The mayor limiting factors for their wider use in chemical industry are
11 connected with increased energy requirements because of great viscosity and high boiling points.
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34 **Figure 2.** Polyethylene glycols (PEG) and examples of the bio-derived solvents
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37 Today, there is almost no area of chemical synthesis and technology which is not influenced by
38 the implementation of green replacement alternatives for well-established solvents. Still, some of
39 the science fields are under-exploited in this sense and there is big space for study progress. Our
40 aim here is to present the results achieved in the area of application of non-conventional solvents
41 in organoselenium chemistry, from the first described examples up to the new directions in this
42 field. We believe that our review will highlight possibilities that alternative solvents can offer in
43 organoselenium chemistry and inspire researchers in this field in their efforts and constant search
44 for the better green candidates.
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52 Organoselenium chemistry presents powerful source of key intermediates for various organic
53 transformations and applications in total synthesis of many naturally occurring compounds
54 (Bugarcic et al. 2016; Kostic et al. 2016; Santi and Santoro 2011; Santi 2014; Wirth 2012). The
55 advantages of organoselenium-induced transformations are reflected in high yields of obtained
56 selenium-functionalized compounds, easy experimental procedures and good regioselectivity.
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4 The possibility for further manipulation of the organoselenium moiety throughout oxidative or
5 reductive synthetic protocols increases the values of these transformations and makes them
6 unavoidable step in design and synthesis of many biologically active compounds. However, most
7 of these synthetic protocols involve use of common organic solvents, mostly halogenated, harsh
8 reaction conditions, as well as unstable reaction precursors. This is the main reason why
9 organoselenium chemistry is becoming an active research area for the implementation and
10 application of alternative reaction media during past years (Freundendahl 2009; Perin et al. 2016;
11 Santi and Tidei 2013; Santoro et al. 2014). In addition, organoselenium compounds have been
12 extensively studied in the sense of the green catalytic processes and use of alternative energy
13 sources (Lenardão 2018; Wang et al. 2017; Jing 2017; Sancineto 2017; Vieria et al. 2017).
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23 **2. IL- and DES- mediated organoselenium transformations**

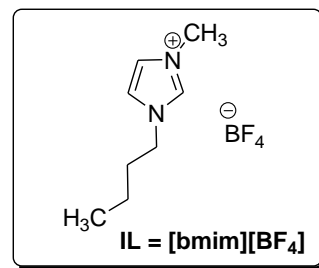
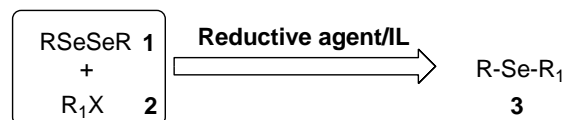
24 **2.1. Synthesis of selenoethers and selenoesters**

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29 After the discovery and first reports on air stable room temperature ionic liquids with fluorinated
30 anions BF_4 , PF_6 and their analogues (Wilkes and Zaworotko 1992), in the middle of the 1990s,
31 their chemistry has experienced the extensive growth and numerous applications in the field of
32 designer solvents. This first rapid expansion was partly stopped after discovery that ILs bearing
33 PF_6 and BF_4 anions could decompose in the presence of water, giving HF. This was the main
34 reason why ionic liquid chemistry was directed toward the development of other fluoro-
35 containing anions, such as CF_3SO_3^- and $(\text{CF}_3\text{SO}_3)_2\text{N}^-$, which are resistant to the hydrolysis.
36 Organoselenium chemistry, as many other branches of organic chemistry, was not immune to the
37 application of the fluorinated ionic liquids and first reported attempts have arisen exactly from
38 their usage.
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48 Seleno-ethers and-esters present useful reaction intermediates with promising application in
49 material and pharmaceutical area (Jain and Priyadarsini 2017). Still, the most of the described
50 procedures for their synthesis suffer the disadvantages in terms of the use of toxic solvents or
51 catalysts, non-satisfactory yields, as well as of instability of selenium-bearing precursors
52 employed in synthesis (Bowman et al. 1984; Gujadhur and Venkataraman 2003; Kwong and
53 Buchwald 2002; Suzuki et al. 1980; Suzuki et al. 1981). All these circumstances, joined with the
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4 increasing research interest in alternative solvents, have triggered extensive ionic liquid
5 implementation in the methods for their synthesis.
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9 The major advantages of ionic liquid-mediated synthesis, in comparison with already well-
10 known methodologies, are slightly or significantly improved reaction yields, room temperature
11 conditions and easy work-up, recyclability of used solvent/catalyst system and increased
12 environmental impact. Most of the described synthetic procedures have employed reductive
13 cleavage of diselenide bond in corresponding diorganyldiselenide (RSeSeR) as crucial step,
14 followed by reaction with alkyl- (in the case of selenides) or acyl halides (for selenoesters).
15 Using this protocol, assisted by the presence of ionic liquid as reaction medium and certain
16 reductive agents, several research groups have been able to successfully furnish the synthesis of
17 selenoethers and selenoesters in high yields and under mild conditions (**Schemes 1** and **2**). Since
18 most of traditional methods for the synthesis of diorganyl selenides from diselenides imply the
19 use of metal hydrides as reducing agents and harsh reaction conditions, the newly developed
20 protocols have also the advantages in terms of safety of desired transformations.
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	Entry	R	R ₁	X	Yield	References	
Reductive agent	CuO NPs	1	C ₆ H ₅	C ₆ H ₅	Br	82%	(Singh et al. 2009)
		2	C ₆ H ₅	<i>p</i> -MeC ₆ H ₄	Br	82%	
		3	C ₆ H ₅	<i>p</i> -CF ₃ C ₆ H ₄	Br	70%	
		4	<i>p</i> -MeC ₆ H ₄	C ₆ H ₅	Br	80%	
		5	<i>p</i> -CF ₃ C ₆ H ₄	C ₆ H ₅	Br	74%	
	SnCl ₂ /CuBr ₂	6	C ₆ H ₅	<i>n</i> -pentyl	Br	84%	(Gul et al. 2011)
		7	C ₆ H ₅	allyl	I	98%	
		8	C ₆ H ₅	<i>p</i> -MeC ₆ H ₄ CH ₂	Br	94%	
	InI	9	C ₆ H ₅	allyl	Br	97%	(Narayanaperumal 2009)
		10	C ₆ H ₅	<i>n</i> -pentyl	Cl	85%	
		11	C ₆ H ₅	<i>p</i> -MeC ₆ H ₄ CH ₂	Br	92%	
		12	<i>p</i> -MeC ₆ H ₄	C ₆ H ₅ CH ₂	Cl	84%	
		13	<i>p</i> -ClC ₆ H ₄	C ₆ H ₅ CH ₂	Cl	84%	
	Zn	14	C ₆ H ₅	allyl	I	98%	(Narayanaperumal 2010a).
		15	C ₆ H ₅	<i>n</i> -pentyl	Br	92%	
		16	<i>p</i> -MeC ₆ H ₄	C ₆ H ₅ CH ₂	Cl	89%	
		17	<i>p</i> -ClC ₆ H ₄	C ₆ H ₅ CH ₂	Cl	88%	

Scheme 1. Ionic liquid-mediated synthesis of the selenoethers.

The cross-coupling reaction of diaryl diselenides **1** with easily accessible alkyl and aryl halides **2** was utilized for the synthesis of diorganyl selenides **3**. CuO nanopowder in [bmim][BF₄] ionic liquid was used as a promoter of reactions, enabling recyclable, ecofriendly and cheap synthetic protocol (**Scheme 1**) (Singh et al. 2009). The substitution pattern on aromatic part of both starting halide (entries 1, 2 and 3 in **Scheme 1**) and diselenide (entries 4 and 5) hasn't showed a

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4 significant influence on the reaction pathway and efficiency so the variety of selenides has been
5 formed in the yields up to 82%.

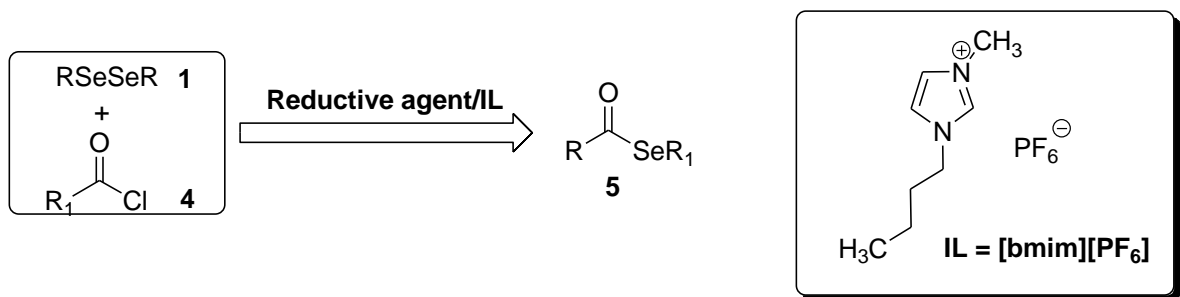
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9 (Gul et al. 2011) have reported the use of Sn(II)/Cu(II) bimetallic system in [bmim][BF₄] as a
10 reusable solvent for the synthesis of variety of selenides within short reaction times, with
11 excellent yields and under mild reaction conditions. It was demonstrated that leaving group
12 ability (bromide, chloride, mesylate) of alkyl halide is a determining factor in the reaction
13 efficiency, and therefore, with alkyl bromides and vinyl iodides the best results have been
14 achieved (entries 6 and 7, **Scheme 1**), while the reactivity of the aromatic halides has been
15 sensitive to the presence of steric disturbances and the highest yield has been achieved with the
16 sterically least demanded example (entry 8).

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24 InI in [bmim][BF₄] has also been employed as a reducing agent for the reductive cleavage of Se-
25 Se bond in the preparation of unsymmetrical diorganyl selenides (Narayanaperumal 2009).
26 Similarly to all previously mentioned methods, this is also high yielding synthetic procedure,
27 with the advantage of several times recycling catalytic system, without observed loss of activity.
28 The reaction has exhibited high efficiency for the wide range of allyl, alkyl- and aryl-halides
29 (even for less active examples, such as 1-chloropentane, entries 9, 10 and 11, **Scheme 1**), as well
30 as for substituted diaryl diselenides (entries 12 and 13).

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38 In a response to very expensive agents used for reductive cleavage of diselenide, a very attractive
39 protocol with zinc dust in [bmim][BF₄] (from the economical point of view) was presented by
40 the same group (Narayanaperumal 2010a). The allyl- and alkyl-phenyl selenides have been
41 obtained in excellent yields (entries 14 and 15, **Scheme 1**), especially with utilization of alkyl
42 halides with longer chain. In the case of diaryl diselenides, a good tolerance has been observed
43 for the different substituents with electron-donating and accepting effects (entries 16 and 17).

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50 Important feature of described ionic-liquid mediated organoselenium transformations is tolerance
51 for different functional groups and therefore, very similar methodologies have been applied for
52 the preparation of corresponding selenoesters. The synthesis of selenoesters **5** can be furnished
53 by the reaction of diorganyl diselenides **1** with corresponding acyl halides **4**, in the presence of
54 reducing agent in ionic liquid as reaction medium. Likewise in the case of ionic liquid –
55 mediated synthesis of selenides, the crucial step is always reductive cleavage of Se-Se bond. For
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4 this purpose, the same agents were used (Zn, In, Sn(II)/Cu(II), CuO nanoparticles), while
5 [bmim][PF₆] was preferably used as ionic liquid medium (**Scheme 2**).
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Reductive agent	Entry	R	R ₁	Yield	References	
Reductive agent	1	C ₆ H ₅	C ₆ H ₅	91%	(Singh et al. 2010)	
	CuO NPs/ Cs₂CO₃	2	C ₆ H ₅	<i>p</i> -MeC ₆ H ₄		90%
	3	C ₆ H ₅	<i>p</i> -BrC ₆ H ₄	84%		
	4	C ₆ H ₅	9-fluorenylmethyl chloroformate	90%		
	5	C ₆ H ₅	C ₆ H ₅	98%	(Tabarelli et al. 2010)	
	In	6	C ₆ H ₅	<i>p</i> -ClC ₆ H ₄		97%
	7	<i>p</i> -ClC ₆ H ₄	C ₆ H ₅	47%		
	8	<i>p</i> -MeC ₆ H ₄	C ₆ H ₅	57%		
	9	C ₆ H ₅	C ₆ H ₅	79%	(Gul et al., 2011)	
	SnCl₂/ CuBr₂	10	C ₆ H ₅	<i>p</i> -BrC ₆ H ₄		75%
	11	C ₆ H ₅	Me	10%		
	12	C ₆ H ₅	C ₆ H ₅	95%	(Narayanaperumal et al. 2011)	
	Zn	13	<i>p</i> -MeC ₆ H ₄	C ₆ H ₅		90%
	14	C ₆ H ₅	<i>p</i> -MeC ₆ H ₄	89%		

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52 **Scheme 2.** [bmim][PF₆]-mediated synthesis of the selenoesters.

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54 (Singh et al. 2010) have presented an efficient CuO nanopowder-catalysed synthesis of
55 selenoesters in [bmim][PF₆], in good to excellent yields (57-90%). The nanocrystalline CuO has
56 been used as a cheap and green catalyst which, together with ionic liquid, can be reused and
57 recovered several times. It has been proved that outcome of the procedure depended on acyl
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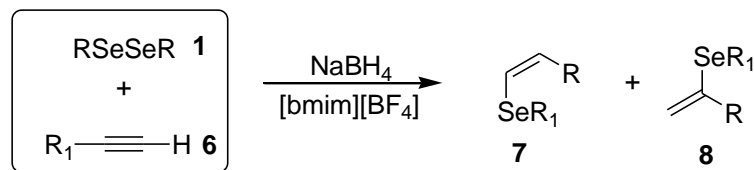
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4 chloride reactivity and the presence of electron donating groups on aromatic part of the molecule
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6 (entries 1-3, **Scheme 2**). The introduction of the selenocarbonate functionality presents one step
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8 forwards in this type of synthetic protocols (entry 4, **Scheme 2**).
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11 The synthesis of series of selenoesters by the use of In as a reducing agent in [bmim][PF₆] was
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13 reported by (Tabarelli et al. 2010). As authors described, the advantage of this synthetic protocol
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15 is reflected in short reaction time, neutral and mild media and use of stable diaryl chalcogenides
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17 instead of malodorous and hazardous selenols or thiols which were employed previously for
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19 these types of transformations. The reaction outcome has been influenced by the structure of
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21 used diselenide, and introduction of the substituent on aryl moiety significantly decreased yields
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23 (entries 7 and 8, **Scheme 2**), in contrast to the usage of neutral diphenyldiselenide (entries 5 and
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25 6, **Scheme 2**).

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27 By the analogy with Sn(II)/Cu(II)/ionic liquid-promoted synthesis of selenides (**Scheme 2**), the
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29 synthesis of selenoesters in short reaction time and under mild reaction conditions, in
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31 [bmim][PF₆] ionic liquid medium was emonstrated (Gul et al., 2011). Very promising results
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33 have been achieved with aromatic acyl chlorides, while the use of the aliphatic acyl chloride has
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35 induced drastic decrease in the reaction yields (entries 9-11, **Scheme 2**).

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37 Selenoesters can also be acquired by the zinc dust/[bmim][PF₆]-assisted synthesis from acyl
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39 chlorides and diorganyl diselenides (Narayanaperumal et al. 2011). As mentioned above, this
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41 achievement is especially interesting from the industrial point of view due to the smaller cost of
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43 zinc in comparison to the cost of other reductive agents, such as In. Since the reaction was more
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45 sensitive to the structure of acyl chloride then to the diorganyl diselenide structure, the use of
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47 benzoyl- and *p*-methyl benzoyl chloride has enabled the best synthetic results (entries 12-14,
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49 **Scheme 2**).

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51 An easy synthetic protocol for the synthesis of vinyl selenides by the use of NaBH₄ and
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53 [bmim][BF₄] was demonstrated by (Lenardão et al 2007). The formation of vinyl chalcogenides
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55 **7** and **8** from diselenides **1** and terminal alkynes **6** has proceeded in diastereoselective manner,
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57 giving preferentially products with *Z*-configuration (entries 1 and 2, **Scheme 3**).
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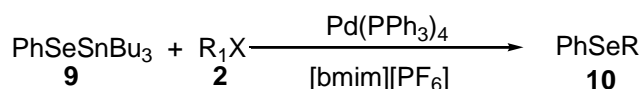
Entry	R	R ₁	Yield	Ratio(7:8)	Reference
1	C ₆ H ₅	HOCH ₂	87%	72:28	(Lenardão et al 2007)
2	C ₆ H ₅	CH ₃ CH ₂ C(OH)CH ₃	90%	91:9	

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Scheme 3. The application of the NaBH₄/[bmim][BF₄] system in the synthesis of the vinyl selenides.

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Diorganyl diselenides are not the only starting materials which were utilized for the ionic liquid mediated synthesis of seleno-ethers and esters. An interesting example of palladium-catalyzed synthesis of diorganyl selenides **10** (entries 1 and 2, **Scheme 4**) has arrived from (Zhao et al. 2011). They have developed a cross-coupling reaction of phenyl tributylstannyl selenide **9** with various alkyl and aryl halides in [bmim][PF₆]. The obtained results were compared with results elucidated under the same conditions in toluene as solvent and, have revealed, that new methodology has improved reaction rates, as well as the yields, with the possibility of palladium catalyst reuse.



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Entry	R ₁	X	Yield	Reference
1	<i>p</i> -MeOC ₆ H ₄	I	91%	(Zhao et al. 2011)
2	<i>p</i> -MeC ₆ H ₄	I	91%	

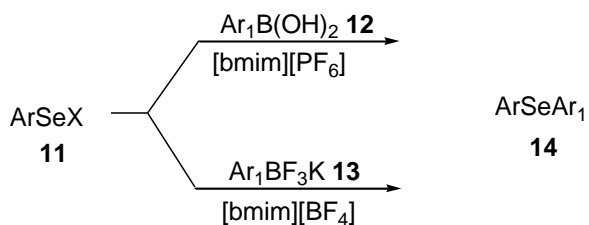
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Scheme 4. Palladium/ionic liquid-mediated synthesis of the diorganyl selenides.

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(Freitas et al. 2011) have described synthesis of diaryl selenides **14** in metal- and catalyst free reaction between arylboron reagents (ArB(OH)₂ **12** or ArBF₃K **13**) and arylselenenyl halides **11**

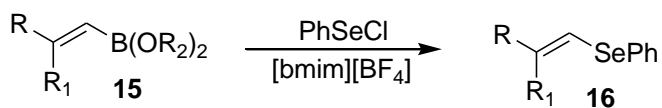
(Scheme 5). Very satisfactory results in the terms of generality of substrate scope and yields have been achieved by changing the type of used ionic liquid ([bmim][PF₆] in the case of ArB(OH)₂ and [bmim][BF₄] in the case of ArBF₃K) (entries 1-6, Scheme 5).



	Entry	Ar	X	Ar ₁	Yield	References
Ar ₁ B(OH) ₂ 12	1	C ₆ H ₅	Cl	<i>p</i> -MeOC ₆ H ₄	95%	(Freitas et al. 2011)
	2	C ₆ H ₅	Cl	<i>o</i> -MeOC ₆ H ₄	94%	
	3	<i>p</i> -ClC ₆ H ₄	Cl	<i>p</i> -MeOC ₆ H ₄	96%	
Ar ₁ BF ₃ K 13	4	C ₆ H ₅	Br	<i>p</i> -MeOC ₆ H ₄	88%	
	5	C ₆ H ₅	Br	<i>p</i> -MeC ₆ H ₄	86%	
	6	C ₆ H ₅	Br	<i>p</i> -BrC ₆ H ₄	86%	

Scheme 5. Aryl-boron reagents in the ionic liquid-mediated synthesis of diorganyl selenides.

(Kabalka and Venkataiah 2002) have published the stereospecific procedure for the synthesis of the (*E*)- and (*Z*)-vinyl selenides **16** from vinylboronic acids **15** (Scheme 6). PhSeCl is reacting smoothly with these substrates in [bmim][BF₄] to afford corresponding selenides in good yields (up to 84%) and stereoselectivity (entries 1-4, Scheme 6). The reaction is showing excellent tolerance for the bromo- and hydroxyl substituents (entries 2 and 3).



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					Reference
1	<i>n</i> -hexyl	H	H	84%	(Kabalka and Venkataiah 2002)
2	<i>n</i> -hexyl	Br	H	78%	
3	HO(CH ₂) ₉	H	H	79%	
4	H	C ₆ H ₅	H	74%	

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Scheme 6. Ionic liquid-mediated synthesis of the (*E*)- and (*Z*)-vinyl selenides.

2.2. Synthesis of β-selenoamines

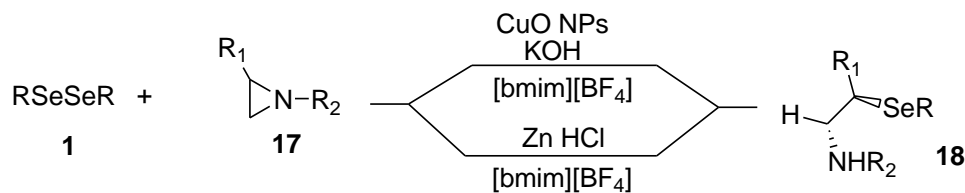
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Reductive cleavage of diorganyl diselenides **1** in ionic liquid, followed by the ring opening of aziridines **17** was employed in an elegant stereo- and regioselective approach for the variety of β-selenoamino derivatives **18** (**Scheme 7**), in good to excellent yields. The [bmim][BF₄] was used as an ionic liquid medium, in the presence of CuO nanopowder (entries 1-3, **Scheme 7**) (Salman et al. 2012). Similarly to most of previously described methodologies, this procedure is also recyclable, since the ionic liquid could be reused several times without loss in activity.

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The similar reaction outcome was achieved by (Vargas et al. 2012) who performed reaction in [bmim][BF₄], using zinc dust as reagent for reductive cleavage of diselenide bond (entries 4 and 5, **Scheme 7**).

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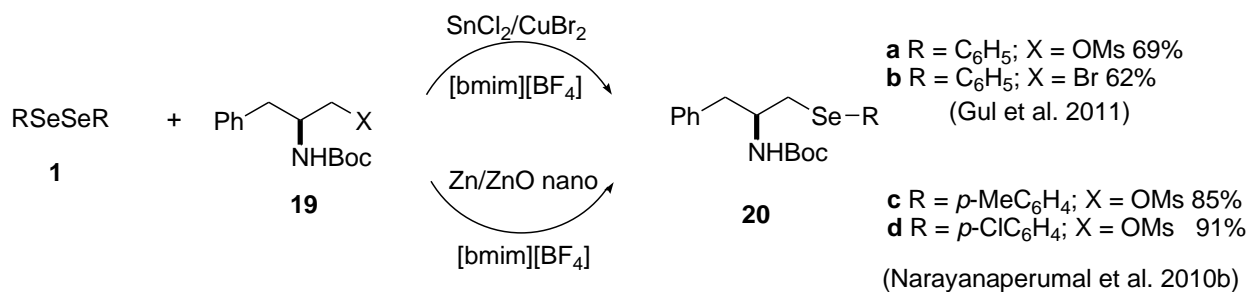
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	Entry	R	R ₁	R ₂	Yield	References
CuO NPs KOH	1	<i>p</i> -ClC ₆ H ₄	C ₆ H ₅ CH ₂	Boc	>99%	
	2	C ₆ H ₅	<i>i</i> -propyl	Boc	95%	(Salman et al. 2012)
	3	C ₆ H ₅	<i>i</i> -propyl	Ts	93%	
Zn HCl	4	C ₆ H ₅	C ₆ H ₅ CH ₂	Boc	88%	(Vargas et al. 2012)
	5	C ₆ H ₅	C ₆ H ₅ CH ₂	Ts	90%	

Scheme 7. Ionic liquid-assisted synthesis of the β -selenoamines.

To verify generality of synthetic protocol developed for the Sn(II)/Cu(II)/ionic liquid supported synthesis of selenoethers and selenoesters, (Gul et al. 2011) have applied the same system for the chiral β -seleno amines **20** from diphenyldiselenide **1** and β -amino mesylate **19** in [bmim][BF₄] ionic liquid medium (**20a-b**, **Scheme 8**).

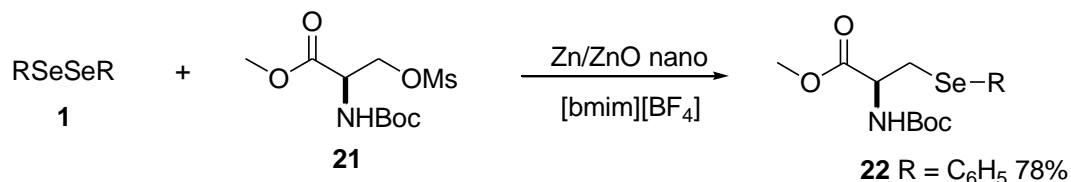
In their attempts to utilize the metal oxides as efficient catalysts for the different ionic liquid-mediated organoselenium transformations, the (Narayanaperumal et al. 2010b) have reported the ZnO nanoparticles-catalyzed synthesis of β -seleno amines from N-protected β -amino mesylates in [bmim][BF₄] as recyclable solvent (**Scheme 8**). The reaction outcome has suffered the highest influence from the nature of the R group at the diselenide. While the presence of electron-donating group (such as Me, **20c-Scheme 8**) gives a rise to the moderate yield of selenoamine product; the electron-accepting chloro substituent increases the efficiency of the reaction, giving product in 91% yield (**20d**, **Scheme 8**).



Scheme 8. Metal catalysts in ionic liquid-mediated synthesis of the β -selenoamines.

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In addition, this group has extended the developed methodology to the biologically important selenocysteine derivative **21**. The corresponding selenoamine **22** was obtained in 78%, demonstrating generality of the protocol even for the more complex substrates (**Scheme 9**).



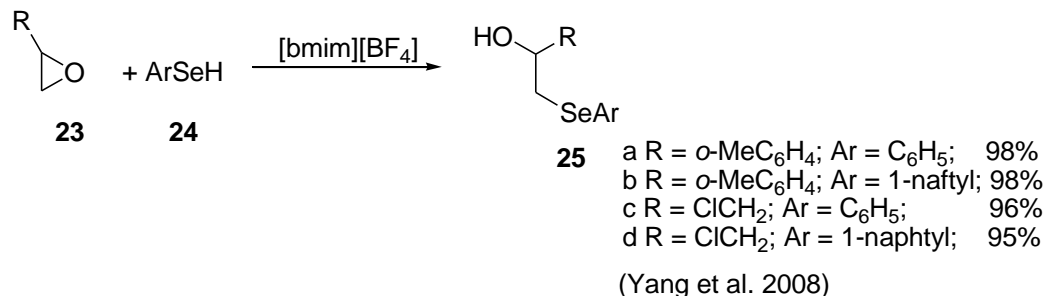
Scheme 9. Zn/ZnO/[bmim][BF₄]-assisted synthesis of the selenocysteine derivative.

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2.3. Synthesis of β -hydroxy selenides

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A number of β -hydroxy selenides **25** were regioselectively synthesized in excellent yields by employing ring-opening reaction of 1,2-epoxides **23** with ArSeH **24** in [bmim][BF₄] ionic liquid medium (**Scheme 10**) (Yang et al. 2008).

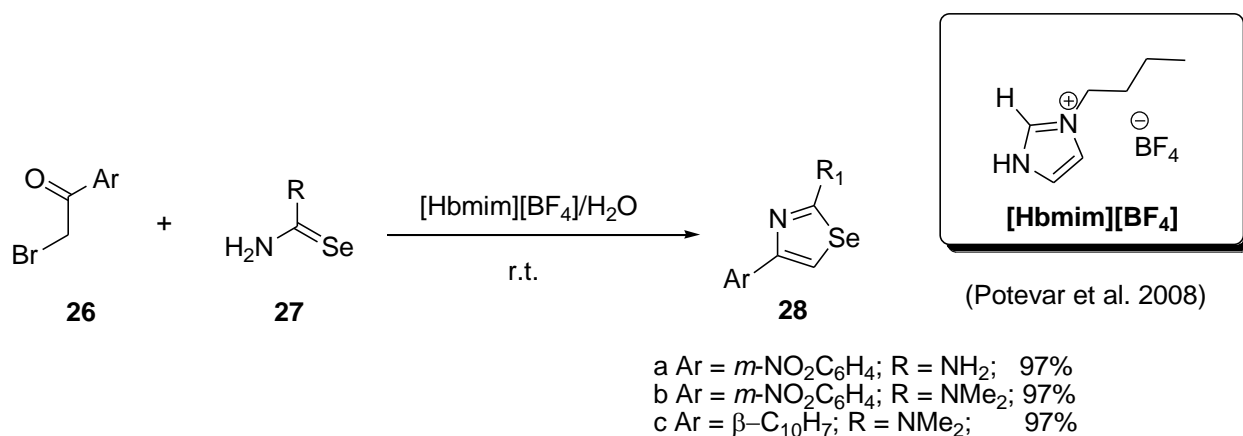


Scheme 10. [bmim][BF₄]-mediated synthesis of the β -hydroxy selenides.

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4 In this case, ionic liquid was used as dual promoter/medium system for the reactions and its use
5 has afforded recyclability of whole process, as well as excellent yields up to 98% (**25a-d**,
6 **Scheme 10**).

11 2.4. Synthesis of 2-amino-1,3-selenoazoles

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14 An eco-friendly method for the synthesis of 2-amino-1,3-selenoazoles **28** via condensation of
15 selenourea derivatives **27** with phenacyl bromide **26** in mixed [Hbmim]BF₄/water system was
16 developed by the (Potevar et al. 2008). The advantage of this protocol is the possibility to avoid
17 use of any catalyst, as well as short reaction times and high yields of selenoazoles products (**28a-**
18 **c**, **Scheme 11**).

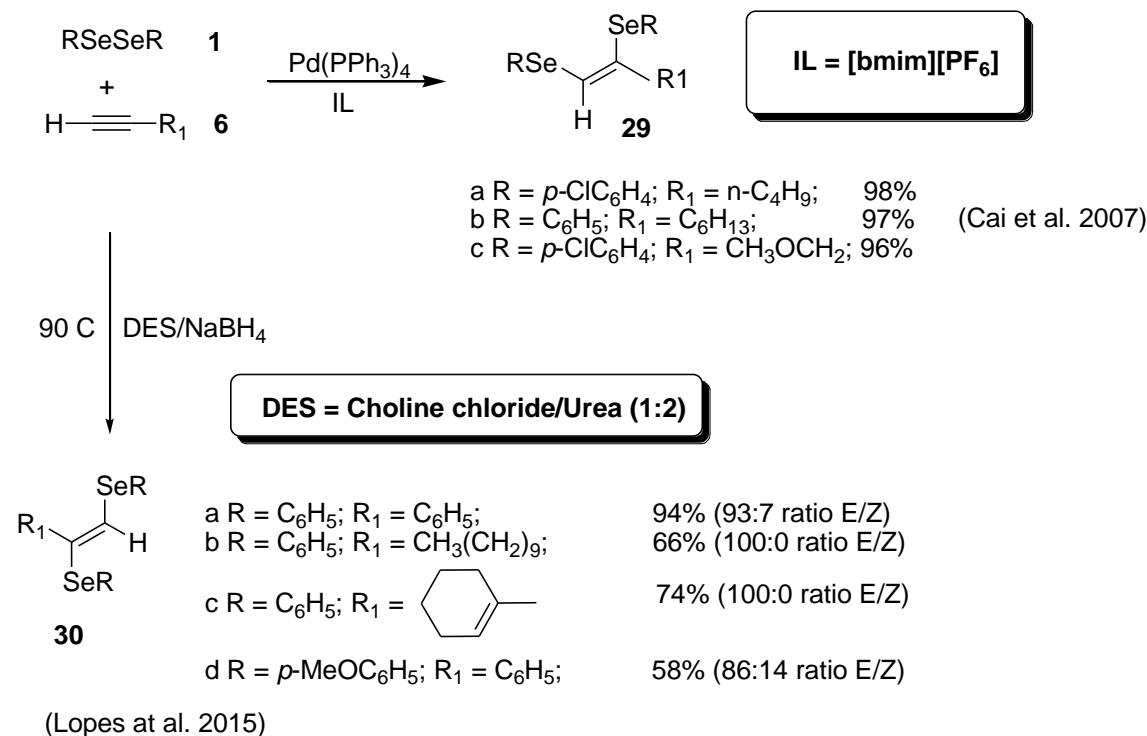


Scheme 11. [Hbmim]BF₄/water-mediated synthesis of the 2-amino-1,3-selenoazoles.

46 2.5. Synthesis of (*Z*)- and (*E*)- bis-selenoalkenes

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51 The fluoro-based ionic liquid [bmim][PF₆] was also used as "green" alternative for benzene or
52 toluene in the palladium-catalyzed stereoselective addition of diorganyl diselenides **1** to terminal
53 alkynes **6** (Cai et al. 2007). The formation of (*Z*)-bis selenoalkenes **29** is proceeding smoothly, in
54 very high yields (**Scheme 12**). Very high tolerance has been observed for the wide range of
55 functionalized-terminal alkynes (**29a-c**, **Scheme 12**), and comparing with the results achieved in

benzene, lower reaction rates, lower required temperature and higher yields were observed. Also, excellent stereoselectivity was accomplished.



Scheme 12. Palladium/[bmim][PF₆]-mediated synthesis of the (*Z*)- and (*E*)- bis-selenoalkenes.

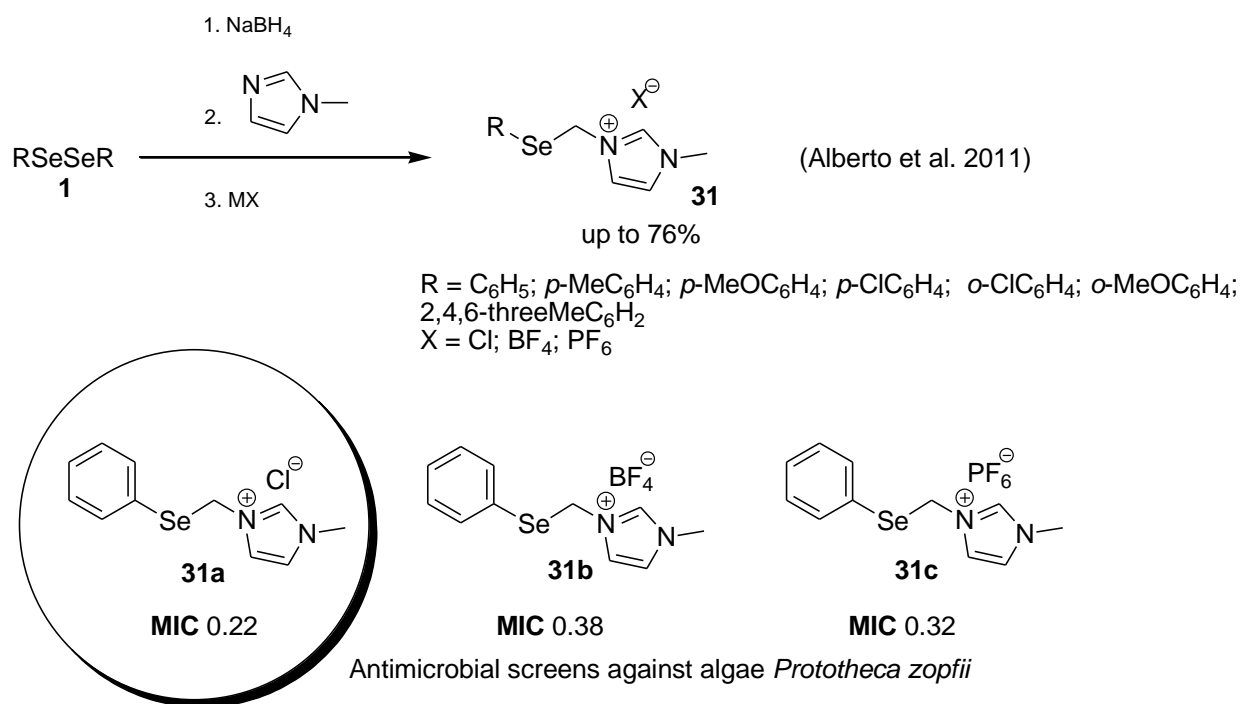
The deep eutectic solvents have been recognized as a green alternative for the fluorinated ionic liquid and the common organic solvents. Beside the biodegradability and lower preparation costs, their physicochemical properties can be also tuned by the adequate selection of the nature and ratio of the hydrogen-bonding elements. Undoubtedly, one of the most explored DES is choline/urea (1:2) mixture, which was successfully applied in the vast number of chemical transformations (Hu et al. 2008; Imperato et al. 2006a; Imperato et al. 2006b; Zhang et al. 2005).

(Lopes et al. 2015) have presented the use of choline chloride/urea (1:2) for the selective synthesis of (*E*)-1,2-bisorganoseleno alkenes **30a-d** starting from terminal alkynes **6** and diorganyl diselenides **1** (Scheme 12). This methodology has advantages due to the possibility for employment of alkyl **30b** and alkenyl monosubstituted **30c** alkynes as substrates, whereas this was not the possibility with other green solvents. The first limitations have been noticed in

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4 arylalkynes where the presence of electron-withdrawing group is increasing reaction time; as
5 well as in electron-rich diselenides **30d** (decreasing yields and selectivity were observed).
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9 3. Selenium-based ionic liquids

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11 One of the several attempts for the introduction of selenium into ionic liquids has arrived from
12 the (Alberto et al. 2011). They have developed a straightforward method for the preparation of
13 desired set of selenium-functionalized imidazolium ionic liquids **31**, employing diselenides **1** as
14 easily approachable and stable starting materials. Moreover, they have reported antimicrobial
15 activity of selenium-functionalized imidazolium ionic liquids, indicating tight connection
16 between ionic liquid structure (aryl group in diselenide and counter ion associated with cationic
17 part, **31a-c** and elucidated biological properties (Antimicrobial screens against algae *Prototheca*
18 *zopfii*, **Scheme 13**).
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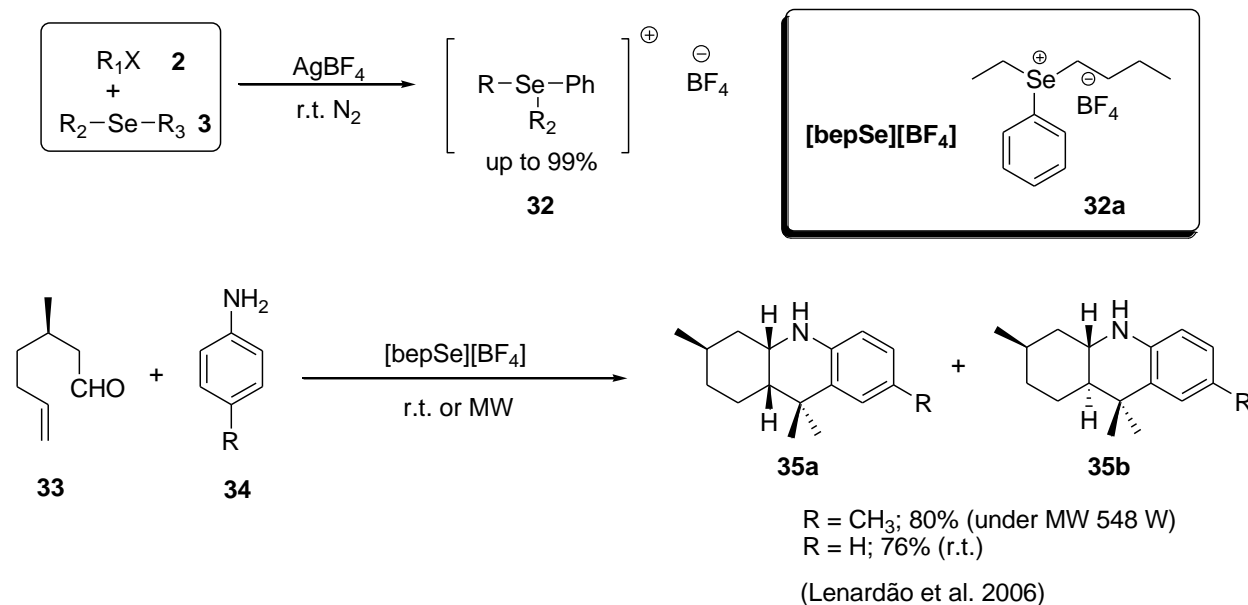


52 **Scheme 13.** The synthesis of the selenium-functionalized imidazolium ionic liquids.
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54 3.1. Ionic liquids with cationic selenium species and their application in organic synthesis

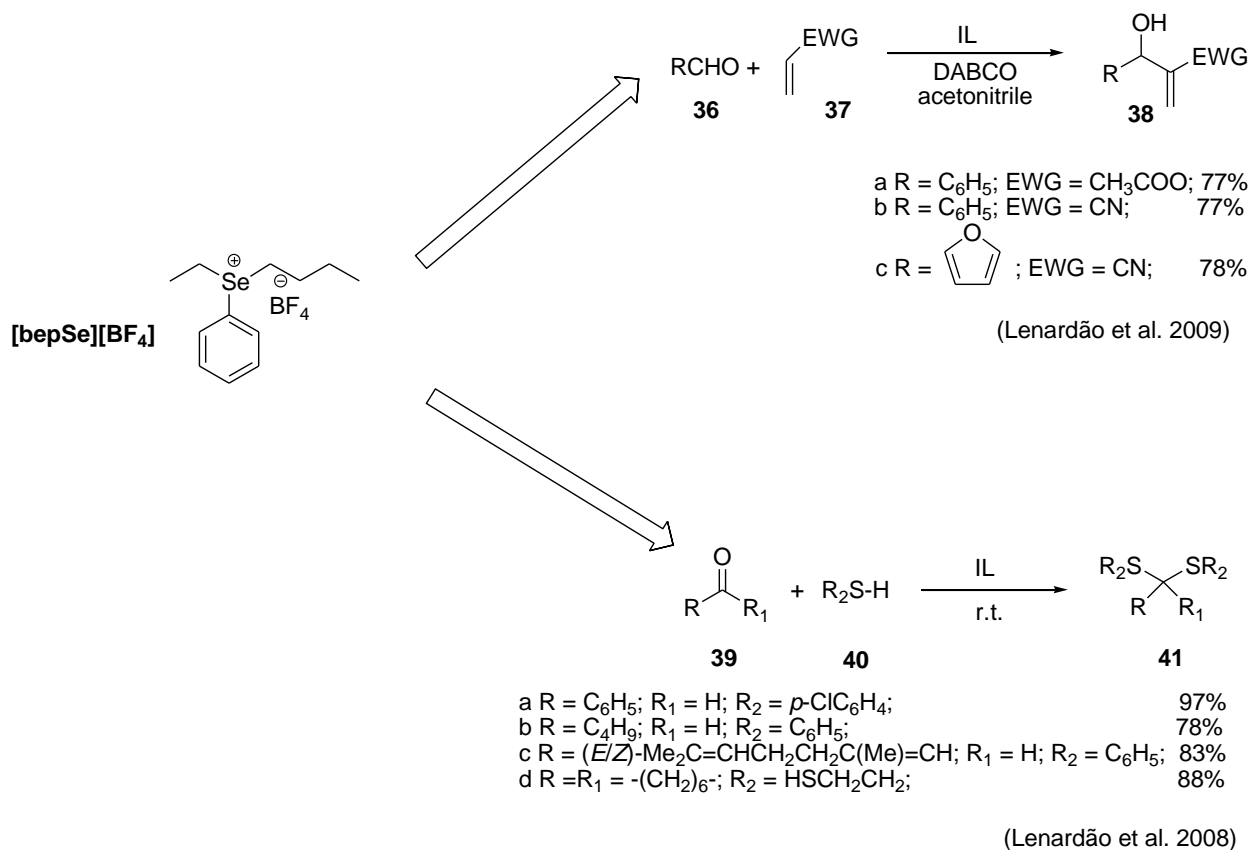
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57 In attempts to create Se and Te salts liquid at room temperature, (Lenardão et al. 2006) reported
58 the method for the preparation of acidic selenonium ionic liquids **32** (**Scheme 14**), as well as
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4 application of selected example (phenyl butyl ethyl selenonium tetrafluoroborate **32a**) for the
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6 hetero-Diels-Alder cyclization of citronellal-derived aryl amines. The outcome of the reaction is
7
8 formation of octahydroacridine products **35a** and **35b** in very economical way and with very
9
10 good yields (**Scheme 14**).



Scheme 14. Synthesis of the acidic selenonium ionic liquid and application of the [bepSe][BF₄] in the synthesis of octahydroacridines.

The same ionic liquid was successfully applied as co-catalyst in Baylis-Hilman reaction between aldehydes **36** and electron-deficient alkenes **37**, affording reaction products **38** in very short times and moderate to good yields (**38a-c**, **Scheme 15**) (Lenardão et al. 2009).



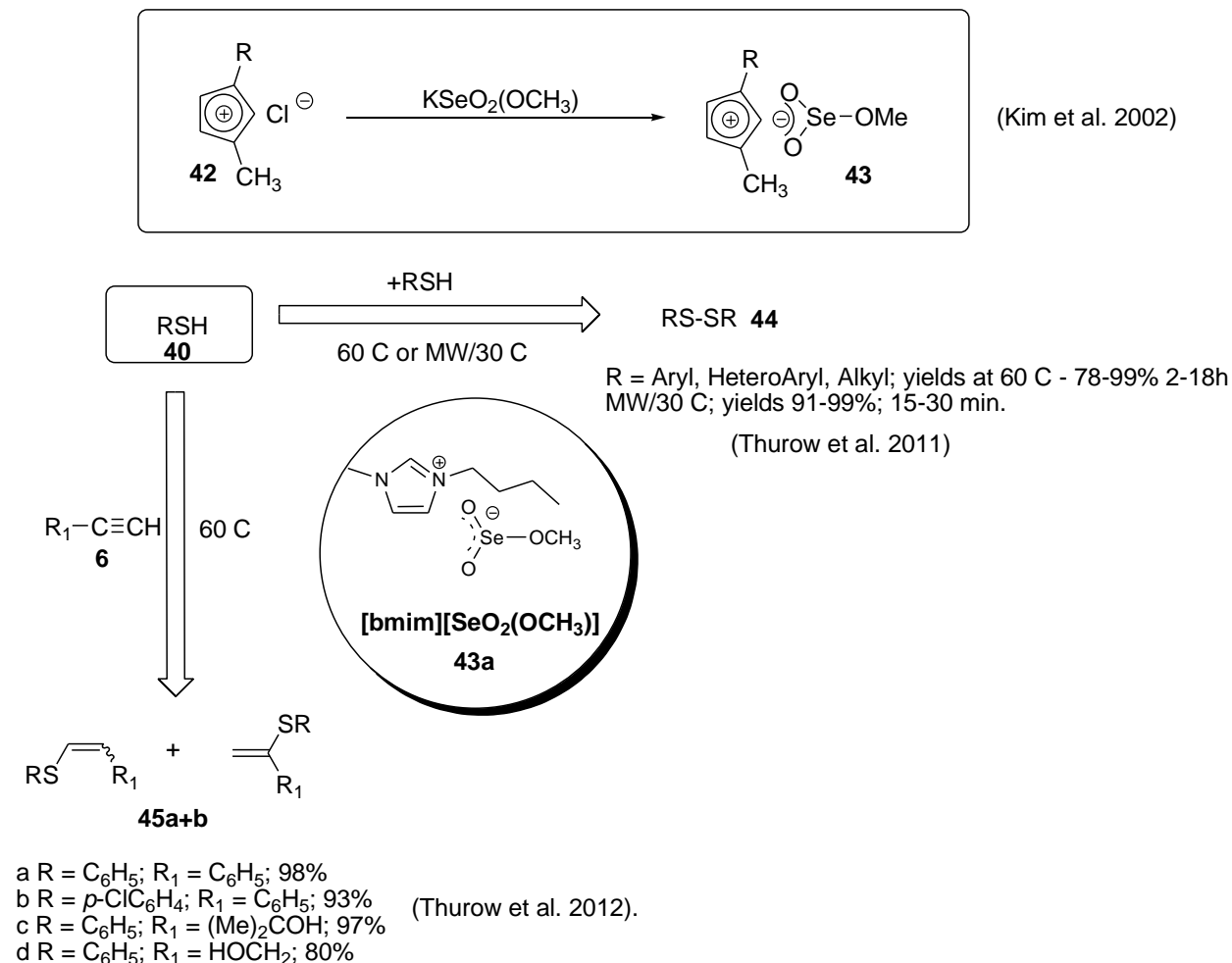
33 **Scheme 15.** The application of the [bepSe][BF₄] in the Baylis-Hilman reaction and dithioacetals
 34 synthesis.
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 38 The catalytic potential of phenyl butyl ethyl selenonium tetrafluoroborate ionic liquid has been
 39 complemented by the results achieved in the same group (Lenardão et al. 2008) in the area of
 40 dithioacetals synthesis (**Scheme 15**). A number of reported methods for the protection of
 41 carbonyl compounds as thioacetals already exist in literature, due to the importance and
 42 utilization of these molecules in different organic synthesis. However, the advantage of the
 43 protocol developed by Lenardão is selective, solvent-free conversion of aromatic, aliphatic, α,β -
 44 unsaturated aldehydes and ketones **39** into corresponding dithioacetals **41a-c** in good yields and
 45 under mild reaction conditions.
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53 3.2. Ionic liquids with anionic selenium species and their application in organic synthesis

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The examples of the synthesis of ionic liquids containing anionic selenium species **43**, have been published by (Kim et al. 2002). For this purpose, the reaction between 1-alkyl-3-methylimidazolium chlorides **42** and $[\text{KSeO}_2(\text{OCH}_3)]$ has been employed (**Scheme 16**).



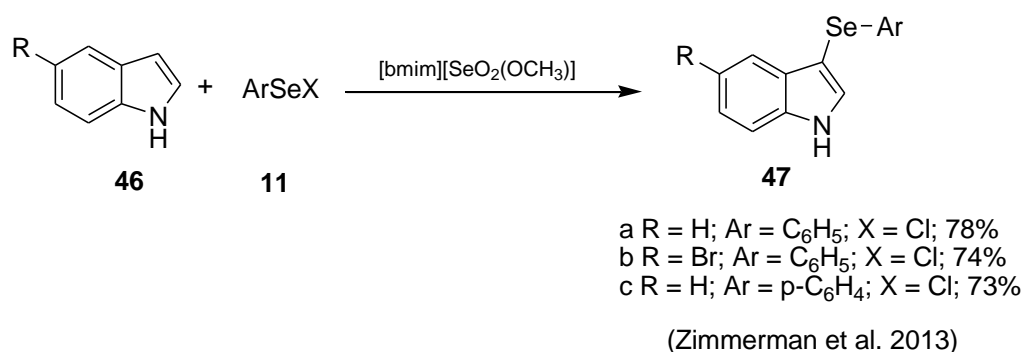
Scheme 16. The synthesis of ionic liquids containing anionic selenium species $[\text{bmim}][\text{SeO}_2(\text{OCH}_3)]$. The application in the base-free oxidation of thiols and hydrothiolation of the terminal alkynes.

The first application, these types of ionic liquids, have found as active catalysts (selected example $[\text{bmim}][\text{SeO}_2(\text{OCH}_3)]$ **43a**, Scheme 16) for the oxidative carbonylation of aniline. Obtained results were compared with data previously acquired with Pd/C system and they have showed better catalytic activity of newly synthesized selenium ionic liquids, even at the temperatures low as 40 °C.

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4 Later, (Thurow et al. 2011) have demonstrated the results achieved by the application of the
5 same anionic selenium ionic liquid for the base-free oxidation of thiols **40** (Scheme 16). The
6 range of symmetric aromatic, aliphatic and functionalized disulfides **44** have been prepared in
7 excellent yields, starting from corresponding thiols. Moreover, the reaction time can be
8 significantly reduced by using microwave irradiation.
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13 The hydrothiolation of the terminal alkynes in the same ionic liquid has been efficiently applied
14 for the wide range of vinyl sulfides **45a** and **45b** (Scheme 16) (Thurow et al. 2012). By applying
15 [bmim][SeO₂(OCH₃)] as catalyst, the assistance of the strong bases, commonly used in these
16 types of transformations, can be avoided. Different aromatic thiols, as well as propargyl alcohols
17 and alkynes have undergone transformation in excellent yields; although with low selectivity
18 (mixtures of Markovnikov and anti-Markovnikov products have been obtained).
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24 (Zimmerman et al. 2013) have presented a selective synthetic protocol for the preparation of 3-
25 arylselenoindoles **47a-c** from indoles **46** and electrophilic selenium reagents (Scheme 17). As a
26 results of the [bmim][SeO₂(OCH₃)] use as solvent, recyclable, general and catalyst-free method
27 has been developed.
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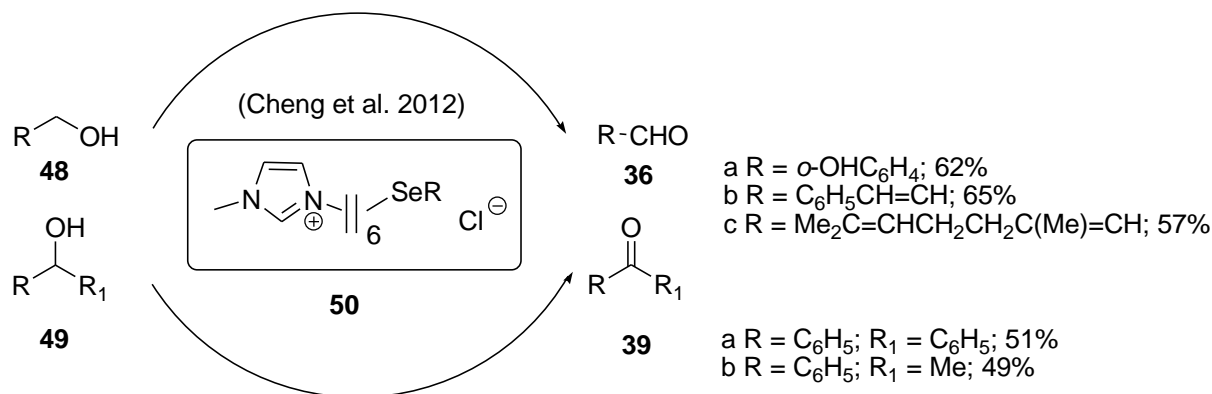
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Scheme 17. The application of the [bmim][SeO₂(OCH₃)] in the preparation of 3-arylselenoindoles.

3.3. Ionic liquid-supported selenium reagents

(Cheng et al. 2012) have published the synthesis of ionic-liquid supported selenium reagent **50** which was further applied for the oxidation of alcohols (**48** and **49**) to aldehydes and ketones (**36a-c** and **39a-c**, Scheme 18) in the presence of 30% H₂O₂. Although with narrow scope of the substrates, the methodology has shown certain advantages which are reflected in recyclability,

easy separation of the oxidation products from crude mixture and moderate to good yields of reaction (**Scheme 18**).



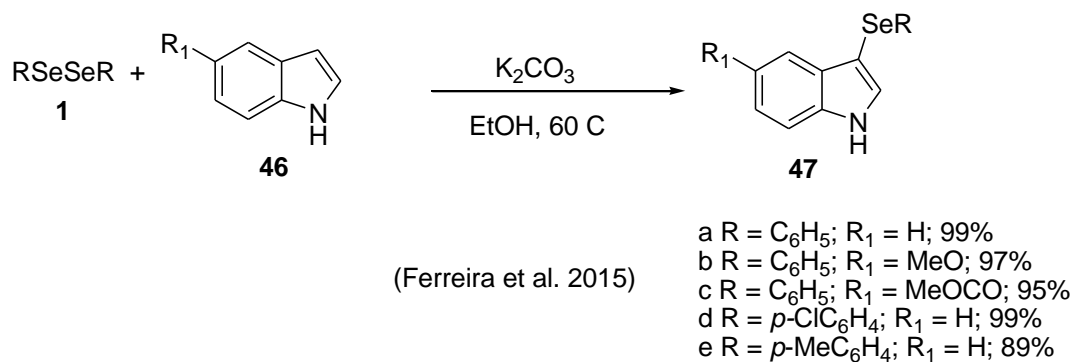
Scheme 18. The application of the ionic-liquid-supported selenium reagent in the oxidation of alcohols.

4. Ethanol- and glycerol-assisted organoselenium transformations

4.1. Synthesis of selenindoles

The possibility for ethanol production from the common agricultural feedstocks, such as potato and sugar cane, make it renewable energy form which is attracting attention of the researcher all over the world. On the other hand, glycerol as by-product of the biodiesel production, as well as some of its synthetically derived analogues, has also found application in different fields of organic synthesis (Clark et al. 2015; Clark et al. 2016; García et al. 2010; Paggiola et al. 2014).

Selenindoles have been receiving special research attention due to their biological potential. An elegant synthetic protocol for their synthesis has been described by the (Ferreira et al. 2015). The methodology consists in use of ethanol as reusable biosolvent and K₂CO₃ in catalytic amounts for the reaction between diorganylselenides **1** and indoles **46**. The number of 3-selenylindoles **47a-e** with different structural variations have been obtained in excellent yields (**Scheme 19**). The nature of the substituents present at the position 5 in the indole core doesn't affect reaction yields, as well as the existence of the substitution pattern in the framework of the diaryldiselenide.



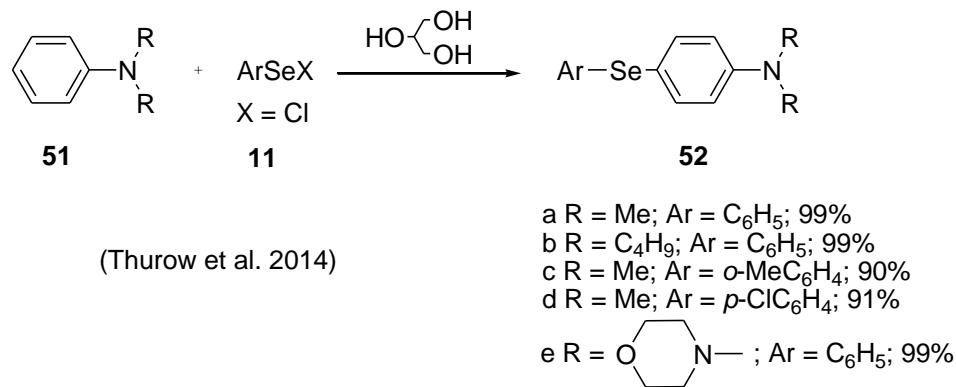
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Scheme 19. Ethanol-assisted synthesis of the selenoindoles.

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4.2. Selenium-functionalized anilines

(Thurow et al. 2014) described the methodology for the approach for arylselanyl anilines **52** by using glycerol as green, non-toxic and renewable solvent, without any metal or base present. The reaction comprehends *N,N*-disubstitued anilines **51** and arylselanyl chloride **11** (**Scheme 20**). Developed method possesses generality for the wide scope of substrates (**52a-e**, **Scheme 20**), high yields and mild reaction conditions.

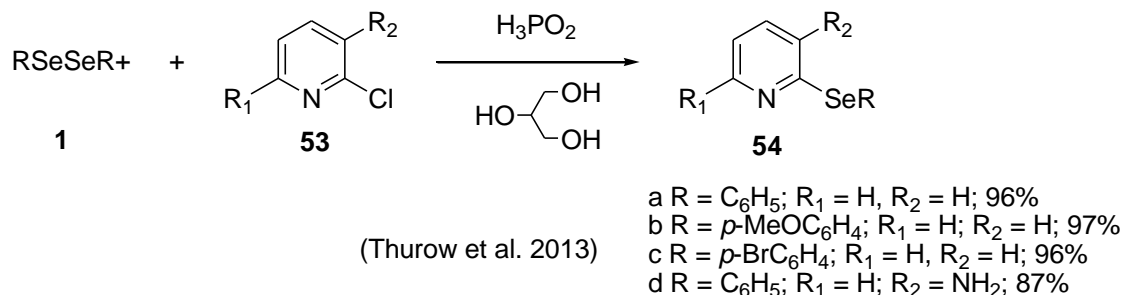


Scheme 20. Glycerol-assisted preparation of the arylselanyl anilines.

4.3. 2-selenosubstitued pyridines

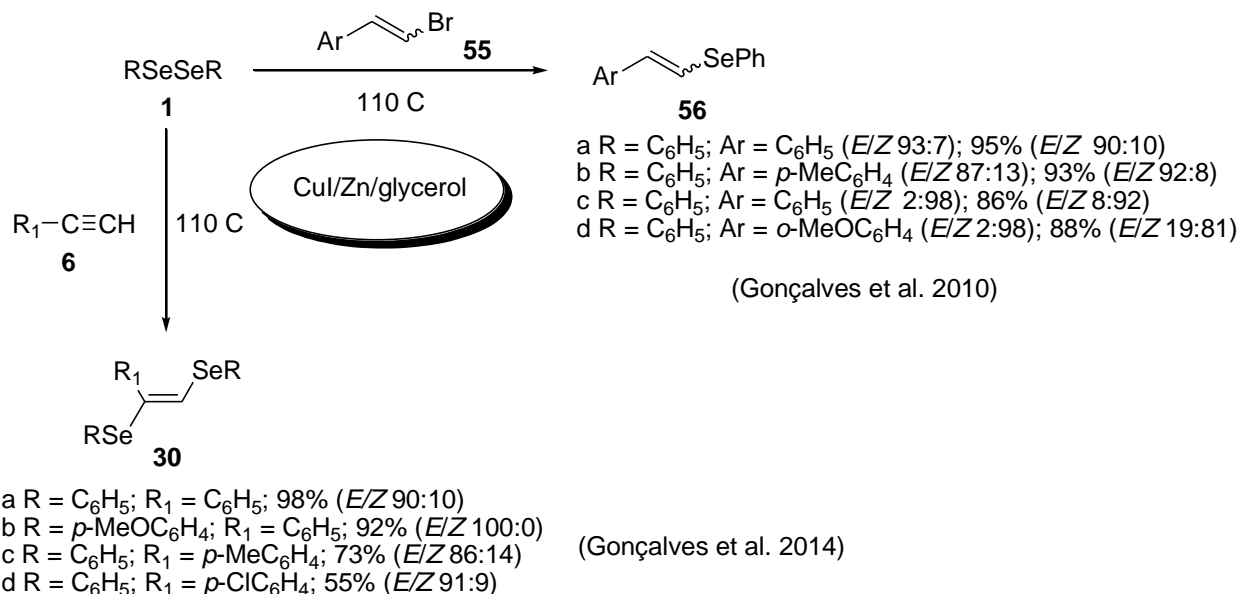
The combination of glycerol as solvent and hydrophosphorus acid as reducing agent was utilized for the efficient synthesis of range of 2-organylselanyl pyridines **54** from 2-chloropyridines **53** and organylselenols **1** (**Scheme 21**) (Thurow et al. 2013). The catalytic activity of this system has been maintained in good extent after four reaction cycles. The scope of the procedure isn't

susceptible to the electronic effects of the diselenide substituents and number of selenium-functionalized pyridines has been obtained in good yields (**54a-d**, **Scheme 21**).



Scheme 21. Glycerol/ hydrophosphorus acid system in the synthesis of the selenium-functionalized pyridines.

(Gonçalves et al. 2010) have described an efficient application of Cu-catalyzed cross-coupling of diorganyl diselenides **1** and vinyl bromides **55** by the using CuI/Zn/glycerol as catalytic system (**Scheme 22**). The reaction has resulted in the formation of vinyl selenides **56** in high yields. Vinyl bromides with (*E*)-configuration have afforded almost exclusively products with the same stereochemistry (**56a,b**), while in the case of (*Z*)-vinylbromides the significant decrease of selectivity has been observed (**56c, d**).



Scheme 22. Cu/Zn/glycerol-catalyzed cross-coupling of diorganyl diselenides.

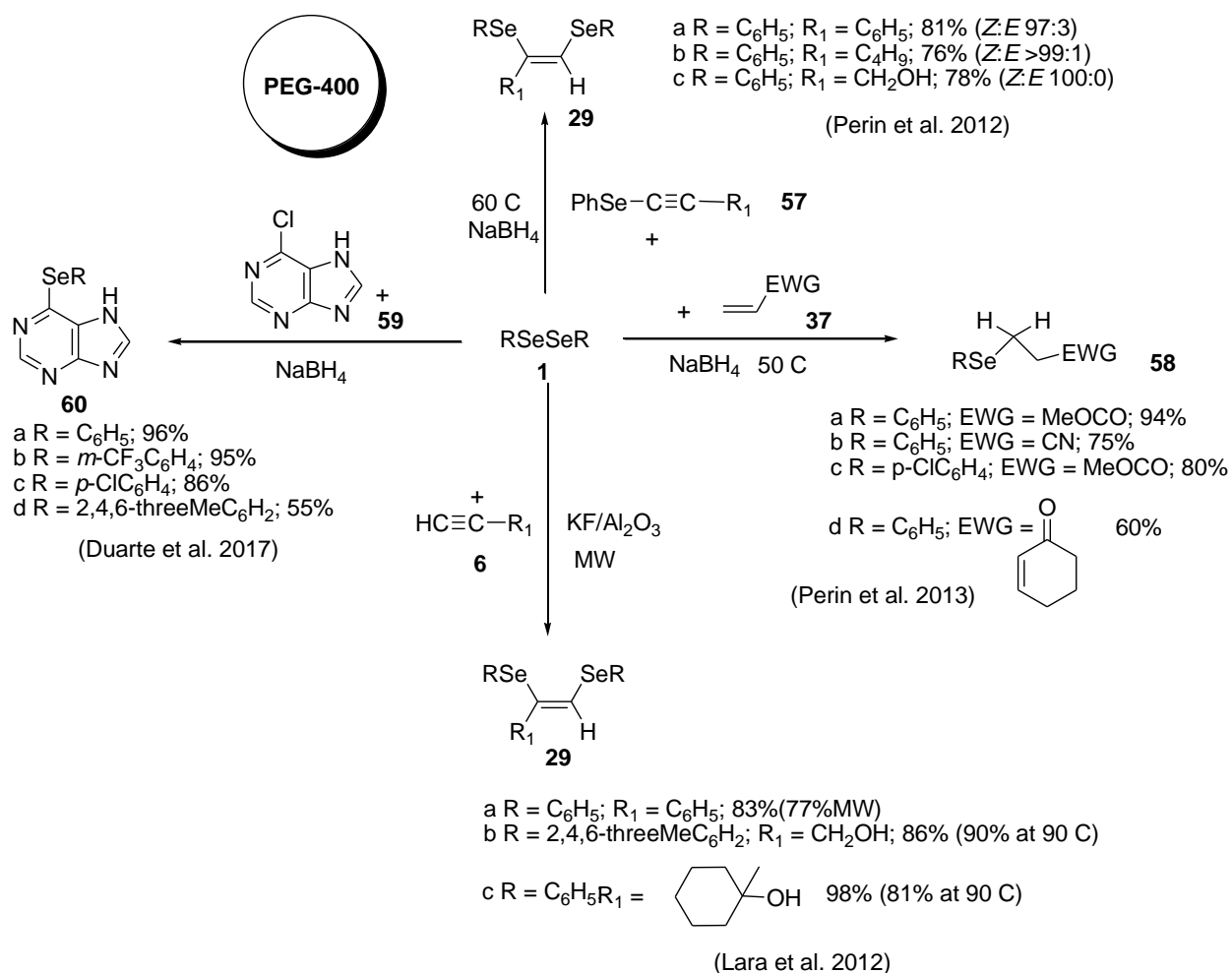
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4 Following the same methodology this group (Gonçalves et al. 2014) have developed the
5 approach for the synthesis of (*E*)-1,2-*bis*-chalcogen alkenes **30a-d** from the reaction between
6 terminal alkynes **6** and diorganyl diselenides **1** (**Scheme 22**). Again, the CuI/Zn/glycerol was
7 used as a recyclable catalytic system. The presence of electro-donating or neutral groups in the
8 molecular backbone of the diaryldiselenide has enabled the best yields and stereoselectivity.
9 Clearly, this observation can be attributed to the higher nucleophilicity of the selenium atom due
10 to the presence of the electron-donor groups. While the electronic effects of substituents in diaryl
11 selenide have significantly influenced the outcome, this behavior was not observed at the alkyne
12 moiety so that very similar results have been achieved. Moreover, the selected examples of the
13 synthesized compounds have expressed significant antioxidant activity.
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23 **5. Peg-400 as solvent**

24 5.1. (*Z*)-1,2-*bis*-phenylseleno alkenes

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26 PEG-based solvents have been introduced as a response to cost and safety of other alternative
27 reaction media. In organoselenium chemistry, PEG-400 has found a numerous applications as
28 solvent for *in situ* preparation of nucleophilic selenium species from diorganyl diselenides and
29 different reductive agents.
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37 For instance, (Perin et al. 2012) have reported the synthetic protocol for the selective preparation
38 of *Z*-1,2-*bis*-phenylseleno alkenes **29** starting from corresponding phenylseleno alkynes **57** and
39 diphenyldiselenide **1** (**Scheme 23**). As a reagent for the reductive cleavage of dichalcogenide
40 bond NaBH₄ was used. Various alkyl, aryl, as well as propargyl selenoalkynes could be
41 subjected to this transformation, giving products in high reaction yields (**29a-c**). Unlike the
42 results obtained with other nucleophilic selenium species, the exclusive formation of the 1,2-*bis*-
43 phenylseleno alkenes have been observed.
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Scheme 23. PEG-400-mediated organoselenium transformations.

5.2. Michael products

The same methodology was applied for nucleophilic addition of *in situ* formed selenium species (by the reaction of diorganyldiselenide **1** with NaBH₄ in PEG-400) to different α,β -unsaturated ketones, esters and nitrile **37** (**Scheme 23**) (Perin et al. 2013). The sort of Michael adducts was formed in good yields under very mild conditions, showing no sensitivity to the electronic effects of the substituents in diarylselenide moiety (**58a-d**, **Scheme 23**).

5.3. (Z)-bis-organyl alkenes

KF/Al₂O₃/PEG-400 system was used for selective conversion of range of terminal alkynes **6** into (Z)-1,2-bis-arylselanyl alkenes **29** by the reaction with diaryldiselenides **1** (**Scheme 23**) (Lara et al. 2012). The system can be reused without significant loss of activity. The procedure has been

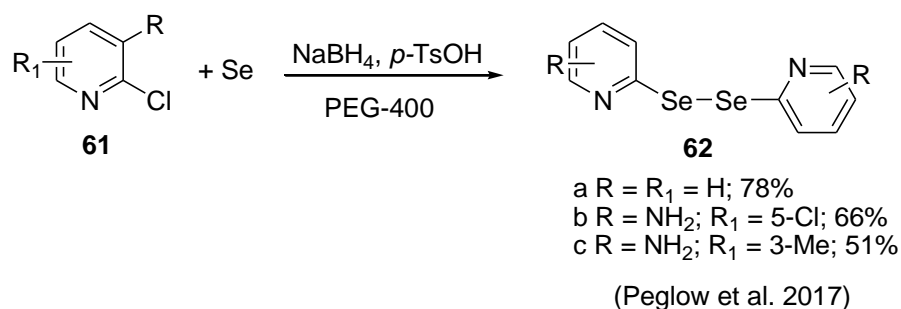
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4 also extended to the preparation of 1-mesitylselanyl and 1-phenyltellanyl alkynes starting from
5 phenylacetylene. In order to minimize energetic demands, a microwave irradiation has been
6 applied with the adjustment of reaction time on few minutes.
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10 11 5.4. Arylselanylpurines

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13 (Duarte et al. 2017) furnished the synthesis of 6-arylselanylpurines **60** by the reaction of 6-
14 chloropurines **59** and diaryl diselenides **1** in the presence of NaBH₄ as reductive agent and PEG-
15 400 as reaction media (**Scheme 23**). The outcome of the reaction is showing interesting
16 sensitivity to the steric hindrances originated from the methyl groups attached on the aryl moiety
17 of starting diselenide (**60d**). Some of the obtained compounds have shown promising therapeutic
18 potential for the Alzheimer's disease due to the inhibiting activity toward acetylcholinesterase
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28 5.5. Bis-(2-pyridil) diselenides

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30 Although not in the domain of organoselenium chemistry, herein we will mention an example of
31 a series of *bis*-(2-pyridil) diselenide derivatives **62** which have been prepared from 2-
32 chloropyridines **61** and selenium species generated in situ reductively (**Scheme 24**) (Peglow et
33 al. 2017). The reaction was accelerated by the *p*-TsOH and PEG-400 was used as a reaction
34 media. This synthetic protocol has enabled approach for the first synthesis of *bis*-(3-amino-2-
35 pyridil)diselenides (**62b,c**) which can be further elaborated into wide range of unsymmetrical
36 diorganyl selenides by the reaction with aliphatic halides in the presence of NaBH₄.
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56 **Scheme 24.** PEG-400-promoted synthesis of the *bis*-(2-pyridil) diselenides.
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58 **Conclusion**

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4 Organoselenium chemistry is a rich source of the useful reaction intermediates and biologically
5 important molecules. To make this area more sustainable, a detailed knowledge of the
6 application of greener alternative methods is necessary. The benefits of the application of
7 environmentally more acceptable mediums (such as room temperature ionic liquids, deep
8 eutectic solvents, naturally sourced solvents (ethanol and glycerol) and liquid polymers (PEG-
9 400)) in organoselenium-induced transformations are reflected in high yields of the reaction
10 products, easier separation methods, avoidance of conventional flammable solvents and
11 expensive catalyst systems, as well as capacity for the recyclability of reaction mediums many
12 times without loss in activity. The potential of the organoselenium compounds as starting
13 material for the preparation of the ionic liquids with cationic and anionic selenium species which
14 can be successfully further used in different synthetic reactions is also overviewed. Despite the
15 fact that there is no universal and ideal green solvent substitute, this review provides the
16 important current guidelines and information about the latest research developments for the
17 future investigators in this field.
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31 **Declarations of interest:** none
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33 **Acknowledgments**

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37 of the Republic of Serbia (Grant: 172011). This research is part of the thematic multidisciplinary
38 network SeS Redox and Catalysis.
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Dear Prof. Robert Didier,

Please consider our revised review entitled **''The origin and current trends of the green organoselenium chemistry''** for the publication in Environmental Chemistry Letters. I appreciate the interest that the editor and reviewers have taken in our manuscript and the constructive criticism they have given – all suggested changes clearly improved our manuscript. I am also including a point-by-point response to the reviewers in addition to the changes described in the manuscript.

Answer on reviewers' comments:

Reviewer #1: The review article entitle The origin and current trends of the green organoselenium chemistry was carefully reviewed.
The presentation is poor and normal, I could not find extensive work in the review paper.
And also recent references are not considered. In each table proper references are missing.

Answer: A new literature survey which covers available literature from 2017 and 2018 is added in a review (all changes are highlighted yellow in the text). In addition, we have added proper references in all Schemes.

Reviewer #2: Dear Author,
it is a good work where, you prepered a series of PtnOm/CeO2 catalysts with n =1-4 and tested them in the CO oxidation reaction, and it was found that all catalysts provide full CO conversion at temperature above 180°C combining with a great thermostability.
But you used only one test to confirm the oxidation reaction and not use any tools to confirm the structure of a series of PtnOm/CeO2 catalysts with n =1-4 prepered, such as raman, FTIR, XRD and others.
I think this work need more measurements.

Answer: Our review is dealing with the application of the alternative solvents in the organoselenium area, so, as you can see, this comment is not related to our review and it is probably some technical error which happened during submission process.

Editorial remark: You are suggested to include a review of literature available for 2017 and 2018.

Answer: We have included literature data for 2017 and 2018 into text of a review (all changes are highlighted yellow).

With this revision, we have responded to all the comments made by Editor and Reviewers. We believe that revised review will now be acceptable for publication in Environmental Chemistry Letters.

Sincerely,
Marina Kostic

Corresponding author