Advanced Synthesis & Catalysis

Title: Iron-Enabled Utilization of Air as the Terminal Oxidant Leading to Aerobic Oxidative Deoximation by Organoselenium Catalysis

Authors: Chao Chen, Xu Zhang, Hongen Cao, Fang Wang, Lei Yu, and Qing XU

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801163

Link to VoR: http://dx.doi.org/10.1002/adsc.201801163

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Iron-Enabled Utilization of Air as the Terminal Oxidant Leading to Aerobic Oxidative Deoximation by Organoselenium Catalysis

Chao Chen,[†,a] Xu Zhang,[†,a] Hongen Cao,[†,a] Fang Wang,[a,b] Lei Yu,[a,]* and Qing Xu[a,c,]*

[a] Guangling College and Institute of Pesticide of School of Chemistry and Chemical Engineering and School of Horticulture and Plant Protection, Yangzhou University, Yangzhou 225002, China
Fax: (+86)-514-87975244; phone: (+86)-13665295901; e-mail: yulei@yzu.edu.cn; xuqing@yzu.edu.cn.
[b] Yangzhou Polytechnology Institute, Yangzhou, Jiangsu 225127, China
[c] College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang 325035, China
Fax: (+86)-577-8668-9302; phone: (+86)-138-5774-5327; e-mail: qing-xu@wzu.edu.cn.
† These authors contributed equally to this work.

Received: ((will be filled in by the editorial staff))

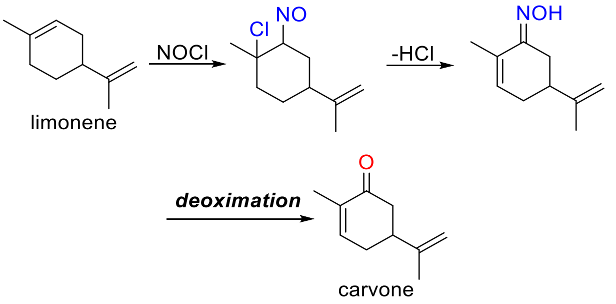
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract. In contrast to conventional organoselenium-catalyzed oxidation reactions that require peroxide oxidants such as hydrogen peroxide, in this work we found that, addition of a low loading of iron (II) could enable the successful utilization of air as the terminal oxidant in organoselenium-catalyzed oxidative deoximation reaction of ketoximes. This led to a new mild and relatively green aerobic oxidative deoximation method. Control reactions and X-ray photoelectron spectroscopy (XPS) analysis suggest that iron is crucial in the catalytic cycle, working to prohibit the deactivation of selenium catalyst through an iron-catalyzed aerobic oxidation of low valent selenium species by air to the active high valent selenium species. Since air can be utilized as the terminal oxidant, this work may contribute to the advance of organoselenium catalysis.

Keywords: aerobic oxidation; deoximation; iron; ketoximes; organoselenium catalysis

In the past decades, organoselenium chemistry has attracted extensive attention because of the unique chemical and biological activities of the organoselenium compounds.[1] Since selenium (Se) compounds are lower in cost than many of the widely-used noble metal catalysts/ligands, can be recovered and reused without much deactivation,[2] and Se itself is an organism-metabolizable and environmental-friendly element,[3] methods using organoselenium compounds as the catalysts has also been unfolding rapidly in recent years.[2,4-7] Besides, since Se-catalyzed reactions generally do not require harsh conditions but relatively greener conditions,[2,4,5] organoselenium catalysis may also be of good potential in industrial application in the future. We have also reported some Se-catalyzed oxidation reactions in the past five years,[2,5] in which hydrogen peroxide (H_2O_2) had to be employed as the oxidant. Although H_2O_2 is known as a relatively clean oxidant due to generation no other waste than the water,[2,4,5] it is on the other hand explosive and may become a dangerous reagent especially in large scale reactions. Therefore, new synthetic methods that can assemble the advantages of organoselenium catalysis and aerobic oxidation (using air or O_2 as the oxidant instead of H_2O_2) are highly desirable in the field as this may resolve the remaining issues in Se-catalyzed oxidation reactions.[7a,7b,7f]

On the other hand, oxidative deoximation[8] is a significant transformation in organic, pharmaceutical, and total synthesis, because the oxime block is an easily acquired stable functional group that can allow the utilization of oximation-deoximation strategies in protection and purification of carbonyl compounds or in the transformation of other functional groups into carbonyl group. For example, this protocol has been successfully employed by Corey *et al* in the total synthesis of *erythronolide A* in 1970s.[9] Deoximation could also be used in industrial-scale production of useful carbonyl-containing fine chemicals from non-carbonyl compounds. Synthesis of spice *carvone* from *limonene* is one of the typical examples (Scheme 1).[10] However, currently known deoximation methods usually require explosive peroxide oxidants such as H_2O_2,[11] or use potentially hazardous cyanide-containing catalysts or oxidants,[12] or use hazardous reagents such as hexachlorodisilane[13] or halogenated solvents,[14] or use excess hydrochloric acid with iron powder,[15] or use nitrite/nitrate-containing catalysts or additives.[14,16] Due to the use of the above-mentioned environmentally-unfriendly reagents or catalysts, these methods inevitably generate large amounts of wastes. Some even have a very limited scope of the substrates.[12a] Moreover, although the oxidative deoximation reaction could also be accomplished by using enzyme catalysts such as Laccase *T. versicolor*,[17] the method has its own limitations, either. Firstly, the enzyme catalysts are not cheap and can be easily deactivated. Secondly, the method requires additional use of 15 mol % TEMPO as the oxidation co-catalyst, which makes the method less preferable.



Scheme 1. Synthesis of *carvone* from *limonene* involving a key deoximation step.

In our ongoing studies on organoselenium catalysis,[2,5] we recently found that, addition of a low loading of Fe(II) can enable the successful utilization of the safe and economic air as the terminal oxidant in organoselenium-catalyzed oxidative deoximation reaction of ketoximes.[18] This finding leads to a facile aerobic oxidative deoximation method that can be performed in green solvents under mild conditions. Herein we disclose the detail of this work.

As shown in Figure 1, PhSe(O)OH-catalyzed oxidative deoximation of (*Z*)-1-phenylethan-1-one oxime (**1a**) was chosen as the model reaction. The reaction was initially heated in MeCN in open air in the absence of any metal co-catalysts (entry 1). Only a low yield of the product acetophenone (**2a**) was observed with low conversion of **1a**. Since formation of $(PhSe)_2$ was also observed in the reaction, we reckoned it might be the over-reduction of the Se catalyst and its difficulty in re-oxidation to PhSe(O)OH that caused the termination of the deoximation reaction.[19] Consequently, to achieve an effective aerobic re-oxidation reaction of $(PhSe)_2$ with air, various simple metal salts were added as the co-catalyst. Copper and manganese salts were firstly tested since they are both well known catalysts for oxidation reactions. However, $Cu(OAc)_2$, CuCl, and $Mn(OAc)_2$ (1.25 mol%)[20] did not show obvious promoting effect on the reaction (entries 2-4). Noble metal salt $RuCl_3$ also showed no obvious activity in the reaction (entry 5). Although ceric ammonium nitrate (CAN) and $Co(OAc)_2$ showed certain promoting effect, the product yields (34-42%) were still not satisfactory (entries 6-7). Then, $AgNO_3$ was found to be a better co-catalyst, affording **2a** in 61% yield (entry 8). Interestingly, the more abundant and cheaper iron salt $Fe(NO_3)_3$ was even more effective, leading to a higher 67% yield of **2a** (entry 9). Further screenings of the iron salts (entries 9-12) revealed that $FeSO_4$ is the best co-catalyst, which could afford **2a** in 73% yield under the same conditions (entry 12).

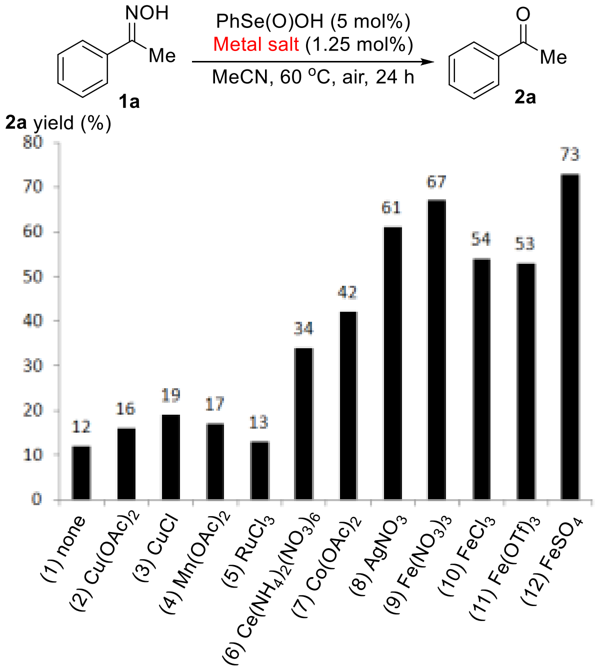


Figure 1. Evaluation of transition metal salts.

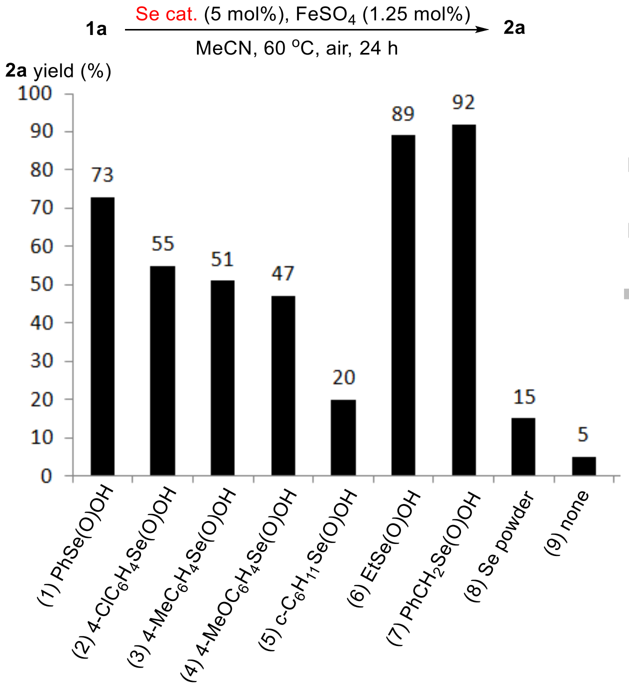


Figure 2. Screening of Se catalysts.

Different organoselenium acid RSe(O)OH were then screened to further optimize the Se catalyst. As shown in Figure 2, in comparison with PhSe(O)OH (entry 1), both electron-enriched and -deficient ArSe(O)OH were found to be less effective catalysts (entries 2-4), showing that introduction of electron-withdrawing and -donating groups is not a preferable protocol. Aliphatic RSe(O)OH were then investigated. Although *c*-C_6H_{11}Se(O)OH showed very poor catalytic activity in the reaction (entry 5), the reaction using EtSe(O)OH as the catalyst interestingly produced a very high 89% yield of **2a** (entry 6). Since *c*-$C_6H_{11}Se(O)OH$ is sterically more bulky than EtSe(O)OH, this suggests that the steric properties of the Se catalysts may affect the reaction greatly (*vide infra*). Further evaluation of $PhCH_2Se(O)OH$ showed that it's a more active catalyst for the reaction, affording **2a** in the highest 92% yield (entry 7). The reaction was also tested using inorganic Se powder as the catalyst or without using any Se catalyst (entries 8-9). The contrastive results suggested that Se acid RSe(O)OH is crucial to achieving a high efficiency of the aerobic oxidative deoximation reaction.

Reduced loadings of $PhCH_2Se(O)OH$ were also investigated to enhance the catalyst's turnover number (TON) (Figure 3, entries 1-4). However, this only led to decreased yields of **2a**. Similarly, increased loadings of $PhCH_2Se(O)OH$ were also not preferable (entries 6-10). Thus, 5 mol% $PhCH_2Se(O)OH$ was still the best catalyst loading for the reaction.

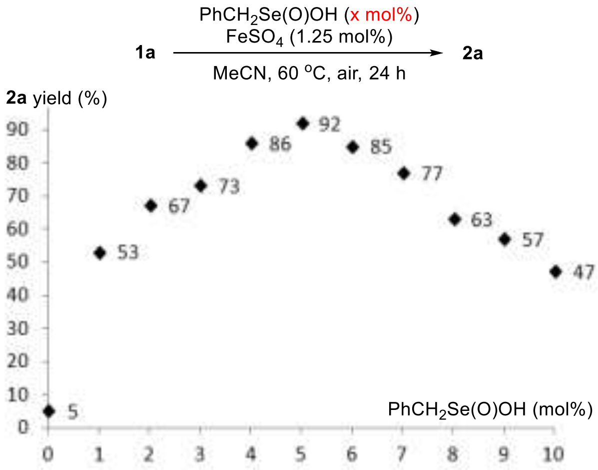


Figure 3. Evaluation of catalyst loading.

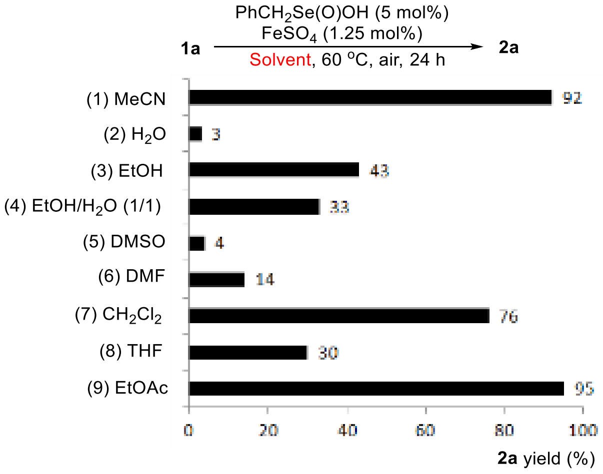


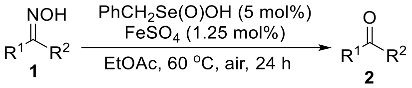
Figure 4. Evaluation of solvents.

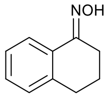
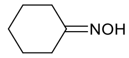
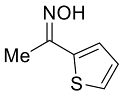
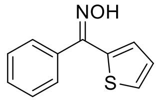
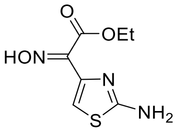
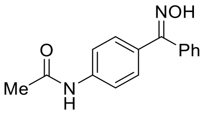
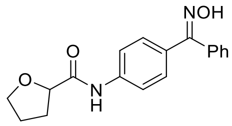
Solvents were then evaluated (Figure 4). Water was firstly considered, but was found rather ineffective (entry 2). Unfortunately, relatively greener solvents like ethanol and aqueous ethanol ($EtOH/H_2O$ 1/1) also gave poor yields of the product (entries 3-4). Usual organic solvents such as DMSO, DMF, CH_2Cl_2 and THF were found less effective than CH_3CN (entries 5-8). To our surprise, ethyl acetate (EtOAc), a cheap, abundant, and relatively green but seldom-used as a solvent in organic reactions, was observed to be the best one for the reaction, giving the highest 95% yield of **2a** under the standard conditions (entry 9).

Therefore, as demonstrated in Figures 1-4, performing the reaction in open air at 60 °C in EtOAc using 5 mol% of $PhCH_2Se(O)OH$ and 1.25 mol% of $FeSO_4$ as the catalysts is the best conditions for this aerobic oxidative deoximation reaction. These conditions were then applied to a series of ketoximes to extend the scope of the method. As shown in Table 1, similar to **1a**, ketoximes with either electron-donating or electron-withdrawing groups substituted at the *ortho*-, *meta*- and *para*-positions on the phenyl ring all afforded the corresponding ketones in excellent yields (entries 2-9), revealing that electronic and steric properties of the substituents do not affect the substrate's reactivity greatly. In addition, 1-phenylpropan-1-one oxime **1j** and 1-phenylbutan-1-one oxime **1k**, substrates with relatively short alkyl chains, also produced the target ketones **2j** and **2k** in high yields under the standard conditions (91-93%) (entries 10-11). In great contrast, in the cases of ketoximes with longer alkyl chains such as *n*-C_4H_9 and *n*-C_6H_{13}, much lower yields of the products were obtained (entries 12-13). This is mostly likely due to the increased steric hindrance derived from the longer alkyl chains that could prevent the addition of the catalyst to the C=N bond of the ketoximes according to the reaction mechanism (*vide infra*). Thus, even performing the reactions at a higher temperature of 80 °C, it was still difficult to improve the products' yields (entries 12-13, yields in parenthesis). Diaryl ketoximes **1n-r** were then investigated. Regardless of the substituents on both phenyl rings, all substrates gave the ketone products in excellent yields (entries 14-18). Contrarily, the reaction of 3,4-dihydronaphthalen-1(2*H*)-one oxime **1s** was less efficient, giving **2s** in a lower yield of 45% under the standard conditions (entry 19). This may also attributed to the steric hindrance of the fused phenyl moiety according to the reaction mechanism (*vide infra*); whereas, a higher 66% yield of **2s** could be obtained by performing the reaction at a higher temperature (entry 19, yield in parenthesis). Most likely due to the same reason and also the volatile nature of product cyclohexanone **2t**, although a moderate GC yield of **2t** could be observed, the reaction of cyclohexanone oxime (**1t**) only gave **2t** in a lower isolated yield (entry 20).

Substrate scope of the method was further investigated by employing more complex substrates with other functional groups. Thus, the deoximation reaction of 1-(thiophen-2-yl)ethan-1-one oxime (**1u**) bearing a hetroaryl group also proceeded smoothly under the standard conditions to give **2u** in a good yield (entry 21). With a more bulky phenyl group than **1u**, the reaction of phenyl(thiophen-2-yl)methanone (**1v**) became more sluggish and gave only a moderate yield of **2v** in an extended reaction time (entry 22). Employing the same protocol, ethyl 2-(2-aminothiazole-4-yl)-2-hydroxyiminoacetate **1w**, an important pharmaceutical intermediate bearing sulphur, nitrogen, and ester groups, also afforded the desired product **2w** in a moderate yield (entry 23). Moreover, oximes **1x** and **1y** bearing amide and non-aryl ether groups could also produce the corresponding carbonyl compounds **2x** and **2y** under similar conditions (entries 24-25), albeit the yields of the products were not high. This is most likely due to the great steric hindrance generated from these complex substrates.

Table 1. Substrate scope of the Se/Fe co-catalyzed aerobic oxidative deoximation reaction.[a]

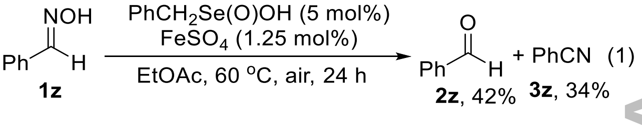


Entry	**1**: R^1, R^2	**2**: yield (%)[b]
1	**1a**: Ph, Me	**2a**: 95
2	**1b**: 4-MeC_6H_4, Me	**2b**: 90
3	**1c**: 3-MeC_6H_4, Me	**2c**: 91
4	**1d**: 2-MeC_6H_4, Me	**2d**: 88
5	**1e**: 4-$MeOC_6H_4$, Me	**2e**: 89
6	**1f**: 4-ClC_6H_4, Me	**2f**: 92
7	**1g**: 3-ClC_6H_4, Me	**2g**: 89
8	**1h**: 2-ClC_6H_4, Me	**2h**: 90
9	**1i**: 4-$NO_2C_6H_4$, Me	**2i**: 83
10	**1j**: Ph, C_2H_5	**2j**: 91
11	**1k**: Ph, *n*-C_3H_7	**2k**: 93
12[c]	**1l**: Ph, *n*-C_4H_9	**2l**: 36 (44)[d]
13[c]	**1m**: Ph, *n*-C_6H_{13}	**2m**:27(35)[d]
14	**1n**: Ph, Ph	**2n**: 96
15	**1o**: 4-MeC_6H_4, 4-MeC_6H_4	**2o**: 96
16	**1p**: 4-$MeOC_6H_4$, 4-$MeOC_6H_4$	**2p**: 80
17	**1q**: 4-ClC_6H_4, 4-ClC_6H_4	**2q**: 85
18	**1r**: 4-FC_6H_4, 4-FC_6H_4	**2r**: 93
19[c]	**1s**: 	**2s**: 45 (66)[d]
20[c,d]	**1t**: 	**2t**: 22 (47[e])
21	**1u**: 	**2u**: 83
22[c]	**1v**: 	**2v**: 68[f]
23[c]	**1w**: 	**2w**: 50 [d,f,g]
24[c]	**1x**: 	**2x**: 36
25	**1y**: 	**2y**: 21

---

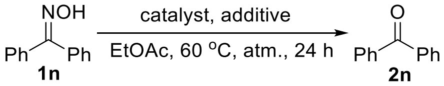
[a] 1 mmol of **1**, 5 mol % of PhSe(O)OH, 1.25 mol % of $FeSO_4$ and 2 mL of EtOAc were employed.
[b] Isolated yields based on **1**.
[c] Reactions incomplete.
[d] 80 °C.
[e] GC yield.
[f] 48 h.
[g] EtOH was used as the solvent instead of EtOAc.

To probe whether the present Se/Fe-catalyzed method can be extended to aldoximes to transform the oxime group to aldehyde group, benzaldehyde oxime (**1z**) was also investigated under the standard conditions [Eq. (1)]. However, in addition to the generation of 42% target benzaldehyde (**2z**), the dehydration by-product benzonitrile (**3z**) was also obtained in 34% yield. This result suggests that the present method may not be suitable for transformation of aldoximes to aldehydes.



Control reactions were then investigated to help understanding the mechanism of this interesting Se/Fe co-catalyzed aerobic oxidative deoximation reaction (Table 2). Initially, addition of water as the free radical scavenger or azodiisobutyronitrile (AIBN) as the free radical initiator to the reaction of **1n** was found unable to affect the reaction greatly (Table 2, entries 1-2), suggesting that a free-radical mechanism can be excluded. In contrast to the preceding aerobic conditions (condition screening section and Table 1), a control reaction under N_2 gave a very low yield of the product **2n** (entry 3); whereas, addition of a stoichiometric amount of $PhCH_2Se(O)OH$ under N_2 could improve the product yield to 80% (entry 4). These results indicated that an oxidant, either air or $PhCH_2Se(O)OH$, is indispensible in the reaction.

Table 2. Control reactions for Se/Fe co-catalyzed aerobic oxidative deoximation reaction.[a]



Entry	Catalyst (mol%), additive (mol%), atm.[b]	**2n**%[b]
1	$PhCH_2Se(O)OH$ (5), $FeSO_4$ (1.25), H_2O (100), open air	90
2	$PhCH_2Se(O)OH$ (5), $FeSO_4$ (1.25), AIBN (50), open air	89
3[c]	$PhCH_2Se(O)OH$ (5), $FeSO_4$ (1.25), N_2	10
4	$PhCH_2Se(O)OH$ (100), $FeSO_4$ (1.25), N_2	80
5	$PhCH_2Se(O)OH$ (100), N_2	84
6	$PhCH_2Se(O)OH$ (5), H_2O_2 (100), N_2	92
7	H_2O_2 (100), N_2	17
8[c]	$FeSO_4$ (100), N_2	trace
9[c]	$Fe_2(SO_4)_3$ (100), N_2	18

[a] 1 mmol of **1n** in 2 mL of EtOAc.
[b] Isolated yield based on **1n**.
[c] Reactions incomplete.

Moreover, in reactions using stoichiometric amounts of $PhCH_2Se(O)OH$ or H_2O_2 as the oxidant (entries 5-6), it was found $FeSO_4$ is not needed. In contrast, the reaction with stoichiometric amount of H_2O_2 alone without adding Se and Fe catalysts afforded only a poor yield of the product (entry 7). These results are consistent with the known Se-catalyzed oxidative deoximation reaction,[2a] indicating that $PhCH_2Se(O)OH$ should be the active oxidant for the deoximation process and H_2O_2 or air as the terminal oxidant for the reaction. It may further suggest that Fe's role in the reaction is most likely to enable the generation of the active oxidant for the reaction. Meanwhile, control reactions with stoichiometric amount of $FeSO_4$ or $Fe_2(SO_4)_3$ alone led to poor yields of **2n** under N_2 (entries 8-9), suggesting that Fe(II) even the more oxidative Fe(III) are not the active oxidant for the deoximation reaction. The above contrastive results implied that Fe most likely works to catalyze the aerobic oxidation of the reduced low valent Se species for generation of an active high valent Se oxidant such as $PhCH_2Se(O)OH$ by employing air as the oxidant.

Thereafter, X-ray photoelectron spectroscopy (XPS) analysis was employed to further disclose the role of Fe in the catalyst system. As shown in Figure 5, 1 mmol of $(PhCH_2Se)_2$ was heated in 2 mL of EtOAc in air under the standard conditions (60 ºC, 24 h) either in the absence or in the presence of 0.25 equiv. of $FeSO_4$. The XPS spectra obtained from the sample without $FeSO_4$ (Figure 5A) showed that there is still 24% ratio of the low valent Se^{2+} species. In contrast, in the spectra of the sample with $FeSO_4$ added (Figure 5B), the low valent Se^{2+} species disappeared almost completely and a high selectivity (96%) for the high valent Se^{4+} species [corresponds to $PhCH_2Se(O)OH$] could be observed. This suggested that Se^{2+} could be effectively oxidized to Se^{4+} by air in the presence of $FeSO_4$. Moreover, after correcting the C1s peak to 284.8 eV, the Se^{4+} peaks were at 58.95 eV and 59.59 eV, while the Se^{2+} peaks were at 55.93 eV and 56.57 eV (Figure 5A). These peaks shifted to 58.38 eV, 59.02 eV, 56.01 eV, and 56.95 eV, respectively, after the addition of $FeSO_4$ (Figure 5B). These shifts suggest that an interaction between Se and Fe might have occurred, which may further contribute to the Fe-catalyzed aerobic oxidation of low valent Se species.

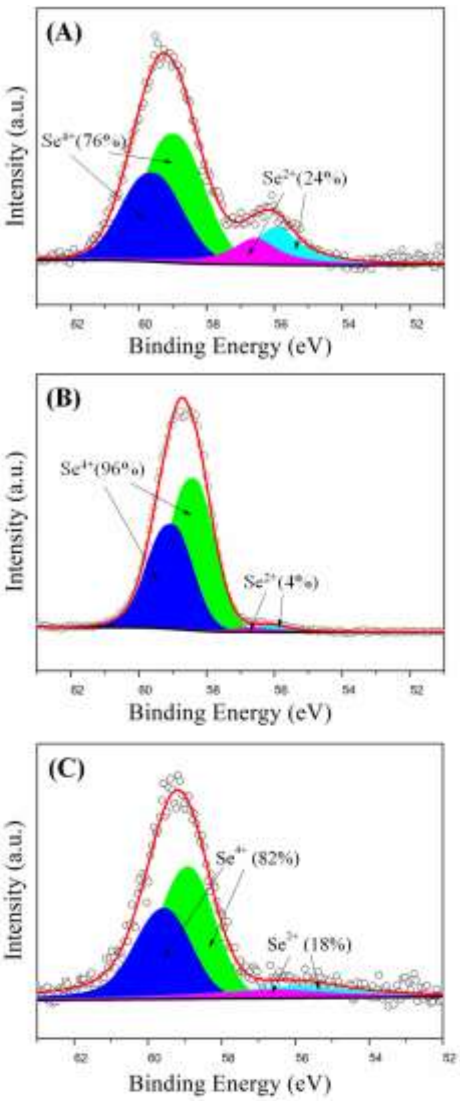
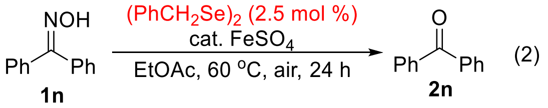


Figure 5. XPS analysis: heating $(PhCH_2Se)_2$ in air without $FeSO_4$ (A) or with 0.25 equiv. of $FeSO_4$ (B) and heating oxime **1a** with 5 mol% $PhCH_2Se(O)OH$ under N_2 (C).

On the other hand, in addition to the observation of the generated small amount of $(PhCH_2Se)_2$ in the reaction of 5 mol% of $PhCH_2Se(O)OH$ with 1 mmol of **1a** (2 mL EtOAc, under N_2, 60 °C, 24 h), XPS analysis of the reaction residue also clearly showed the generation of low valent Se species Se^{2+} (Figure 5C). To confirm that $(PhCH_2Se)_2$ was indeed generated in the above reaction, a tenfold reaction [10 mmol **1a** with 0.5 mmol of $PhCH_2Se(O)OH$] was also carried out under the same conditions and subjected to purification by column chromatography. As a result, 5.2 mg of $(PhCH_2Se)_2$ could be isolated and confirmed by comparison with the authentic sample. These observations clearly confirmed that $PhCH_2Se(O)OH$ could be easily reduced to $(PhCH_2Se)_2$ by the ketoxime substrates.[19]

The above contrastive results (Figure 5) are consistent with those of the control reactions (Table 2), clearly supporting the point that Fe's role in the reaction should be working as the catalyst for the aerobic re-oxidation of low valent Se species to high valent Se species such as $PhCH_2Se(O)OH$. Hence, an organoselenium-catalyzed aerobic oxidative deoximation reaction could be achieved using air as the terminal oxidant by using Fe(II) as an effective Se catalyst's oxidation catalyst. In this sense, in comparison with some preceding reports using iron slats as the catalyst or oxidant,[12,16,18] the role of $FeSO_4$ in the present reaction is obviously different. In those reports, NO_3^- works as the catalyst other than Fe in the deoximation reactions.[12,16,18]

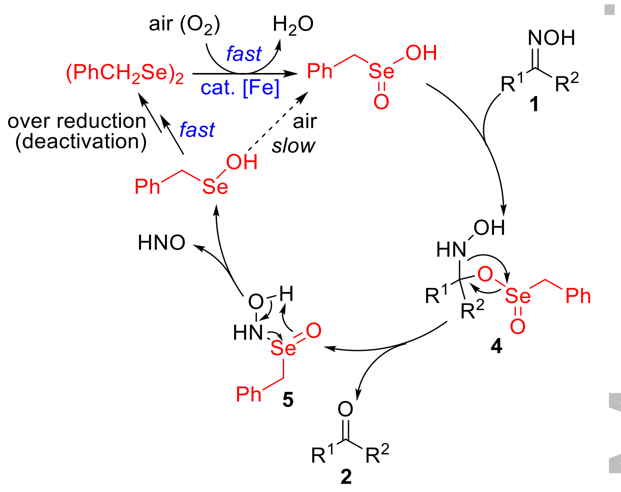
Since $(PhCH_2Se)_2$ can be re-oxidized to $PhCH_2Se(O)OH$ by Fe catalysis based on above findings, we also investigated a few control reactions using $(PhCH_2Se)_2$ as the catalyst instead of $PhCH_2Se(O)OH$ as $(PhCH_2Se)_2$ is also readily available. However, under the standard conditions using 2.5 mol% $(PhCH_2Se)_2$ and 1.25 mol% $FeSO_4$, only a low yield of **2n** was obtained with recovery of a considerable amount of starting **1n** [Eq. (2), entry 1]. Clearly this result cannot compete with those obtained from $PhCH_2Se(O)OH$, but it may suggest that the loading of $FeSO_4$ is not adequate. Hence, reactions with higher loadings of $FeSO_4$ were investigated [Eq. (2), entries 2-3], which indeed afforded high yields of **2n** as expected. Although $PhCH_2Se(O)OH$ is still the more preferable catalyst as it require a much lower loading of $FeSO_4$, the above results also support Fe's role in the reaction as a catalyst for aerobic oxidation of low valent Se species to high valent Se species.



1n **2n** (2)

entry	$FeSO_4$ (mol%)	**2n**%
1	1.25	31 (standard condition)
2	5	90
3	10	96

Based on above results and the literature knowledge,[2,5,19,21] a plausible mechanism is proposed for the Se/Fe co-catalyzed aerobic oxidative deoximation reaction. As shown in Scheme 2, nucleophilic addition of $PhCH_2Se(O)OH$ to oximes **1** may firstly occur to give adduct **4**, which then rearranges to afford product ketones **2** and organoselenium species **5**.[2a] Decomposition of **5** may then occur to afford the possible byproduct hyponitous acid (HNO) and a reduced Se species $PhCH_2SeOH$.[21] It is known that $PhCH_2SeOH$ can be easily reduced to the more stable and difficult-to-oxidize diselenides under the reaction conditions, most likely by the substrates or the solvents.[19] Hence, only a low yield of the product could be obtained in the reaction with lone $PhCH_2Se(O)OH$ catalyst. Contrarily, addition of Fe(II) as the catalyst's oxidation catalyst can cause a dramatic effect on improving the catalytic performance of the reaction by a re-oxidation of the diselenide to the active oxidant $PhCH_2Se(O)OH$ to finally furnish the catalytic cycle.



Scheme 2. Possible mechanism of the Se/Fe co-catalyzed aerobic oxidative deoximation reaction.

In conclusion, by employing a low loading of Fe(II) as the Se catalyst's aerobic oxidation catalyst, the abundant and economic air can be successfully utilized as the terminal oxidant instead of the conventionally used peroxide oxidants in the oxidative deoximation of ketoximes. This led to a Se/Fe co-catalyzed mild and relatively green aerobic oxidative deoximation method. Control reactions and X-ray photoelectron spectroscopy (XPS) analysis confirmed that Fe is crucial in the catalytic cycle, working to prohibit the deactivation of the Se catalyst through a Fe-catalyzed aerobic oxidation of the generated low valent Se species such as $(PhCH_2Se)_2$ by air to the active high valent Se species such as $PhCH_2Se(O)OH$. Since air can be well utilized as the terminal oxidant, this work may contribute to the advance of organoselenium-catalyzed oxidation reactions. Further extension and applications of the Fe-facilitated organoselenium-catalyzed aerobic oxidation reaction are under way in this group.

Experimental Section

General

All reagents were purchased with purities >98% and used directly as received. Solvents are analytical pure (AR) and directly used without any further treatment. IR spectra were measured on a Bruker Tensor 27 Infrared spectrometer. NMR spectra were recorded on a Bruker Avance instrument (400 MHz for ^{1}H NMR) using CDCl$_3$ as the solvent and Me$_4$Si as the internal standard. Chemical shifts for ^{1}H NMR were referred to internal Me$_4$Si (0 ppm) and *J*-values shown in Hz. GC-MS analysis were performed on a Thermofisher Trace ISQ instrument, with initial temperature 50 °C and temperature increasing rate at 15 °C/min for 50-200 °C and at 10 °C/min for 200-300 °C. The XPS spectra were determined on ThermoScientific ESCALAB 250Xi X-ray photoelectron spectrometer.

Typical procedure for the deoximation reaction.

The mixture of 1 mmol of ketoxime (**1**), 0.05 mmol of PhCH$_2$Se(O)OH and 0.0125 mmol of FeSO$_4$·7H$_2$O in 2 mL of EtOAc in a reaction tube was heated at 60 °C in open air for 24 h. After cooling to room temperature, the solvent was removed by a rotary evaporator and the residue separated by flash column chromatography (eluent: petroleum/EtOAc = 20/1) to afford the ketone product (**2**).

Acknowledgements

We thank NNSFC (21202141, 21672163), Jiangsu Provincial Six Talent Peaks Project (XCL-090), Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), Top-notch Academic Programs Project of Jiangsu Higher Education Institutions (TAPP), and the Nature Science Foundation of Guangling College (ZKZD17005) for financial support.

References

[1] For selected recent articles, please see: a) A. M. S. Recchi, D. F. Back, G. Zeni, *J. Org. Chem.* **2017**, *82*, 2713–2723; b) S. Kodama, T. Saeki, K. Mihara, S. Higashimae, S. Kawaguchi, M. Sonoda, A. Nomoto, A. Ogawa, *J. Org. Chem.* **2017**, *82*, 12477–12484; c) C. Santi, C. Tomassini, L. Sancineto, *Chimia* **2017**, *71*, 592-595; d) Y.-X. Zhen, M. Yang, H. Zhang, G.-S. Fu, J.-L. Wang, S.-F. Wang, R.-N. Wang, *Sci. Bull.* **2017**, *62*, 1530-1537; e) H. Luan, H. Sun, B. Xue, X. Li, *Chin. J. Org. Chem.* **2017**, *37*, 1392-1397; f) S. Fiorito, F. Epifano, V. A. Taddeo, S. Genovese, L. Sancineto, C. Santi, *Planta Med.* **2016**, *82*, P732; g) A. A. Vieira, J. B. Azeredo, M. Godoi, C. Santi, E. N. da Silva Jr., A. L. Braga, *J. Org. Chem.* **2015**, *80*, 2120–2127.

[2] a) Y. Wang, L. Yu, B. Zhu, L. Yu, *J. Mater. Chem. A* **2016**, *4*, 10828–10833; b) L. Yu, Z. Bai, X. Zhang, X. Zhang, Y. Ding, Q. Xu, *Catal. Sci. Technol.* **2016**, *6*, 1804–1809; c) L. Yu, J. Ye, X. Zhang, Y. Ding, Q. Xu, *Catal. Sci. Technol.* **2015**, *5*, 4830–4838; d) L. Yu, H. Li, X. Zhang, J. Ye, J. Liu, Q. Xu, M. Lautens, *Org. Lett.* **2014**, *16*, 1346−1349.

[3] Se is metabolizable and does not accumulate in the organisms: a) M. P. Rayman, *Lancet* **2012**, *379*, 1256–1268; On the other hand, although Se compounds may be toxic, organoselenium compounds are generally less toxic than the inorganic ones. Some are even non-toxic (such as diphenyl diselenide and ebselen): a) F. C. Meotti, V. C. Borges, G. Zeni, J. B. T. Rocha, C.W. Nogueira, *Toxicol. Lett.* **2003**, *143*, 9–16;

[4] a) L. Sancineto, F. Mangiavacchi, C. Tidei, L. Bagnoli, F. Marini, A. Gioiello, J. Scianowski, C. Santi, *Asian J. Org. Chem.* **2017**, *6*, 988–992; b) L. Sancineto, C. Tidei, L. Bagnoli, F. Marini, E. J. Lenardao, C. Santi, *Molecules* **2015**, *20*, 10496–10510; c) C. Santi, R. Di Lorenzo, C. Tidei, L. Bagnoli, T. Wirth, *Tetrahedron* **2012**, *68*, 10530–10535; d) S. Santoro, C. Santi, M. Sabatini, L. Testaferri, M. Tiecco, *Adv. Synth. Catal.* **2008**, *350*, 2881–2884; e) G.-J. ten Brink, B. C. M. Fernandes, M. C. A. van Vliet, I. W. C. E. Arends, R. A. Sheldon, *J. Chem. Soc. Perkin Trans. 1* **2001**, 224–228.

[5] a) T. Wang, X. Jing, C. Chen, L. Yu, *J. Org. Chem.* **2017**, *82*, 9342−9349; b) L. Yu, F. Chen, Y. Ding, *ChemCatChem* **2016**, *8*, 1033–1037; c) X. Zhang, J. Sun, Y. Ding, L. Yu, *Org. Lett.* **2015**, *17*, 5840–5842; d) L. Yu, Y. Wu, H. Cao, X. Zhang, X. Shi, J. Luan, T. Chen, Y. Pan, Q. Xu, *Green Chem.* **2014**, *16*, 287–293.

[6] For reviews, please see: a) D. M. Freudendahl, S. Santoro, S. A. Shahzad, C. Santi, T. Wirth, *Angew. Chem.* **2009**, *121*, 8559–8562; *Angew. Chem. Int. Ed.* **2009**, *48*, 8409–8411; b) C. Santi, S. Santoro, B. Battistelli, *Curr. Org. Chem.* **2010**, *14*, 2442–2462; c) S. Santoro, J. B. Azeredo, V. Nascimento, L. Sancineto, A. L. Braga, C. Santi, *RSC Adv.* **2014**, *4*, 31521–31535; d) J. Młochowski, H. Wójtowicz-Młochowska, *Molecules* **2015**, *20*, 10205–10243; e) A. Breder, S. Ortgies, *Tetrahedron Lett.* **2015**, *56*, 2843–2852; f) R. Guo, L. Liao, X. Zhao, *Molecules* **2017**, *22*, 835.

[7] a) C. Depken, F. Krätzschmar, R. Rieger, K. Rode, A. Breder, *Angew. Chem.* **2018**, *130*, 2484–2488; *Angew. Chem. Int. Ed.* **2018**, *57*, 2459–2463; b) A. Breder, K. Rode, M. Palomba, S. Ortgies, R. Rieger, *Synthesis* **2018**, *50*, 3875–3885; c) X. Liu, Y. Liang, J. Ji, J. Luo, X. Zhao, *J. Am. Chem. Soc.* **2018**, *140*, 4782–4786; d) J. Luo, Q. Cao, X. Cao, X. Zhao, *Nat. Commun.* **2018**, *9*, 527; e) R. Guo, J. Huang, X. Zhao, *ACS Catal.* **2018**, *8*, 926–930; f) S. Ortgies, R. Rieger, K. Rode, K. Koszinowski, J. Kind, C. M. Thiele, J. Rehbein, A. Breder, *ACS Catal.* **2017**, *7*, 7578–7586; g) L. Liao, R. Guo, X. Zhao, *Angew. Chem.* **2017**, *129*, 3249–3253; *Angew. Chem. Int. Ed.* **2017**, *56*, 3201–3205; h) W. Jin, P. Zheng, W.-T. Wong, G.-L Law, *Adv. Synth. Catal.* **2017**, *359*, 1588–1593; i) R. Guo, J. Huang, H. Huang, X. Zhao, *Org. Lett.* **2016**, *18*, 504–507; j) S. Ortgies, C. Depken, A. Breder, *Org. Lett.* **2016**, *18*, 2856–2859; k) A. J. Cresswell, S. T.-C. Eey, S. E. Denmark, *Nat. Chem.* **2015**, *7*, 146–152; l) Z. Deng, J. Wei, L. Liao, H. Huang, X. Zhao, *Org. Lett.* **2015**, *17*, 1834–1837; m) S. Ortgies, A. Breder, *Org. Lett.* **2015**, *17*, 2748–2751; n) F. Chen, C. K. Tan, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2013**, *135*, 1232–1235; o) J. Trenner, C. Depken, T. Weber, A. Breder, *Angew. Chem.* **2013**, *125*, 9121–9125; *Angew. Chem. Int. Ed.* **2013**, *52*, 8952–8956.

[8] G. Zhang, X. Wen, Y. Wang, W. Mo, C. Ding, *Prog. Chem.* **2012**, *24*, 361–369 and references cited therein.

[9] E. J. Corey, P. B. Hopkins, S. Kim, S. E. Yoo, K. P. Nambiar, J. R. Falck, *J. Am. Chem. Soc.* **1979**, *101*, 7131–7134.

[10] a) C. Isart, D. Bastida, J. Burés, J. Vilarrasa, *Angew. Chem.* **2011**, *123*, 3333–3337; *Angew. Chem. Int. Ed.*, **2011**, *50*, 3275–3279; b) A. Grirrane, A. Corma, H. Garcia, *J. Catal.* **2009**, *268*, 350–355; c) R. Reitsema, *J. Org. Chem.* **1958**, *23*, 2038–2039; d) E. E. Royals, S. E. Horne Jr., *J. Am. Chem. Soc.* **1951**, *73*, 5856–5857.

[11] a) X. Jing, D. Yuan, L. Yu, *Adv. Synth. Catal.* **2017**, *359*, 1194–1201; b) N. C. Ganguly, S. Nayek, S. K. Barik, *Synth. Commun.* **2009**, *39*, 4053–4061.

[12] a) A. García-Ortiz, A. Grirrane, E. Reguera, H. García, *J. Catal.* **2014**, *311*, 386–392; b) A. A. Manesh, B. S. Shaghasemi, *J. Chem. Sci.* **2015**, *127*, 493–497.

[13] L. Du, J. Gao, S. Yang, D. Wang, X. Han, Y. Xu, Y. Ding, *Russ. J. Gen. Chem.* **2014**, *84*, 2200–2204.

[14] G. Zhang, X. Wen, Y. Wang, W. Mo, C. Ding, *J. Org. Chem.* **2011**, *76*, 4665–4668.

[15] P. K. Pradhan, S. Dey, P. Jaisankar, V. S. Giri, *Synth. Commun.* **2005**, *35*, 913–922.

[16] a) Y. Li, N. Xu, G. Mei, Y. Zhao, Y. Zhao, J. Lyu, G. Zhang, C. Ding, *Can. J. Chem.* **2018**, *96*, 810–814; b) H. Firouzabadi, N. Iranpoor, K. Amani, *Synth. Commun.* **2004**, *34*, 3587–3593; c) G.-C. Arash, S. Lotfi, Z. Javad, *Bull. Korean Chem. Soc.* **2008**, *29*, 2496–2498.

[17] J. González-Sabín, N. Ríos-Lombardía, I. García, N. M. Vior, A. F. Braña, C. Méndez, J. A. Salas, F. Morís, *Green Chem.* **2016**, *18*, 989–994.

[18] Although the use of iron salts such as $Fe(NO_3)_3$, $K_3[Fe(CN)_6]{\cdot}3H_2O$, or $FeCu_2[Co(CN)_6]_2$ in deoximation reactions have been reported in the literature (refs. 12 and 16), Fe is not the working catalyst in those reactions. Instead, either the iron salts work as a kind of oxidant or the nitrate ion (NO_3^-) but not Fe is the working catalyst.

[19] High valent Se catalysts may be reduced to the more stable diselenides, leading to deactivation of the Se catalyst. This can occur even under strong oxidation conditions with excess H_2O_2. Diselenide generation could also be observed by TLC/GC-MS. Please see: L. Yu, J. Wang, T. Chen, K. Ding, Y. Pan, *Chin. J. Org. Chem.* **2013**, *33*, 1096–1099.

[20] The metal salts were initially evaluated in more amounts. Then, evaluation of the Fe salts showed that 0.25 equiv. of Fe to Se is the best. Therefore, 1.25 mol% of the metal salts were later re-evaluated.

[21] a) H. J. Reich, *Acc. Chem. Res.* **1979**, *12*, 22–30; b) D. Liotta, *Acc. Chem. Res.* **1984**, *17*, 28–34.

UPDATE

Iron-enabled utilization of air as the terminal oxidant leading to aerobic oxidative deoximation by organoselenium catalysis

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

C. Chen, X. Zhang, H. Cao, F. Wang, L. Yu,* and Q. Xu*