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Dehydration of Aldoximes Using PhSe(O)OH as the *Pre*-Catalyst in Air

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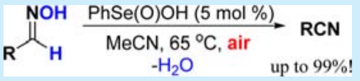
S *Supporting Information*

ABSTRACT: PhSe(O)OH was found to be a good *pre*-catalyst for aldoxime dehydrations in open air. Compared with the previously reported $(PhSe)_2$-H_2O_2 system, it is more stable and milder, affording broader application scopes due to a higher functional group tolerance. The control experiments for mechanism study disclosed that air was the key factor for the reaction to maintain enough concentration of PhSeOH, which should be the real catalytic species.

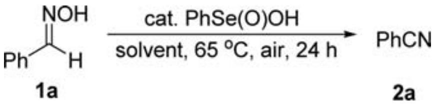


Selenium is an important and necessary trace element for human beings and has very wide applications in biochemistry, medicinal chemistry, organic synthesis, and material science.[1,2] Despite its toxicity,[3] the green side of this element began to draw attention in recent years.[4] Among reported works, organoselenium catalysis is an important and unique subject that presents additional opportunities to develop novel green synthetic methods with industrial potential.[5] Compared with transition metals, selenium can be metabolized in organisms and thus does not accumulate in the body and is safe for the environment.[3] Selenium is much less expensive than noble metals,[6] and the organoselenium catalysts are sufficiently robust to be recycled and reused with little deactivation.[7] The organoselenium-catalyzed reactions are performed under mild conditions, free of ligands or additives with green procedures.[7,8] Recently, organoselenium catalysts have been successfully employed in a series of useful transformations.[7−9]

During our ongoing investigations of green synthetic methodologies, we also paid attention to organoselenium catalysis.[7b−e,8a,b] In 2014, we reported the dehydration of aldoximes to produce nitriles. The reaction was catalyzed by 3-FC_6H_4SeOH, which was generated *in situ* from $(3\text{-}FC_6H_4Se)_2$ with equal molar ratio of H_2O_2.[7d] The method is clean because of the recyclable catalyst that generates no waste and the avoidance of chemical dehydrant and transition metal catalyst. However, since H_2O_2 is a strong and somewhat unstable oxidant, it is not convenient to be accurately weighted in a catalytic amount, especially for such small-scaled reactions. In addition, H_2O_2 may also react with the sensitive functional groups in substrates, thus leading to the limited application scopes of the reaction. Therefore, developing a more stable catalyst-system will obviously improve the practicability of the methodology. In our investigations on organoselenium-catalyzed reactions, we observed $(PhSe)_2$ in GC or TLC analysis, even when the reaction was performed with excess H_2O_2.[8b] It was suggested that the high valence organoselenium species might be unstable and could be reduced by substrates or solvents to the low valence $(PhSe)_2$ and the transformations possibly happened via the intermediate PhSeOH, the catalytic species for aldoxime dehydration. Inspired by the above phenomena and speculations, we tried to employ the stable and accessible PhSe(O)OH as a *pre*-catalyst in aldoxime dehydration. Herein, we wish to report our findings.

The dehydration of benzaldoxime **1a** was chosen as the model reaction for conditional optimizations. Based on our previous reports, 1 mmol of **1a** and 0.05 mmol of PhSe(O)OH were initially heated in 2 mL of MeCN at 65 °C for 24 h. The GC analysis indicated that the desired product **2a** was generated in more than 99% yield (Table 1, entry 1). Using DMSO as the solvent, the dehydration of **1a** also led to **2a** in excellent yield (Table 1, entry 2), but in DMF, the product yield decreased (Table 1, entry 3). The reaction in the nontoxic solvent EtOH gave **2a** in very poor yield (Table 1, entry 4), but interestingly, it

Table 1. Condition Optimizations[a]



entry	solvent	cat. loading (mol %)[b]	2a (%)[c]
1	MeCN	5	>99
2	DMSO	5	97
3	DMF	5	76
4	EtOH	5	27
5	$EtOH/H_2O$ (1:1)[d]	5	76
6	H_2O	5	77
7	cyclohexane	5	72
8	toluene	5	73
9		5	74
10	MeCN	4	95
11	MeCN	3	92
12	MeCN	2	91
13	MeCN	1	88
14	MeCN	0.5	76

[a] 1 mmol of **1a** and 2 mL of solvent were employed; Unless given special instructions, the reaction scales in this article were 1 mmol. [b] Catalyst loadings based on **1a**. [c] GC yields based on **1a** with biphenyl used as the internal standard. [d] Volume ratio inside the parentheses.

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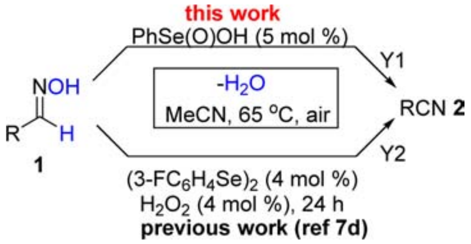
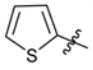
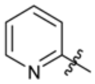
proceeded smoothly in aqueous conditions (Table 1, entries 5–6), possible because of the fact that ethanol over reduced the catalyst to the inactive $(PhSe)_2$, as acetaldehyde was detected by GC–MS.[10] The nonpolar solvents such as cyclohexane and toluene were also tested, giving **2a** in moderate yields (Table 1, entries 7–8). It should be noted that the reaction could also occur without solvent, indicating the great potential of this methodology in industry production (Table 1, entry 9). We also tried to perform the reaction with less catalyst, but the product yields decreased gradually with the reduction in the catalyst loadings (Table 1, entries 10–14). Thus, using 5 mol % of PhSe(O)OH and with MeCN as the solvent should be the optimized conditions. There is no need to further screen the organoselenium catalysts as in the previous works[7b−e] because PhSe(O)OH is one of the most accessible organoselenium compounds, and it afforded almost quantitative product yield.

The application scopes of this methodology were also examined. In order to facilitate the readers to understand the advantages of the reactions using PhSe(O)OH as *pre*-catalyst over those with $(PhSe)_2/H_2O_2$ in product yields, the results were listed in parallel (Table 2). The Y1 indicate the product yields of the reactions using PhSe(O)OH as *pre*-catalyst, while Y2 was those with $(3\text{-}FC_6H_4Se)_2/H_2O_2$. It was clear that the reactions catalyzed by PhSe(O)OH afforded the nitriles **2** in higher yields than those by $(3\text{-}FC_6H_4Se)_2/H_2O_2$, as previously reported (Table 2, entries 1–20),[7d] especially for the dehydrations of **1f**, **1j**, **1k**, **1n**, **1p**, **1q**, and **1r**, which might be sensitive to H_2O_2 and thus resulted in very poor product yields previously.[7d] It was noticed that the dehydration of thiophene-2-carbaldehydoxime **1q** afforded thiophene-2-carbonitrile **2q** in very low yield, while thiophene-2-carbaldehyde **3q**, the byproduct, was generated (Table 1, entry 18). A series of organoselenium catalysts were then tested to improve the reaction, and $3\text{-}FC_6H_4Se(O)OH$ was screened out to be the better one, giving **2q** in the acceptable 52% yield (Table 1, entries 19 vs 18).[10] The example indicated that the methodology could be further improved by screenings of the catalysts for certain unfavorable substrates.

Table 2. Application Scope Examinations

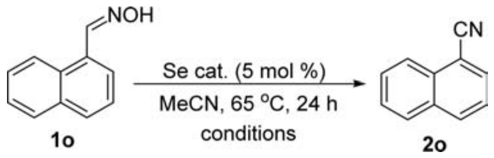


entry	R (**1**)	**2**	Y1/%[a] (*t*/h[b])	Y2/%[c]
1[d]	Ph (**1a**)	**2a**	85(24)	81[7d]
2[d]	$4\text{-}FC_6H_4$(**1b**)	**2b**	77(24)	70[7d]
3[d]	$4\text{-}ClC_6H_4$(**1c**)	**2c**	82 (24)	81[7d]
4[d]	$4\text{-}BrC_6H_4$(**1d**)	**2d**	88(24)	80[7d]
5[d]	$4\text{-}CF_3C_6H_4$(**1e**)	**2e**	84(24)	82[7d]
6	$3\text{-}NO_2C_6H_4$(**1f**)	**2f**	81(24)	10
7	$4\text{-}MeC_6H_4$(**1g**)	**2g**	75(3)	73[7d]
8[d]	$3\text{-}MeC_6H_4$(**1h**)	**2h**	88(24)	81[7d]
9	$4\text{-}MeOC_6H_4$(**1i**)	**2i**	98(6)	76[7d]
10	$4\text{-}Me_2NC_6H_4$(**1j**)	**2j**	48(24)	12
11	$4\text{-}HOC_6H_4$ (**1k**)	**2k**	46(48)	33
12			70(16)[e]	
13	$4\text{-}CH_2{=}CHCH_2OC_6H_4$(**1l**)	**2l**	90(24)	66[7d]
14	4-*t*-BuC_6H_4(**1m**)	**2m**	83(5)	74[7d]
15	$2,4,6\text{-}Me_3C_6H_2$(**1n**)	**2n**	73(24)	<5[7d]
16	$1\text{-}C_{10}H_6$(**1o**)	**2o**	>99(4)	82[7d]
17	*t*-Bu(**1p**)	**2p**	30(24)	<5[7d]
18	 (**1q**)	**2q**	25(24)	<5
19			52 (24)[f]	
20	 (**1r**)	**2r**	79(10)	26

[a]Isolated yields of **2** for reactions performed under the optimized conditions of Table 1, entry 1. [b]The reactions were monitored by TLC. [c]Isolated yields of **2** for reactions performed using $(3\text{-}FC_6H_4Se)_2/H_2O_2$ as in ref 7d. [d]Reactions performed in 5 mmol scale. [e]Reaction performed at 100 °C in a sealed tube. [f]$3\text{-}FC_6H_4Se(O)OH$ was employed as catalyst.

The reaction mechanisms were our next concern. In order to gain enough hints for study, a series of control experiments were taken. For its excellent performances (Table 2, entry 16), aldoxime **1o** was chosen as the model substrate and its dehydrations were performed using various catalysts under different conditions. The role of air in the reaction was investigated. As shown in Table 3, the dehydration of **1o** under air afforded the nitrile **2o** in nearly quantitative yield, but when it was taken in N_2, almost no reaction happened (Table 3, entries 1 vs 2). Considering the fact that $(PhSe)_2$ was recycled in >99% yield after the reaction in N_2 (Table 3, entry 2), it was suggested that PhSe(O)OH was reducible in the reaction and air was the key to reoxidize it into the active catalytic species. The reaction with pure O_2 also resulted in the incomplete reaction and the reduced product yield (Table 3, entries 3 vs 1) because PhSeOH, the medium valent selenium intermediate as we previously reported, should be the real catalytic species in the reaction.[7d] The reactions using $(PhSe)_2$ as *pre*-catalyst were examined. In air, it gave **2o** in very low yield, but with the assistance of strong oxidant O_2, **2o** was obtained in moderate yield (Table 3 entries 4 vs 5). The phenomena further supported the above hypothesis on mechanism. Further GC–MS analysis showed that the starting material aldoxime reduced the PhSe(O)OH, while the solvent MeCN and product nitrile were stable.[10]

Table 3. Control Experiments

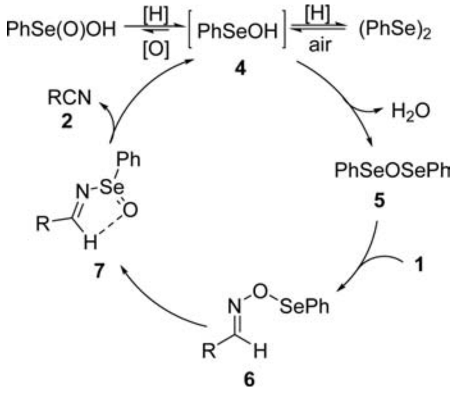


entry	Se cat. (loading/mol %)	conditions	**2o** (%)[a]
1	PhSe(O)OH (5)	air	>99
2	PhSe(O)OH (5)	N_2[b]	<5[c]
3	PhSe(O)OH (5)	O_2[d]	87[c]
4	$(PhSe)_2$ (2.5)	air	12[c]
5	$(PhSe)_2$ (2.5)	O_2[d]	67[c]

[a]Isolated yields based on **1o**. [b]$(PhSe)_2$ was recovered in >99% yield based on the precatalyst PhSe(O)OH. [c]Reactions not completed. [d]Introduced by a tiny glass tunnel (1 atm; flow rate, 0.88 cm^3/s).

Based on the above experimental results as well as refs 7 and 8, a plausible mechanism is given below (Scheme 1). As found in our previous work and proved by GC–MS analysis, the PhSe(O)OH was reducible by the starting material aldoxime to give the $(PhSe)_2$.[8b,10] The transformation proceeded through PhSeOH **4**, the active catalytic species for aldoxime dehydra-

Scheme 1. Possible Mechanisms



tion.[7d] Air should be the key factor to maintain enough PhSeOH concentration for the dehydration (Table 3, entries 1 vs 2), but stronger oxidant such as O_2 might oxidize **4** to PhSe(O)OH and thus restrained the reaction (Table 3, entries 3 vs 1). The dehydration of **4** led to the highly active species **5**,[7d,11] which reacted with the aldoximes **1** to produce the intermediates **6**. The rearrangement of **6** led to the intramolecular hydrogen bond-stabilized intermediate **7**,[7d] which decomposed to nitriles **2** and regenerated the catalytic species **4** through a well-known selenoxide *syn*-elimination.[12]

In conclusion, we developed a more practical methodology for the dehydration of aldoxime to produce nitriles using PhSe(O)-OH as the *pre*-catalyst. The methodology has more comprehensive application scopes and produces nitriles in higher yields than in previous work. Air was found to be the key factor for the reaction and its role has been well investigated through control experiments. The continuous systematic studies on organoselenium catalysis are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03011.

> Experimental details, mechanism study by GC−MS, product characterizations, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(3) The organoselenium compounds are obviously less toxic than inorganic selenium compounds such as SeO_2, H_2SeO_3, etc. Moreover, compared with transitional metals, selenium could be metabolized by creatures and is thus much safer to environment. An adequate englobement of selenium is even good for health. For details, see: Rayman, M. P. *Lancet* **2012**, *379*, 1256.

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